Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2016

Cytokines and chemokines in Mycobacterium tuberculosis infection

Racquel Domingo-Gonzalez

Washington University School of Medicine in St. Louis

Oliver Prince

Washington University School of Medicine in St. Louis

Andrea Cooper

University of Leicester

Shabaana A. Khader

Washington University School of Medicine in St. Louis

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

Recommended Citation

Domingo-Gonzalez, Racquel; Prince, Oliver; Cooper, Andrea; and Khader, Shabaana A., "Cytokines and chemokines in Mycobacterium tuberculosis infection." *Microbiology Spectrum*. 4, 5. (2016).

https://digitalcommons.wustl.edu/open_access_pubs/5654

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.

Cytokines and Chemokines in *Mycobacterium tuberculosis* Infection

RACQUEL DOMINGO-GONZALEZ,¹ OLIVER PRINCE,¹
ANDREA COOPER,² and SHABAANA A. KHADER¹

¹Department of Molecular Microbiology, Washington University in St. Louis, St. Louis, MO 63130; ²Department of Infection, Immunity and Inflammation, University of Leicester, Leicester LE1 7RH, United Kingdom

ABSTRACT Chemokines and cytokines are critical for initiating and coordinating the organized and sequential recruitment and activation of cells into *Mycobacterium tuberculosis*-infected lungs. Correct mononuclear cellular recruitment and localization are essential to ensure control of bacterial growth without the development of diffuse and damaging granulocytic inflammation. An important block to our understanding of TB pathogenesis lies in dissecting the critical aspects of the cytokine/chemokine interplay in light of the conditional role these molecules play throughout infection and disease development. Much of the data highlighted in this review appears at first glance to be contradictory, but it is the balance between the cytokines and chemokines that is critical, and the “goldilocks” (not too much and not too little) phenomenon is paramount in any discussion of the role of these molecules in TB. Determination of how the key chemokines/cytokines and their receptors are balanced and how the loss of that balance can promote disease is vital to understanding TB pathogenesis and to identifying novel therapies for effective eradication of this disease.

INTRODUCTION

Cytokines are soluble, small proteins that are produced by cells and act in a largely paracrine manner to influence the activity of other cells. Currently, the term “cytokine” describes proteins such as the tumor necrosis factor family, the interleukins, and the chemokines. Virtually every nucleated cell can produce and respond to cytokines, placing these molecules at the center of most of the body’s homeostatic mechanisms (1). Much of our knowledge of the function of cytokines has been derived from studies wherein homeostasis has been dis-

rupted by infection and the absence of specific cytokines results in a failure to control the disease process. In this context, infection with *Mycobacterium tuberculosis* has proven to be very informative and has highlighted the role of cytokines in controlling infection without promoting uncontrolled and damaging inflammatory responses (2–4). Herein, we focus on the key cytokine and chemokines that have been studied in the context of human TB using experimental medicine as well as *M. tuberculosis* infection of various animal models, including non-human primates (NHPs), mice, and rabbits. Perhaps the most important message of this review is that in a complex disease such as TB the role of any one cytokine cannot be designated either “good” or “bad” but rather that cytokines can elicit both protective and pathologic consequences depending on context.

Received: 19 April 2016, **Accepted:** 1 August 2016,
Published: 21 October 2016

Editors: William R. Jacobs Jr., Howard Hughes Medical Institute, Albert Einstein School of Medicine, Bronx, NY 10461; Helen McShane, University of Oxford, Oxford OX3 7DQ, United Kingdom; Valerie Mizrahi, University of Cape Town, Rondebosch 7701, South Africa; Ian M. Orme, Colorado State University, Fort Collins, CO 80523.

Citation: Domingo-Gonzalez R, Prince O, Cooper A, Khader S. 2016. Cytokines and chemokines in *Mycobacterium tuberculosis* infection. *Microbiol Spectrum* 4(5):TBTB2-0018-2016. doi:10.1128/microbiolspec.TBTB2-0018-2016.

Correspondence: Andrea Cooper, amc72@le.ac.uk; Shabaana Khader, khader@wustl.edu

© 2016 American Society for Microbiology. All rights reserved.

Why is TB such an informative probe allowing for detailed investigation of the function of cytokines and chemokines in immunity? One recent development in our understanding of TB stems from theories of coevolution between modern humans and *M. tuberculosis* (5). Evolutionary patterns based on genetic analyses suggest that *M. tuberculosis* and humans coexisted for tens of thousands of years in Africa but that, when humans left Africa and developed a more urban lifestyle, TB developed into a substantial health problem (6). During coevolution between humans and *M. tuberculosis*, *M. tuberculosis* likely evolved tools and stratagems with which to manipulate the human immune response to ensure effective transmission (7); this manipulation has been so successful that it is thought that over one-third of the world's population harbors some form of *M. tuberculosis* infection (8).

Two facts illustrate the focus of *M. tuberculosis* on manipulating the human immune response. First, *M. tuberculosis* is the major active constituent of complete Freund's adjuvant, which has been used for decades to stimulate long-lived cellular immune responses in vertebrate animals. Second, we have exploited the strong and sensitive T-cell-based inflammatory response to *M. tuberculosis* antigens as a skin test to indicate infection with *M. tuberculosis*. Thus, teleologically speaking, we may suggest that *M. tuberculosis* does not fail to induce immunity, it simply manipulates it such that its need to be transmitted is met. This manipulation occurs from the start of the human *M. tuberculosis* interaction when immune surveillance cells of the lung recognize danger through binding of their pattern recognition receptors to exquisitely refined *M. tuberculosis* pathogen-associated molecular molecules. It is this initial interaction that results in production of chemokines and cytokines, which then recruit and activate inflammatory cells (9). Following this initial interaction, bacteria migrate to the draining lymph node where they initiate (quite effectively) antigen-specific T cells that differentiate into cytokine-producing cells capable of expressing a variety of chemokine receptors that allow them to traffic away from the lymph node and into sites of tissue inflammation (7, 9). These antigen-specific T cells must then migrate via chemokine gradients, colocalize with *M. tuberculosis*-infected phagocytic cells, and release cytokines that activate the infected cells to kill the *M. tuberculosis* (7, 9). If this induction of immunity is not met by *M. tuberculosis*, then the host dies rapidly with no effective transmission of the bacterium to further hosts.

The need for communication between cells both for efficient migration and for specific instruction during

expression of immunity is where the critical role of cytokines and chemokines in controlling TB lies. Indeed, for the majority of those infected with *M. tuberculosis*, the efficient expression of immunity via competent cytokine and chemokine expression results in no sign of disease other than an ability to exhibit an inflammatory response to *M. tuberculosis* antigen (i.e., the skin test response). However, for *M. tuberculosis* to be efficiently transmitted, a degraded inflammatory lesion capable of delivering live bacteria to the airways must develop, and it is this evolutionary need that likely drives the development of the disease process in the lung. *M. tuberculosis* expresses molecules that promote inflammatory responses, which then need to be regulated to avoid tissue damage. If the bacterial burden is large or if the bacteria proliferate rapidly, then the coordination between cells mediated by cytokines and chemokines cannot occur quickly enough and immunity cannot be expressed, despite the presence of all of the required components. Understanding the functions and interactions between cytokines and chemokines is therefore critical to our attempts to limit TB. Herein, we discuss the roles of specific cytokines (Table 1) and chemokines (Table 2) in the context of *M. tuberculosis* infection and how they function to stop the development of TB, and also how they might contribute to the progression of disease.

CYTOKINES

Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF α) is a cytokine that is released following activation of the immune system. Although it is primarily produced by macrophages, TNF α can also be secreted by lymphocytes, mast cells, endothelial cells, and fibroblasts (10). Because most cells exhibit responsiveness to TNF α , it is considered a major proinflammatory mediator. It is produced as a type II transmembrane homotrimeric protein (mTNF) that can become released into the extracellular milieu through the proteolytic action of TNF α -converting enzyme (TACE) (11). Soluble TNF (sTNF) exists as a 51-kDa trimeric protein that is unstable on reaching nanomolar concentrations (12), but which on binding to cognate TNF receptors (TNF-R) induces activation of proinflammatory responses mediated by NF κ B, JNK, and p38, as well as promotion of apoptosis (10, 13–16). There are two TNF receptors, TNF-R1 and TNF-R2. Both TNF-R1, also known as CD120a and p55/60, and TNF-R2, also known as CD120b and p75/80, can

TABLE 1 The positive and negative roles of cytokines in TB

Cytokine	Receptor/signal	Role in TB
TNF α	TNFR1, TNFR2 JNK, p38, NF κ B	Positive: Essential for survival following <i>M. tuberculosis</i> infection. Initiation of innate cytokine and chemokine response and phagocyte activation. Negative: Mediator of tissue damage.
IFN γ	IFNGR1, IFNGR2 JAK/STAT	Positive: Essential for survival following <i>M. tuberculosis</i> infection. Coordinates and maintains mononuclear inflammation. Expressed by antigen-specific T cells. Negative: Potentially pathogenic.
IFN α /IFN β	IFNAR1, IFNAR2 JAK, TYK, ISG, ISRE	Positive: Required for initial recruitment of phagocytes to the lung. Negative: Overexpression of IFN α /IFN β results in recruitment of permissive phagocytes and regulation of T-cell accumulation and function.
IL-6	IL-6R, gp130 JAK, STAT3, MAPK	Positive: Potentiates early immunity – nonessential unless a high-dose infection.
IL-1 α /IL-1 β	IL-1R1, IL1RAcP MyD88, IRAK4, NF κ B	Positive: Essential for survival following <i>M. tuberculosis</i> infection. Induction of IL-17. Promotes PGE ₂ to limit type I IFN.
IL-18	IL-18R α , IL-18R β MyD88, IRAK, NF κ B	Positive: May augment IFN γ – nonessential. Regulator of neutrophil and monocyte accumulation, optimal induction of IFN γ by T cells.
IL-12 p40,p35	12R β 1, IL-12R β 2 JAK2, TYK2, STAT4	Positive: IL-12p40 and IL-12p35 essential for survival following <i>M. tuberculosis</i> infection. Mediate early T-cell activation, polarization, and survival. Negative: Overexpression of IL-12p70 is toxic during <i>M. tuberculosis</i> infection.
IL-23 p40,p19	IL-23R, IL-12R β 1 JAK2, TYK2, STAT3	Positive: Required for IL-17 and IL-22 expression during <i>M. tuberculosis</i> infection. Nonessential in low-dose challenge required for long-term control. Negative: Mediates increased pathology during chronic challenge.
IL-27 EBI3,p28	IL-27R α , gp130 JAK1/2, TYK2, STAT1/3	Positive: May control inflammation and reduce pathology. Negative: Regulates protective immunity to <i>M. tuberculosis</i> infection by limiting the migration and survival of T cells at the inflamed site.
IL-35 p35,EBI3	IL-12R β 2, gp130 STAT1/4	Positive: Regulate the availability of subunits of IL-12, IL-27. Negative: Potential immunoregulatory role.
IL-17A/F	IL-17RC, IL-17RA	Positive: Essential for survival following infection with some strains of <i>M. tuberculosis</i> . Induction and maintenance of chemokine gradients for T-cell migration. Negative: Drives pathology via S100A8/A9 and neutrophils.
IL-22	IL-22R1, IL-10R2 TYK2, JAK1, STAT3	Positive: Induces antimicrobial peptides and promotes epithelial repair, inhibits intracellular growth of <i>M. tuberculosis</i> in macrophages.

bind either the membrane or the soluble form of TNF α (17–19). An important regulator of activation is localization of receptor expression, as TNF-R1 is ubiquitously expressed, whereas TNF-R2 expression is restricted to subsets of neuronal cells, T cells, endothelial cells, microglia, oligodendrocytes, cardiac myocytes, thymocytes, and human mesenchymal stem cells (20). Signaling through TNF-R2 can only be activated through mTNF, and not sTNF. This complex interplay between positive and negative regulators of TNF activity reflects the potential disruptive power of TNF α , and this regulation of immunity provides tempting targets for manipulation by *M. tuberculosis*.

Originally described for its ability to promote necrosis of tumors (21), TNF α has since been implicated in proliferation and differentiation of immune cells, as well as multiple inflammatory processes including migration (20) and apoptosis of *M. tuberculosis*-infected cells *in vitro* (22, 23). Upon initial *M. tuberculosis* infection, the interaction between immune surveillance cells such as phagocytes in the lung and the invading *M. tuberculosis*

results in the production of multiple proinflammatory cytokines, including TNF α (4) (Fig. 1). Although both virulent and avirulent *M. tuberculosis* are able to induce comparable levels of TNF α by human alveolar macrophages, TNF α produced in response to infection with virulent *M. tuberculosis* strains has less bioactivity (24). This is an example of the ability of the bacterium to manipulate the host response, because the decreased TNF α bioactivity has been attributed to the induction of IL-10 by the virulent strain, which then results in release of soluble TNF-R2 that binds the induced TNF α , thereby inhibiting its function (24). As infection progresses, TNF α plays a role in coordinating the chemokine response within the lung and in facilitating the development of the granuloma; it is also produced by both CD4 and CD8 T cells and plays an important role in optimal macrophage activation (25).

In *M. tuberculosis* infection models, the importance of TNF α is exemplified by mice deficient in the TNF receptor or following TNF neutralization (26). In these models, TNF α deficiency results in increased suscep-

TABLE 2 The positive and negative roles of chemokines in TB

Chemokine	Receptor	Role in TB
CCL-3,-4,-5	CCR1	Positive: Upregulated during infection. Nonessential in mouse model
CCL-2,-7,-12	CCR2	Positive: Maximizes and organizes early macrophage and T-cell accumulation in the lung Negative: Mediates recruitment of permissive phagocyte accumulation into the lung
CCL-17,-22	CCR4	Positive: Mediates optimal granuloma formation to mycobacterial antigen Negative: May limit T-cell proliferation via T _{REG}
CCL-3,-4,-5	CCR5	Positive: Regulation of pulmonary infiltrates – nonessential. May mediate early dendritic cell accumulation in the lymph node. May augment macrophage <i>M. tuberculosis</i> killing via CCL5?
CCL-20	CCR6	Positive: Expression of CCR6 on T cells specific for <i>M. tuberculosis</i> antigens Negative: CCL-20 seen at high levels in active TB
CCL-19,-21,	CCR7	Positive: Mediates efficient migration of dendritic cells and <i>M. tuberculosis</i> -specific T-cell activation.
CXCL-1,-2,-3,-5,-6,-7,-8	CXCR1	Positive: Expressed on neutrophils mediates accumulation
	CXCR2	Negative: Absence of CXCR2 or CXCL5 results in improved bacterial control and reduced neutrophil accumulation
CXCL-9, -10,-11	CXCR3	Positive: Required for optimal granuloma formation. Expressed on <i>M. tuberculosis</i> -specific T cells. Use of CXCL9-11 levels to indicate disease level? Required for early recruitment of T cells to lung
CXCL-13	CXCR5	Positive: Required for correct location of T cells within granulomas. Required for B-cell follicle formation in <i>M. tuberculosis</i> -infected lungs. Required for optimal protection.

tibility with mice succumbing to infection within 2 to 3 weeks, while harboring a high bacterial burden (26). Critically, although inflammatory cells accumulate at the site of *M. tuberculosis* infection in TNF α -deficient mice, they do not coalesce to form granulomas (26–29). Granulomas are considered to be a hallmark of TB and are composed of macrophages, multinucleated giant cells, CD4⁺ and CD8⁺ T cells, B cells, and neutrophils (30). In one of the earliest studies of the role of TNF α in mycobacterial disease, it was shown that TNF α neutralization following BCG infection led to the loss of granulomas (31). Neutralization of TNF α also leads to decreased expression of key chemokines such as CCL5, CXCL9, and CXCL10. CXCL9 and CXCL10 both bind to the receptor CXCR3 (32, 33), expressed on activated T cells, while CCR1 and CCR5, expressed on both innate (i.e., macrophages and neutrophils) and adaptive cells (i.e., T and B cells), bind to CCL5 (34). Thus, TNF α sits at the crossroads where innate immunity and acquired immunity, as well as cytokines and chemokines interact. In the absence of TNF α , T cells expressing CXCR3 fail to encounter the ligands CXCL9 and CXCL10 required to recruit these cells into the granuloma. Thus, the required communication between infected phagocytes and the instructive T cells does not occur, resulting in loss of immunity.

The importance of the granuloma in restricting the movement of *M. tuberculosis* to more immunoprivileged sites has long been appreciated (35). Indeed, inhibition of TNF α promotes dissemination of *M. tuberculosis* to sites such as the central nervous system (CNS) (36, 37) wherein adverse events are profound and often irreversible. It is thought that *M. tuberculosis* migrates to the CNS secondarily from a primary site elsewhere in the

host (38, 39), although how it crosses the blood-brain barrier is not clear. Although TNF α is produced in the CNS and is thought to exacerbate progression of TB-related damage in the CNS in a rabbit model (40), use of neuron-specific TNF α -deficient mice has shown that neuron-derived TNF α production is dispensable for protection against CNS-TB (41). These data support the notion that TNF α is critical for the initiation and coordination of cellular responses, but that it has the potential to be pathogenic when expressed in the absence of immunity.

TNF α is required throughout the life of the infected host because reactivation of pulmonary TB occurs in latently infected mice upon neutralization of TNF α (42). Upon neutralization, less defined granuloma formation is seen along with increased bacterial burden in the lung and extrapulmonary sites such as the liver and spleen (42) (Fig. 2). Enhanced histopathology is also observed in TNF α -neutralized mice, supporting the importance of a regulated cellular interaction during *M. tuberculosis* infection. The protective role of TNF α is further highlighted in those patients with autoimmune and chronic diseases who are undergoing anti-TNF α -neutralizing therapies, including infliximab, adalimumab, and etanercept (43, 44). Although this therapy is successful at treating the autoimmune disease, a significant correlation between reactivation of latent TB in patients undergoing anti-TNF α therapy has been reported (45–52). Patients using infliximab and/or adalimumab have a higher incidence of TB reactivation in extrapulmonary sites compared with etanercept (50). While a mechanism for this has not been determined, mathematical modeling and bioinformatic analysis suggest that reactivation is related to drug tissue penetration, drug half-life,

FIGURE 1 The role of chemokines and cytokines in the innate response to *M. tuberculosis* infection. Upon early infection of the lower airways, *M. tuberculosis* encounters alveolar macrophages and lung epithelial cells. Alveolar macrophages are a major source of pro-inflammatory cytokines (TNFα), although stromal cells can produce cytokines and chemokines that will also modulate immune responses. During early infection, dendritic cell trafficking from the lungs to the lymph node via CCR7 results in primed naive T cells and initiation of adaptive immune responses. Replicating bacteria generate a fulminant reaction that results in the mobilization and recruitment of both neutrophils and monocytes from the bone marrow via the induction of proinflammatory cytokines and chemokines. Regulation of cellular recruitment occurs via coordinated cytokine and chemokine induction. While initial recruitment of monocytes requires type I IFN, overexpression of this cytokine results in high levels of CCR2-expressing monocytes with limited ability to control bacterial growth. Type II IFN (IFNγ) regulates the recruitment of neutrophils, which is promoted by IL-17. CXCL5 and CXCR2 mediate the recruitment of damaging neutrophils. Mtb, *M. tuberculosis*.

and relative specificity for membrane-bound TNFα or soluble TNFα (53). An intriguing mechanism for the effect of infliximab on immunity to *M. tuberculosis* infection has been suggested by the observation that this antibody-based drug binds to mTNF expressed on effector

memory CD8 T cells, thereby facilitating complement-mediated lysis and likely loss of *M. tuberculosis*-specific CD8 T cells (54). In a cynomolgus macaque model of TB, latently infected primates were given either soluble TNFα or adalimumab and exhibited increased reactivation

FIGURE 2 The role of chemokines and cytokines in the adaptive response to *M. tuberculosis* infection. Following *M. tuberculosis* infection of the lung, migratory cells take the bacteria to the draining lymph node likely using both cytokine (IL-12p40) and chemokine (CCR2, CCR7) pathways. Antigen is then transferred to antigen-presenting cells that stimulate naïve T cells via MHC class I and class II. Antigen-presenting cells make cytokines and chemokines to potentiate T-cell proliferation and polarization. Activated T cells migrate from the draining lymph node through the vasculature to the inflamed site. Some T cells remain in the vasculature (CX3CR3⁺) while others migrate into the parenchyma (CXCR3⁺CCR6⁺). Expression of CXCR5 on antigen-specific T cells allows them to respond to IL-23- and IL-17-dependent CXCL13 and locate effectively within the granuloma, where they activate *M. tuberculosis*-infected macrophages. T cells express a variety of cytokines in the lung including IFNγ, TNFα, IL-17, and IL-10 that have both protective and negative effects depending upon the context.

and harbored higher bacterial burdens than their latently infected untreated counterparts (55). As would be expected because of the higher bacterial burden and the role of TNFα in limiting bacterial spread, there were more granulomas in the lungs of the treated monkey (26, 55). In the zebrafish model of *Mycobacterium marinum* infection, TNFα is required for control of mycobacterial growth and to regulate macrophage necrosis (56).

The ability to rapidly diagnose active disease from latent infection would be highly beneficial in identification and prompt treatment of TB. TNFα has recently been proposed as a biomarker to distinguish between active pulmonary disease and latently infected individuals who do not exhibit disease symptoms (57). Using polychromatic flow cytometric analysis, patients with pulmonary TB disease have a higher proportion of single positive TNFα-producing *M. tuberculosis*-specific CD4⁺

T cells compared with individuals with latent infection (57). This was further confirmed in a blinded study whereby this parameter was the sole diagnostic for pulmonary TB disease (57). TNFα lies at the crux of the TB conundrum. It is critical for control of infection with both phagocyte-activating and granuloma-organizing functions, but too much TNFα can mediate tissue damage and promote transmission (Table 1).

The Interferons

The interferon family demonstrates the potential for similar cytokines to play protective and pathologic roles in TB disease. Based on receptor specificity and sequence homology, the interferons (IFNs) are classified into two types (58). IFNγ is the only type II interferon and, while structurally related to the type I interferons IFNα and IFNβ, these cytokines use different receptors and have

distinct chromosomal locations (58). Unlike type I IFNs that bind to a common heterodimeric receptor composed of IFNAR1 and IFNAR2 chains, IFN γ binds to the IFN γ receptor (IFNGR) which comprises two ligand-binding IFNGR1 chains that associate with two signal-transducing IFNGR2 chains (58). In addition, while IFN γ is essential for survival following *M. tuberculosis* infection the type I IFNs appear to be largely detrimental to the host during TB and may be coopted by the bacterium for its own ends (Table 1).

Type II interferon (IFN γ)

IFN γ -IFNGR binding induces signaling within the cell primarily through the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways and results in changes in both the migratory and functional capacity of multiple cell types such as macrophages, NK cells, and T cells (59–61). Innate production of IFN γ by phagocytes stimulated through their pattern recognition receptors results in early proinflammatory responses to infection (58, 62) and, unlike TNF α , which is regulated tightly by highly related molecules, production of IFN γ is regulated by cytokines such as IL-12 and IL-18, which are also secreted by immune surveillance cells upon ligation of their pattern recognition receptors (58, 63, 64).

Genetic deficiency in the IFN γ pathway in humans is associated with increased risk for mycobacterial disease and Mendelian susceptibility to mycobacterial disease (MSMD) (65, 66). Autosomal complete recessive IFN γ R1-deficient patients exhibit a predisposition for mycobacterial infections manifesting early in life and with poor prognosis (67). IFN γ R2 deficiency (either total protein loss or loss of function) has also been observed and results in a similar outcome to IFN γ R1 deficiency (68, 69). Similarly, mice that do not express IFN γ because of targeted gene disruption are severely susceptible to both low-dose aerosol (70) and intravenous infection (71, 72) and exhibit poor macrophage activation and exacerbated granulocytic inflammation (70, 71).

The classic function of IFN γ is as a phagocyte-activating cytokine which instructs macrophages and other cells to change function. In particular, in the absence of IFN γ *M. tuberculosis* occupies an intracellular environment wherein there is little reactive radical production; the phagosome does not fuse with lysosomes and remains at neutral pH. There is also an ample supply of iron due to the location of the phagosome in the early endosomal pathway (73). While innate sources of IFN γ can activate macrophages, there is very little control of

M. tuberculosis growth in the absence of α/β T cells or major histocompatibility complex (MHC) class II following aerosol infection (74), suggesting that both IFN γ and antigen-specific T cells are required for control of this infection. However, whether it is T cells producing IFN γ that are critical has not been definitively demonstrated, but the strongest support of a critical need of CD4⁺ T cells to make IFN γ is from a transfer model in mice (75). In contrast, memory T cells can mediate protection in the absence of either IFN γ or TNF α , suggesting other functions need to be identified (76). Both CD4⁺ and CD8⁺ T cells produce IFN γ and accumulate within the infected lung and, while absence of CD4⁺ T cells results in rapid susceptibility to *M. tuberculosis* infection, the absence of CD8⁺ T cells results in susceptibility later in the infection (77). The organization of the granuloma is also disrupted in the absence of CD4⁺ T cells with predominantly perivascular cuffing of lymphocytes observed (78), suggesting that, in the absence of CD4⁺ T cells, chemokine gradients are not established for T-cell migration. It is also the case that, while CD8⁺ T cells can make IFN γ during *M. tuberculosis* infection, they require CD4⁺ T cells to do so optimally (79).

The induction of IFN γ -producing T cells has been the focus of anti-TB vaccine design but has not been particularly fruitful. It is clear that humans need antigen-specific T-cell responses to control TB (because those with human immunodeficiency virus [HIV]/AIDS develop TB readily) and that absence of IFN γ promotes mycobacterial disease in humans, so why have we not progressed? Again, we come back to the issue of the communication between the T cells and the infected phagocytes. If the T cells are unable to colocalize with the phagocytes and/or the phagocytes are unable to respond to the signals delivered by the T cells, then the number of IFN γ -producing T cells circulating throughout the body is meaningless. It is therefore the case that IFN γ production by activated T cells is not a correlate of protection, rather the ability of antigen-specific T cells to penetrate and survive within the infected site may be. In this regard, recent studies demonstrate that not all cytokine-producing antigen-specific T cells are able to penetrate the TB granuloma and some remain in the vasculature or cuff around the vessels and this is related to their expression of transcription factors, chemokine receptors, and differentiation state (80–82); these markers should perhaps be considered as correlates of protection.

IFN γ can act on cells other than macrophages; indeed, its most critical function in TB may not be to activate macrophages but rather to limit polymorphonuclear

(PMN) inflammation (Fig. 1). Most susceptible mouse strains exhibit high PMN infiltration in the lungs once infected (83–86), and inhibition of this infiltration improves survival (83). Mice that lack IFN γ exhibit high PMN infiltration as do mice lacking CD4 $^{+}$ T cells (70, 78). Neutrophils that lack the IFN γ R fail to undergo apoptosis and accumulate in the lungs of *M. tuberculosis*-infected mice, and their removal improves survival without altering bacterial burden (87). Similarly, chimeric mice lacking IFN γ R on their radio-resistant cells overexpress IL-17 and have excessive neutrophil recruitment and reduced survival (88). It is possible that the high IFN γ -producing CD4 $^{+}$ T cells that populate the vasculature (80, 82) are located in such a position to reduce neutrophil accumulation.

Production of IFN γ is a very useful diagnostic tool that has been developed to be more selective than the older skin test assay. In this prominent test for *M. tuberculosis* exposure, *M. tuberculosis* antigens (selected to be unique for *M. tuberculosis* versus other mycobacteria) are used to stimulate IFN γ release (89–91). While this test selects for those who are exposed, it is not optimized to distinguish between those individuals who are infected but healthy and those in the process of developing active disease. Recently, studies have shown that patients that have more IFN γ -producing T cells are actually more likely to progress to active disease, suggesting that this test may be optimized to identify those progressing toward disease (92).

Type I interferon (IFN)

The interferons were first identified more than half a century ago for their antiviral activity (93). Type I IFNs represent the largest group, with at least 13 gene products identified in humans and mice, with IFN α and IFN β being the best classified and the focus of this section. For clarity, IFN α and IFN β will be collectively referred to as IFN α/β throughout this section. The innate response to pathogens occurs via Toll-like receptor (TLR) engagement resulting in a complex cytosolic cascade of signal transduction toward IFN-regulatory factor 3/7 (IRF3/7)-mediated transcription of IFN α/β genes (94). Secreted IFN α/β engages IFN subunit receptors 1 and 2 (IFNAR1/2) at the cell surface, which then activate dimers of the tyrosine kinases JAK and tyrosine kinase (TYK) (94, 95). The end result is activation of IFN-stimulated gene factor (ISG) that then interacts with IFN-stimulated response elements (ISRE) at the promoters of IFN α/β -regulated genes (94, 95).

The type I IFNs were not thought to play a major role in *M. tuberculosis* infection and indeed infection

of IFNAR-deficient mice with a low-dose aerosol of *M. tuberculosis* Erdman strain did not indicate any major impact of the loss of this receptor (96). However, use of strains with increased virulence, such as the W-Beijing strain HN878, has revealed an important strain-dependent outcome in relation to type I IFNs. The pathogenesis of *M. tuberculosis* strain HN878 is associated with IFN α/β -dependent reduction in the activity of the proinflammatory cytokines IFN γ , TNF α , IL-6, and IL-12, as well as in the anti-inflammatory IL-10 (97, 98) (Fig. 1). Intranasal delivery of IFN α/β also results in increased bacterial burden and reduced survival in contrast to IFN γ -treated mice (97). Furthermore, IFN α/β signaling interferes with IFN γ -mediated killing of *M. tuberculosis* (99). One hypothesis regarding the role of type I IFNs during chronic *M. tuberculosis* infection is that the accumulation of plasmacytoid dendritic cells in the lung provides a source of excess type I IFN which then inhibits the accumulation of CD4 $^{+}$ and CD8 $^{+}$ T cells in the lung (98) (Fig. 1). Finally, transcriptional analysis of peripheral blood cells from those exposed to TB shows that both IFN γ and type I IFN signatures occur, but that the type I IFN signature is predominantly associated with neutrophils (100).

In a mechanistic analysis of the function of IFN α/β in TB, polyinosinic-polycytidylic acid and poly-L-lysine and carboxymethylcellulose (poly-IC) were used to induce elevated levels of IFN α/β during *M. tuberculosis* infection (101). This poly-IC treatment results in elevated bacterial burden and increases the recruitment of an apparently permissive CD11b $^{+}$ GR1 int cell phenotype recruited via chemokine (C-C motif) ligand 2 (CCL2) and C-C chemokine receptor type 2 (CCR2) (101) (Fig. 1). Similarly, careful analysis of the cells recruited to the lungs of mice lacking either type I or type II IFN receptors demonstrates a protective function for type I IFN signaling in that, in its absence, initial recruitment of target host cells for *M. tuberculosis* does not occur and immunity is compromised (102).

IFN α/β is another perfect example of a “goldilocks” cytokine in TB (Table 1). Just enough is required to initiate recruitment of phagocytes that provide activatable host cells for *M. tuberculosis* to invade; however, production of too much IFN α/β results in large numbers of permissive cells that cannot be effectively activated. Also, too much of this cytokine can limit the activation state of the infected phagocytes and potentially limit the accumulation and function of the T cells required to regulate the mononuclear structure of the granuloma.

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic cytokine produced in response to inflammatory stimuli (103) and is involved in the essential cellular processes of differentiation, proliferation, and apoptosis. Many cell types express IL-6, including those of lymphoid and nonlymphoid origin (103), and expression can be induced by other cytokines including IL-1, TNF α , and IFN γ (104, 105). IL-6 signals through soluble and membrane-bound IL-6R of which the glycoprotein 130 dimer (gp130) is an essential component (106). Downstream signaling is mediated by a phosphorylation cascade involving JAK, mitogen-activated protein kinase (MAPK), and STAT pathways (106, 107). The pluripotency of IL-6 warrants regulation and this is mediated by suppressor of cytokine signaling (SOCS), which inhibits STAT signaling (106, 107).

The relative importance of IL-6 during TB depends upon the route and dose of infection. As we have discussed, communication between cells is critical for successful expression of immunity and, if the dose is low or bacteria are slow to grow, then the kinetics of the cellular response are not critical. However, if the dose is high and systemic, then the kinetics of the response becomes critical. This concept is illustrated by IL-6, because in its absence (either by antibody treatment or by gene deletion) there is increased susceptibility to intravenous challenge with a large dose of mycobacteria (108, 109). In contrast, in a low-dose aerosol *M. tuberculosis* challenge model, while modestly increased bacterial burden occurs in the lungs of IL-6-deficient mice, the impact is not lethal (110). In both the low- and high-dose challenge models, increased IL-4, as well as reduced or delayed T-cell accumulation and IFN γ expression, is observed, suggesting that IL-6 can act to potentiate IFN γ expression at the site of infection (108, 110). It appears also that IL-6 is required for optimal induction of protective responses during vaccination, because, in its absence, both BCG and a subunit vaccine are less effective (109, 111).

Interpretation of the role of IL-6 in TB is complicated by the fact that the soluble IL-6 receptor can mediate *trans*-signaling and is implicated in inflammatory diseases such as inflammatory bowel disease (112). To address the role of IL-6 further, a gp130 construct capable of sequestering IL-6 in the blood (sgp130FC) was delivered to mice during *M. tuberculosis* infection, but no impact on disease progression was seen. In contrast, when mice are made to overexpress this construct, a temporary but significant increase in bacterial burden occurs during acute infection (113).

This observation is consistent with an early role of IL-6 in potentiating immunity during early *M. tuberculosis* infection.

In vivo data support a protective role for IL-6 in the induction of early protective responses mediated through IFN γ (108, 110). Human studies also give us considerable insights into the role of IL-6 during TB. Cavitory TB is the most destructive form of caseous TB whereby necrosis liquefies cellular material and results in compromised lung function. Humans with cavitory TB express lower levels of IL-6 and the chemokine IP-10 in their bronchial alveolar lavage (BAL) fluid in comparison with TB patients without cavitory disease, thereby indicating IL-6 and IP-10 as potential markers of controlled (noncavitory) TB (114). As would be expected, elevated neutrophils were observed in BAL from cavitory TB patients, while noncavitory TB patients presented with elevated alveolar macrophages (114); interestingly, there was no correlation between cytokine expression in BAL fluid and serum cytokine production (114). In contrast, an earlier study identified elevated blood plasma levels of IL-6 from TB patients with developed lung lesions (115). Based on the mechanistic data from animal studies and the human data, IL-6 appears to be associated with effective early expression of immunity in the lung via the combination of regulated mononuclear inflammation and rapid accumulation of lymphocytes. Its effects are modest but may be critical following high-dose exposure or during immunodeficiency.

IL-1 Cytokines

The proinflammatory cytokines IL-1 α , IL-1 β (collectively called IL-1 here), and IL-18 are members of the IL-1 family (116). IL-1 was first identified in the 1940s as an endogenous pyrogen (117–119). IL-1 and IL-18 as well as their respective receptors (IL-1R1 and IL-18R) are widely expressed by all nucleated cells of the body including endothelial cells, monocytes, macrophages, and neutrophils (116). Expression of IL-1 and IL-18 is mediated in part by the canonical pathway of inflammasome activation, which involves the sensor (e.g., TLR), an adaptor molecule such as myeloid differentiation primary response gene 88 (MyD88), and caspase-1 (120–122). Alternatively, IL-1 β and IL-18 can also be induced by the noncanonical inflammasome pathway that is distinguished by the activation of caspase-8 and -11 on the precursor of the cytokines in the cytosol (123, 124). MyD88 is an important cytosolic mediator linking TLR signaling to the transcription of inflammasome components (122).

IL-1 α is mostly associated with sterile cell injury (e.g., cigarette smoke), but is also induced during nonsterile cell injury (e.g., bacterial) where it functions locally as an alarmin (125–130). IL-1 β is induced during infection and is primarily produced by monocytes, macrophages, and dendritic cells (131–134). IL-1 signals through the IL-1R1 receptor present on a number of cells including endothelial cells, monocytes, macrophages, and T lymphocytes (116, 128, 135, 136). IL-18 is expressed constitutively in the cytosol at low levels as a precursor, which is activated by caspase-1 activity following bacterial stimulation, stimulation by neutrophils or by IL-4 or IFN γ (137–139). IL-18 activity results from colocalization of IL-18 receptor alpha (IL-18R α) and IL-18 receptor beta (IL-18R β) on host cells including monocytes and epithelial cells (140).

IL-1R/IL18R/MyD88

Signaling through MyD88 is shared between TLR, IL-1R, and IL-18R (141–143). MyD88 is an essential component in innate signaling in response to TB, because MyD88 gene-deficient mice exhibit profound susceptibility to *M. tuberculosis* infection (143). Importantly, following mycobacterial stimulation, MyD88 gene-deficient macrophages and dendritic cells exhibit reduced IL-6, TNF, and IL-12p40 production, suggesting a critical role for MyD88 in pattern recognition responses to *M. tuberculosis* infection (143). Aerosol infection results in dramatically increased lung burden coinciding with increased inflammation and accumulation of neutrophils and macrophages (143). Despite the poor innate response to *M. tuberculosis* infection in the MyD88 gene-deficient mice, the accumulation of IFN γ -producing T cells was not affected. It is likely that these antigen-specific cytokine-producing T cells were unable to mediate protection because of failures within the phagocytes accumulating at the site or as a result of being unable to communicate with the infected phagocytes (143). That BCG vaccination results in protection against *M. tuberculosis* infection in MyD88-deficient mice suggests that it is a failure of T cells to accumulate rapidly enough in naive mice that contributes to their susceptibility (143).

What then is MyD88 signaling doing? Comparison of the phenotype of IL-1-deficient mice and MyD88-deficient mice is suggestive in this regard, because both exhibit increased susceptibility with focal necrosis despite generation and accumulation of cytokine-producing T cells (144). These observations suggest that induction of IL-1 is likely Myd88 dependent and that this pathway plays a critical role in protective immunity to TB.

IL-1

IL-1 α and IL-1 β are interdependent proinflammatory cytokines critical to defense against TB (145–149). Mice lacking either IL-1 α or IL-1 β or both are susceptible to acute and chronic infection, respectively, following challenge with *M. tuberculosis* (145–148). IL-1 α/β double-deficient mice share a similar susceptibility to infection as IL-1R1KO and MyD88KO mice (143, 144, 148, 150). Deficiencies in the IL-1 pathway (IL-1 α/β or IL-1R1) have no impact on the protection against BCG delivered intravenously, suggesting that virulence of the pathogen is a factor in the role of the IL-1 pathway (146). Anti-IL1 α and anti-IL-1 α/β antibodies delivered subcutaneously to *M. tuberculosis*-infected mice have also been shown to result in loss of body weight and lethality (148). Furthermore, lung sections from anti-IL-1 α -treated mice exhibit lung parenchyma consumed by cellular infiltrates (148). During sterile mediated inflammation, IL-1 α appears to be involved in the expression of proinflammatory cytokines such as IL-6 in primary fibroblasts (151), which may be associated with mobilization of neutrophils (152). It has also recently been observed that, upon activation of the inflammasome, IL-1 β and IL-18 are capable of inducing expression of the neutrophil-recruiting cytokine IL-17 (153–155). IL-17 responses are essential in the protection against some *M. tuberculosis* strains, such as HN878 and for recall responses to H37Rv (149, 156, 157). Consistent with this, IL-1R1 gene-deficient mice infected with the *M. tuberculosis* strain HN878 produce decreased levels of IL-17 and decreased populations of IL-17-producing cells *in vitro* and *in vivo* (149).

IL-1 is produced by CD11b⁺Ly6G[−] cells following *M. tuberculosis* infection (145), and rescue of the lethal phenotype in IL-1 α mice can be accomplished by directed viral expression of IL-1 α in CD11c⁺ cells transplanted in IL-1 α gene-deficient mice (147). It would seem, therefore, that a primary function of the IL-1/IL-1R pathway is to mediate the recruitment and coordination of cellular responses by the induction of proinflammatory cytokines from the stroma (145, 147). One critical aspect of IL-1 function is in promotion of prostaglandin E₂ (PGE₂), which in turn mediates inhibition of type I IFN-induced accumulation of permissive macrophages at the site of infection (158) (Fig. 1). Prostaglandins such as PGE₂ are produced by the action of cyclooxygenase (COX) enzymes on arachidonic acid, and, in the absence of inducible COX enzymes, mice are highly susceptible to *M. tuberculosis* infection, and delivery of PGE₂ during *M. tuberculosis* infection results in a partial rescue of the lethal phenotype in IL-1 α/β -

infected mice (158). Taken together, the underlying function of IL-1 in *M. tuberculosis* appears to be in regulating type I IFN function and helping to maintain the balance between sufficient phagocytes to mediate control of the intracellular pathogen, while inhibiting the overrecruitment of permissive macrophages mediated by type I IFN (102).

IL-18

IL-18 is essential for the production of IFN γ from T cells under some conditions (159–163), and, in some instances, its absence can result in increased susceptibility to *M. tuberculosis* (150), although, in other conditions, increased susceptibility to *M. tuberculosis* infection is not observed (162, 163). Interestingly, when susceptibility is observed, the accumulation of neutrophils and inflammatory chemokines CXCL1 and CXCL2 is elevated, and depletion of neutrophils and monocytes from the lung results in decreased bacterial burden (150). In *M. tuberculosis*-infected IL-18-deficient mice, an increased frequency of IFN γ -producing CD4⁺ and CD8⁺ T cells in the lungs is seen, but total IFN γ production by these T-cell populations is decreased, suggesting that IL-18 could contribute to optimal IFN γ induction during TB (150, 162, 163). It would appear, therefore, that IL-18 plays a role in inducing high IFN γ production in T cells, but that this is not required for protection, and that its more critical role (perhaps when dose or virulence of the *M. tuberculosis* strain is high) is that of regulator of phagocyte accumulation, possibly mirroring the role of IL-1 and MyD88.

Our working model of immunity to TB places the emphasis on rapid and correct accumulation of both phagocytes (macrophages and neutrophils) and T cells to the site of infection. This accumulation is initiated by the innate sensors within the lung and results in the induction of TNF, IFNs, and IL-1 family members. The correct ratio of these cytokines is essential for the balance of permissive and nonpermissive phagocytes and for the development of a granuloma such that infected phagocytes and antigen-specific T cells can communicate effectively to stop *M. tuberculosis* growth. How the antigen-specific T cells develop and are regulated is covered below.

IL-12 Cytokine Family

The IL-12 family of cytokines belongs to the IL-6 superfamily and is the only family composed of heterodimeric cytokines (164, 165), and this unique feature bestows diverse and pleiotropic functions because of promiscuous chain pairing (166). The alpha chains of

the IL-12 family (p19, p28, and p35) contain four-helix bundle structures and pair with one of two beta chains (either p40 or Epstein-Barr virus-induced gene 3 [Ebi3]) (164–166). IL-12 is composed of the subunits p35/p40, IL-23 of p19/p40, IL-27 of p28/Ebi3, and IL-35 of p35/Ebi3 with expression of the distinct subunits being regulated independently (166). In addition, IL-12p40 can also be secreted both as a homodimer (IL-12p80 or IL-12p(40)₂) and as a monomer (IL-12p40) (167). Both macrophages and dendritic cells are major producers of IL-12p40, IL-12, IL-23, and IL-27 (168). These cytokines are largely associated with the induction and regulation of cytokine expression within antigen-stimulated T-cell populations.

IL-12

IL-12 plays an important role as a link between innate and adaptive immune responses, and is produced by and influences multiple effector cells (169, 170). Composed of IL-12p35 and IL-12/23p40, IL-12 (IL-12p70) is primarily secreted by macrophages, dendritic cells, and B cells (166, 171, 172). The importance of IL-12 in TB is dramatically illustrated by several experiments of nature wherein humans with IL-12p40 deficiency display an inherent predisposition to *M. tuberculosis* infection (173–178). Furthermore, patients with MSMD harbor deficiencies in IL-12R β 1, IFN γ R1, and IL-12p40, and exhibit susceptibility to *M. tuberculosis* and develop BCGosis following delivery of the BCG vaccine (66, 178–181). Genetic etiology for MSMD is associated with mutations in the autosomal genes *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12BR1*, and X-linked gene *IKK β* , encoding NF- κ B essential modulator (NEMO) (66). All these autosomal genes are associated with IL-12/IFN γ -dependent signaling and the IFN γ -mediated activation of macrophages. Mutations in *IKK β* impair CD40-dependent IL-12 production in monocytes and dendritic cells, despite normal CD40-mediated induction of costimulatory molecules on dendritic cells (182). These human data highlight the importance of this pathway to TB control.

IL-12 is expressed within the lung at the site of TB (183) and delivery of IL-12 to *M. tuberculosis*-infected mice decreases bacterial burden, while reduction of IL-12 by antibody increases bacterial burden (184). Interestingly, delivery of IL-12 also modestly improves the outcome for mice lacking acquired cellular immunity, suggesting that it can mediate immunity via direct action on innate cells (184). Mice genetically deficient for the IL-12p40 subunit are acutely susceptible to *M. tuberculosis* infection (185, 186), whereas those

lacking IL-12p35 exhibit prolonged survival relative to the IL-12p40-deficient mice (186). This, in turn, is dependent on the availability of the IL-23p19 subunit (187). The absence of IL-12p40 results in the substantial loss of antigen-specific IFN γ production (185, 186) (Fig. 2), while the presence of IL-23p19 in the IL-12p35-deficient mice appears to promote sufficient antigen-specific IFN γ production to increase protection relative to the IL-12p40-deficient mice (187). It also appears that stable and prolonged IL-12 production is required to maintain IFN γ production and to limit bacterial growth long term (188). This requirement for long-term function may also apply in humans, because absence of the IL-12R1 results in poor accumulation of IFN γ -producing memory T cells (189). The innate pattern recognition receptors, TLR2 and TLR9, are necessary for optimal production of IL-12p40 in response to *M. tuberculosis* exposure (190), while the *M. tuberculosis* lipoarabinomannans have been shown to negatively regulate TLR-mediated IL-12 production by inducing an inhibitor of TLR signaling, IRAK-M (191). In contrast, mycobacterial LprA is a TLR2 agonist and promotes IL-12p40 production (192), reflecting the need for *M. tuberculosis* to both induce and regulate IL-12p40 for its own ends.

IL-12 signals through interactions between IL-12/23p40, and IL-12p35 with IL-12R β 1 and IL-12R β 2, respectively (193–195), with the IL-12p40 interacting with IL-12R β 1 on the target cell surface, thereby allowing the IL-12R β 2 to induce JAK and STAT signaling and activate STAT4 homodimers (166). The homodimer IL-12p40, IL-12(p40)₂, antagonizes IL-12-mediated immune responses through competitive binding of IL-12R β 1 (196–198). However, in TB, it appears that IL-12(p40)₂ can also function as an agonist (199), and supports dendritic cell migration to the draining lymph nodes (200, 201), to promote T-cell priming and differentiation (200). Specifically, following *M. tuberculosis* infection, dendritic cells are thought to be the first immune cells to traffic to the draining lymph node (202), and this may occur in an IL-12p40- and IL-12R β 1-dependent manner (200, 203). Bone marrow-derived dendritic cells from mice deficient in IL-12p40 are unable to activate naive T cells in the draining lymph node following delivery to the lung and fail to confer protective adaptive responses (200). However, treatment of the IL-12p40-deficient dendritic cells with the homodimer IL-12(p40)₂ is sufficient to restore migration of the dendritic cells to the draining lymph node and for activation of naive T cells to occur (200). Expression of IL-12R β 1 is also required to facilitate dendritic cell

migration to the draining lymph node (203) and, indeed, CD11c⁺ cells in the *M. tuberculosis*-infected lung express an alternative splice variant of IL-12R β 1 that augments IL-12R β 1-mediated effects (203). In particular, dendritic cells expressing the splice variant exhibit enhanced migration from the infected lung to the draining lymph nodes and supported activation of *M. tuberculosis*-specific T cells (203) (Fig. 2). In an interesting example of cytokine cross talk, mice lacking the p75 receptor for TNF (TNFRp75) exhibit increased IL-12p40 and enhanced IL-12p40-mediated dendritic cell trafficking to draining lymph nodes (204). Thus, IL-12R β 1 is important for the effector function of IL-12p40 on dendritic cells, as well as mediating recruitment and function of CD4 T cells in response to TB.

IL-23

IL-23 utilizes the p40 beta subunit paired with the alpha chain p19 (205). Before the discovery of IL-23, the interpretation of data from IL-12p40- and IL-12p35-deficient models of disease had been difficult (206). Specifically, studies found that the outcome of IL-12p35 deficiency was not always the same as in IL-12p40-deficient models (207–209). The discovery of IL-23 led to the reassessment of the role of IL-12p40 (205, 206, 208, 209), and disease models previously associated with IL-12 were, in fact, shown to be primarily driven by IL-23 and not IL-12 or they clarified unique disease-driving features of the two cytokines (206, 208–211). Currently, IL-23 and IL-23 pathway antagonists are in phase 2 and phase 3 clinical trials for treating patients with moderate to severe psoriasis (207), making the determination of the role of IL-23 in TB a critical undertaking. IL-23 stabilizes the induction of the T_H17 cell subset, which produces IL-17A, IL-17F, and IL-22, and it is also required for the double expression of IL-17 and IFN γ (212). However, IL-23 alone is not sufficient to drive differentiation of T_H17 cells, which requires the key cytokines transforming growth factor β (TGF β) and IL-6 (213). In addition, IL-23 can also induce IFN γ production in human T cells as well as support the proliferation of mouse memory T cells (205, 214). The interaction with its receptor, composed of IL-23R and IL-12R β 1 subunits, activates the downstream signaling molecules, JAK and STAT, for production of its signature cytokines (166, 205, 214–216). IL-23 primarily signals through STAT3, while IL-12 can signal through STAT1, 3, 5, and 4, but preferentially signals through STAT4 (166). Upon infection with *M. tuberculosis*, lung dendritic cells produce IL-23, likely mediating the induction of IL-17 production (187, 217, 218).

Although IL-23 is important for generation of *M. tuberculosis*-specific IL-17-producing T cells (Fig. 2), mice deficient in IL-23p19 control *M. tuberculosis* effectively for up to 90 days whereupon bacterial growth increases relative to intact mice (187, 219). In addition, treatment of *M. tuberculosis*-infected mice with adenovirus-expressing IL-23 reduces *M. tuberculosis* burden and increases cellular responses (220). In the absence of IL-23p19, *M. tuberculosis*-infected mice did not develop well-organized B-cell follicles, and this was associated with a complete absence of IL-17 and IL-22 in the lung. In addition, there was very little expression of the B-cell follicle-associated chemokine CXCL13 resulting in increased accumulation of lymphocytes around the vessels rather than within the granulomatous regions (219) (Fig. 2). Thus, in support of our working model, coordinated communication between lymphocytes and infected macrophages is inefficient in the absence of specific cytokines/chemokines (in this case, IL-23-dependent CXCL13) and bacterial growth occurs in the absence of this efficient communication.

IL-23 also plays a chemokine-dependent role in the efficient expression of vaccine-induced mucosal immunity. This role was first highlighted in mice subcutaneously vaccinated with an adjuvant-paired I-A^b-restricted ESAT6₍₁₋₂₀₎ peptide, which induces both IFN γ - and IL-17-producing antigen-specific CD4⁺ T cell responses (157). Critically, the improved kinetics of the vaccine-induced IFN γ -producing T cells is lost in the absence of IL-23, because this cytokine is required for the generation of lung resident IL-17 producing CD4⁺ memory T cells that generate a chemokine gradient facilitating the accelerated IFN γ response. In the absence of IL-23, vaccine-induced protection to *M. tuberculosis* challenge is lost (157). Coimmunization of mice with a DNA vaccine composed of *M. tuberculosis* antigen 85B (Ag85B) and an IL-23-expressing plasmid also confers enhanced protection through the induction of augmented T-cell proliferation and IFN γ production in comparison with Ag85B alone (217). Other studies also support an important role for IL-17-producing CD4⁺ T-cell subsets in mediating mucosal vaccine-driven protection (156, 221–223). Specifically, adoptive transfer of *M. tuberculosis*-specific IL-17-producing T cells into unchallenged mice confers protection following exposure to *M. tuberculosis* (156). Furthermore, use of adjuvants capable of driving lung-resident IL-17-producing cells is able to initiate early CXCL13 expression, thereby promoting appropriate accumulation of CXCR5⁺ T cells within the *M. tuberculosis*-induced inflammatory site (221). These IL-17-producing T cells are long lived (222) and are

associated with improved protection when recombinant BCG vaccines are used (223).

IL-27

IL-12 and IL-23 are proinflammatory cytokines with the capacity to drive cytokine production in T cells (168, 224, 225). In contrast to this clear role for IL-12 and IL-23, IL-27 is pluripotent and has a complex and sometimes apparently contradictory capacity to influence inflammation and lymphocyte function (166, 226–228), indicating a pleiotropic nature for IL-27. IL-27 is composed of the p28 alpha and Ebi3 beta chains, and signals through the IL-27R α (WSX-1 or TCCR) and gp130 receptor subunits (166, 229, 230). IL-27 can mediate suppression of IL-17-production by T cells (231) via STAT1 signaling to promote IL-10-producing Tr1-cell-like regulatory populations (232). It also promotes proliferation (229) and polarization via T-bet (233) in naive T cells (Fig. 2).

In the context of *M. tuberculosis* infection, IL-27R-deficient mice challenged with *M. tuberculosis* exhibit lower bacterial burden in the lungs and increased granuloma-localized lymphocytes (234, 235), but these mice succumb to disease earlier than control animals (235). Thus, while IL-27R activity appears to limit expression of immunity locally, it may actually protect from undue pathologic damage. Because of the pleiotropic nature of IL-27 it is very difficult to dissect out its specific function in TB. The absence of the gp130 component of the IL-27R on phagocytes during *M. tuberculosis* infection results in loss of the increased inflammatory consequences of IL-27R deficiency but does not impact the reduced bacterial burden seen in mice lacking IL-27R on all cells, suggesting that these two aspects of IL-27R deficiency are independent (236). In contrast, mice lacking IL-27R only on T cells exhibit the improved ability to control bacterial burden over the long term (82). This improvement was associated with enhanced localization and reduced differentiation (i.e., reduced T-bet expression) of IL-27R-deficient CD4⁺ T cells within the infected lung parenchyma. *M. tuberculosis*-specific CD4⁺ T cells lacking IL-27R are also intrinsically fitter than IL-27R-sufficient CD4⁺ T cells in mice within the same environment (82) (Fig. 2). The importance of IL-27 is further confirmed in human patients, wherein IL-27 is significantly increased in patients with active TB compared with latently infected individuals (82). In our working model of TB immunity, IL-27 appears to play the role of mediator of increased inflammation within the phagocyte population while also serving to limit the efficacy of the T-cell population

by driving them to a state of differentiation that limits their ability to locate to, and persist within, the inflamed granuloma.

IL-35

IL-35, a dimeric protein encoded by IL-12 α and IL-27 β chains, has been shown to suppress CD4⁺ T-cell responses (237). It is thought to be primarily expressed by regulatory T (T_{REG}) cells (238) and is required for optimal function both *in vivo* and *in vitro* (239). IL-35 is important for the generation of human and mouse T_{REG} cells, termed iT_R35 cells (239), which function independently of IL-10 and TGF β . While a specific function for IL-35 in *M. tuberculosis* infection has not been directly addressed, the relative availability of IL-35 in the presence and absence of the other IL-12 family subunits makes consideration of this cytokine an important part of any interpretation of outcome in mice or humans lacking IL-12 family subunits.

IL-23-Dependent Cytokines

IL-17

The IL-17 cytokine family is composed of six members, IL-17A to IL-17F, with IL-17A and IL-17F being the most studied. Production of IL-17 is conventionally attributed to T cells, but other lymphocytes as well as innate immune cells can produce this cytokine (240). IL-17 cytokines are proinflammatory and can be protective or pathogenic depending on the nature of the challenge faced by the host (241, 242). It is at mucosal sites that IL-17 plays its most important regulatory and protective role against invading pathogens.

Following mycobacterial infection, lung-resident $\gamma\delta$ T cells are a primary source of early IL-17 (218), and likely support early neutrophil accumulation (243) (Fig. 1). Following BCG infection, IL-17 expression can be detected as early as day 1 postinfection and is dependent on IL-23 expression (243). One recently identified capacity of IL-17 is to regulate mycobacterially induced IL-10 (244). Following vaccination with BCG, dendritic cells produce PGE₂, which is required for the induction of both IL-10 and IL-23 with the IL-23 being required for IL-17 production (244). This IL-17 is then thought to downregulate IL-10 production, thereby allowing increased IL-12 that subsequently promotes IFN γ production. In the absence of IL-10, the IL-23-mediated IL-17 is not required and, in the absence of IL-23, BCG fails to effectively induce protective IFN γ -producing T cells (244). This study was the first to show that PGE₂ induction of IL-17 was sufficient to overcome

the inhibitory effects of IL-10 and support the generation of antigen-specific and cytokine-producing T cells during mycobacterial vaccination and challenge.

As with IL-23, low-dose challenge with some strains of IL-17A (i.e., H37Rv and CDC1551) in the absence of IL-17 results in no obvious phenotype (149, 187, 245) until late in disease (219). In contrast, following infection with the W-Beijing strain HN878 of *M. tuberculosis*, IL-17R expression on radio-resistant cells (likely fibroblasts) of the lung is required to coordinate the rapid accumulation of cells within the lung via the induction of CXCL13 and recruitment of CXCR5⁺ T cells to lymphoid follicles within the tissue (149) (Fig. 2). Importantly, the W-Beijing HN878 *M. tuberculosis* strain induces high levels of IL-1 β and IL-17 relative to other *M. tuberculosis* strains (149) and also induces excess type I IFN (97), which is capable of bringing in permissive macrophages in a CCR2-dependent manner (101) (Fig. 1). HN878 induces an environment that is highly permissive for its growth, and it is this environment that results in the need for the optimum expression of immunity wherein IL-17 promotes rapid accumulation and the correct localization of the T cells needed to change the permissive macrophages to ones that limit bacterial growth (149).

The role of IL-17 in initiating early coordination of cellular responses in naive mice is apparent when the challenge is significant as in the case of HN878; however, the concept of IL-17 as a coordinator of early mucosal responses in TB actually stems from vaccine work. Initial studies using a defined subunit vaccine determined that lung-resident IL-17-producing cells induced by vaccination are vital for the induction of the chemokines (CXCL9, CXCL10, and CXCL11) required for the accumulation of IFN γ -producing memory T cells (157). Further studies have shown that adoptive transfer of *M. tuberculosis*-specific IL-17-producing T cells into naive mice is able to mediate protection in an aerosol challenge model, thereby identifying these types of cells as valid targets for vaccine-mediated induction (156). Finally, mucosal immunization with *M. tuberculosis* antigens induces potent IL-17 responses that improve upon BCG vaccine-induced protection in mice (221). Interestingly, in mucosal vaccine models, IL-17 rather than IFN γ appears to be most important for vaccine-induced protection against *M. tuberculosis*, providing support for the model that it is the coordination of the cellular response that is the determining factor in the success of vaccination (221, 246). Critically, antigen-specific IL-17-producing memory T cells are induced by vaccination and respond up to 2 years postvaccination

(222). These memory T cells appear to be metastable and become IFN γ producers within the lung (222), probably as a result of the action of IL-23 (212). In fact, pluripotent memory T cells capable of producing not only IL-17 but also TNF and IL-2 may be the most appropriate target T cells for vaccination (247). Manipulation of BCG can also result in increased induction of IL-17-producing memory cells, and this is associated with improved protection as in the case of the recombinant BCG strain rBCG Δ ureC:Hly (223). Thus, IL-17 drives the induction of CXCL9-11 to recruit protective antigen-specific T cells, as well as CXCL-13 to localize CXCR5 $^{+}$ cytokine-producing T cells within TB granulomas. Despite the protective outcome of IL-17 discussed above, IL-23-dependent IL-17 production is also associated with damaging neutrophil accumulation during a chronic restimulation model of TB (248). Indeed, exacerbated production of IL-17 appears to drive pathology by inducing S100A8/A9 proteins that recruit neutrophils into the lung (249). Thus, IL-17 also fits the bill as a “goldilocks” cytokine in TB (Table 1).

IL-22

IL-22 is primarily produced by CD4 $^{+}$ T cells as well as $\gamma\delta$ T cells, natural killer (NK) cells, and innate lymphoid cells following exposure to innate or infectious stimuli (250). IL-22 can have dual effects in the context of inflammation, and this has been attributed to its coexpression along with IL-17 (250, 251). The major functions of IL-22 are the regeneration and survival of the intestinal, airway, and external epithelium, as well as stimulating the secretion of antimicrobial peptides such as lipocalin and β -defensin (245, 250, 252). In the context of *M. tuberculosis*, IL-22 is expressed at higher levels than IL-17 at the site of infection and within granulomas from TB patients and NHP models (253, 254). Furthermore, in NHPs infected with *M. tuberculosis*, CD4 $^{+}$ T cells expressing membrane-bound IL-22 limit *M. tuberculosis* intracellular growth in macrophages (255). IL-22 can also inhibit intracellular growth of *M. tuberculosis* in human monocyte-derived macrophages by promoting phagolysosomal fusion and induction of Calgranulin A, a heterodimer of S100A8 and S100A9 proteins (256). Moreover, human NK cells cultured with *M. tuberculosis*-infected macrophages produce IL-22 and mediate macrophage activation (257). Finally, IL-22 increases as patients receive anti-TB treatment, and this has been associated with a decrease in a regulatory B-cell population (CD19 $^{+}$ CD1d $^{+}$ CD5 $^{+}$ B cell), the *in vitro* depletion of which results in enhanced IL-22 production by T cells (258).

Animal studies using low-dose aerosol challenge indicate that, in uncomplicated infection models, IL-22-producing T cells accumulate in the lung and express IFN γ (259). In the absence of this cytokine, however, there appear to be no significant consequences (260). However, in a BCG vaccine model, NK1.1 $^{+}$ cells appear to make IL-22, which contributes to protection by regulating T_{REG} cells (261). Taken together, the current data suggest a protective role for IL-22 in TB disease progression, possibly via antimicrobial peptide production, cellular function, and promotion of epithelial repair.

Regulatory Cytokines

IL-4, IL-5, IL-13

IL-4 was first described as a product of CD4 $^{+}$ T lymphocytes that are now known as T_H2 T cells (262, 263). T_H2 responses inhibit T_H1 responses (264–266). IL-4, IL-5, and IL-13 are the signature cytokines associated with T_H2 responses; they are induced in response to helminth infections and contribute to diseases such as asthma and allergy (267–270); they mediate expulsion of multicellular parasites occupying mucosal tissues. IL-4R signaling requires heterodimerization of IL-4R α (shared with IL-13) and the common gamma chain (shared with IL-2) (271). The IL-4 receptor (IL-4R) is the primary mediator of action, and ligation of IL-4R results in signal transduction via STAT-6 and subsequent GATA-3 transcription (272–275). Both STAT-6 and GATA-3 distinguish T_H2 cells from other T_H cells, including T_H1 and T_H17 (270). IL-4 expression is, in part, regulated by IL-2 and is associated with the differentiation of T_H2 cells, which then express and maintain IL-4 and IL-5 in a positive feedback loop (276, 277). IL-4R is expressed on many cell types, including lymphocytes, epithelial cells, and fibroblasts (278, 279). IL-5 is primarily associated with recruitment of eosinophils (280) and basophils (281) and the development of antibody-producing B cells (282, 283). The IL-5 receptor comes in both low- and high-affinity forms whose activity is context dependent when expressed on the surface of lymphocytes, eosinophils, and basophils (284).

During TB, IL-4 levels are quite variable, with mRNA detectable in peripheral blood mononuclear cells (285) and IL-4-producing T cells isolatable from TB patients (286); however, peripheral blood mononuclear cells from active, *M. tuberculosis* culture-positive patients show decreased IL-4 expression (287–289). While a significant increase in IL-4 is observed in the plasma of TB patients compared with household contacts (290), IL-4 plasma levels are not different between HIV

patients and non-HIV patients with TB (290, 291), and anti-TB treatment is associated with decreased plasma IL-4 levels (290). IL-4 mRNA has been shown to be upregulated in the necrotic areas in the lungs of HIV⁺ patients with pleural TB (292) and is consistent with increased CD4⁺ cells expressing IL-4 in TB patients exhibiting cavitory disease (293). In an NHP model, IL-4-expressing T cells are increased transiently at week 6 post-*M. tuberculosis* infection; however, this population is not sustained (294). One reason for the variable association of IL-4 expression with disease profile may lie in the fact that infection with *M. tuberculosis* is associated with expression of the IL-4 antagonist IL-482, and it may be the relative levels of IL-4 and its splice variant that define the impact of the cytokine on disease outcome (295–297).

Aerosol *M. tuberculosis* infection of mice deficient in IL-4, IL-4/IL-13, IL-4R α , or STAT-6 fails to result in early differences in bacterial burden (298, 299) despite increased levels of IFN γ (110); however, during chronic infection, bacterial burden increases in IL-4R α and STAT-6 gene-deficient mice (298). IL-4 can influence *M. tuberculosis*-induced granulomas, because overexpression of this cytokine by adenovirus results in increased accumulation of monocytes and eosinophils within the granuloma (300). This demonstrates that IL-4 has the potential to deviate the *M. tuberculosis*-induced granuloma from its mononuclear to a more granulocytic characteristic (35, 301), but that its impact on disease is not strong.

Information regarding the role of IL-5 in TB is limited; however, following intranasal infection of IL-4- or IL-5-deficient mice with BCG effective clearance is observed with no differences in bacterial burden or lung pathology among IL-4- and IL-5-deficient mice (302). One area where this cytokine may play a role, however, is in HIV coinfection, because IL-5 is not observed in NHP monocytes infected with *M. tuberculosis*, but, during coinfection with simian immunodeficiency virus (SIV), IL-5 and IL-13 are increased (303). NHP models coinfecting with SIV and *M. tuberculosis* show disrupted CD4⁺ T-cell levels (303), and the mechanism of loss appears to be related to monocyte-derived IL-5 that was induced following SIV infection (303).

IL-13 was originally described as a T-cell-derived cytokine capable of inhibiting proinflammatory cytokine production (304, 305); IL-13 function has since been extended to include regulating airway restriction and antihelminth responses (306–308). Furthermore, IL-13 is not only produced by T_H2 cells, but can also be generated by invariant NK T cells (iNKT), granulocytes

(e.g., basophils, eosinophils, and mast cell), murine group 2 innate lymphoid cells (ILC2s), and human “chemoattractant receptor-homologous molecule expressed on T_H2 lymphocytes” (CRTH2)-type 2 ILCs (309–313). It is structurally similar to IL-4 and signals through cell surface receptor heterodimers composed of IL-4R α and IL-13R α 1 subunits to activate STAT6 (313).

Although not much is known regarding IL-13 in *M. tuberculosis* infection, whole blood mRNA from latently infected children shows increased IL-13 compared with uninfected controls (314), although IL-13 levels are not different between actively and latently infected children (314). IL-13 may play a modulatory role in autophagy, which is an important homeostatic mechanism for intracellular degradation and has a protective function during mycobacterial infection (315–317). Indeed, in both murine and human macrophages, IL-13 and IL-4 are independently capable of inhibiting autophagy as well as IFN γ -induced autophagy-mediated killing of *M. tuberculosis* (317). Transgenic mice overexpressing IL-13 succumb to infection with *M. tuberculosis* sooner than control mice and have more necrotic granulomas within the lung (318), and this is associated with delayed expression of IFN γ and IL-17-producing CD4⁺ T cells and increased arginase production by macrophages within the necrotic granulomas (318). While this overexpression of IL-13 represents an artificial situation, it highlights the potential for disruption of the T-cell response to have a profound effect on TB development. Studies utilizing IL-13 gene-deficient mice are necessary to truly uncover the distinct role for IL-13 in TB.

Transforming Growth Factor β

TGF β is a pleiotropic cytokine and regulates hundreds of genes (319–322) to modulate inflammation, cell proliferation, and differentiation, as well as cell migration (323–325). TGF β can be made by various cell types, including all leukocytes (e.g., lymphocytes, macrophages, monocytes, dendritic cells) (325, 326). Not surprisingly, the impact of TGF β on disease outcomes is dependent on cell type and stage of cellular differentiation, as well as the cytokine milieu (327).

TGF β levels are increased in blood monocytes isolated from TB patients compared with uninfected individuals (328), and TGF β localizes primarily to multinucleated Langhans giant cells within the granulomas of TB patients (328). TGF β is induced in human blood monocytes by *M. tuberculosis* lipoarabinomannans (329), and human monocytes treated with TGF β allow for increased intracellular *M. tuberculosis* sur-

vival, suggesting that TGF β can play a regulatory role and potentially negative role in the context of *M. tuberculosis* infection (330). T cells and monocytes from TB patients cocultured with natural inhibitors of TGF β , such as decorin and latency-associated peptide, exhibit restored T-cell proliferation and monocytic control of *M. tuberculosis*, again suggesting that TGF β is a regulatory inhibitor of both T-cell responses and antibacterial activity (331). TGF β is also able to induce IL-10 and to synergize with this cytokine to suppress IFN γ production (332). The contribution of TGF β polymorphisms to TB susceptibility is not clear (333, 334). The polymorphism +869T/C does not correlate with increased susceptibility in a Chinese population (334), whereas the same polymorphism in an Indian population reveals a significant susceptibility to *M. tuberculosis* in patients harboring this polymorphism. Our knowledge of the importance of context in the function of TGF β suggests that other genetic or indeed cultural differences may mask the contribution of this polymorphism. Taken together, the data suggest that TGF β plays an inhibitory role in host responses to *M. tuberculosis* infection.

IL-10

IL-10 was initially identified as a “cytokine synthesis inhibitory factor” produced by Th2 cells (335). However, IL-10 can be produced by other T-cell subsets including T_H1 and T_H17 cells, macrophages, some dendritic cell subsets, myeloid-derived suppressor cells, B cells, and neutrophils (336). In addition, T_{REG} cells are also a major source of IL-10 and serve to limit potentially pathogenic immune responses (336). IL-10 signals through the IL-10R, which comprises IL-10R1 and IL-10R2 (337). IL-10R1 is induced on hematopoietic cells, while IL-10R2 is expressed constitutively on most tissues and immune cells (336). In myeloid cells, IL-10 production can occur via TLR-MyD88-dependent pathways (338), as well as TLR-independent C-type lectin receptor engagement (339).

In the context of TB, meta-analyses suggest that polymorphisms in the IL-10 gene, specifically –1082G/A polymorphisms in Europeans and –592A/C polymorphisms in Asians, are significantly associated with TB risk (340). Furthermore, antigen-specific IL-10 production is found in pulmonary TB patients (341, 342) and, along with TNF α production, can be used to reliably distinguish between latent TB and pulmonary TB (342). In addition, increased accumulation of T_{REG} cells expressing IL-10 correlates with increased bacterial burden and more severe TB in an Indian population (343, 344),

and a high level of IL-10 at the end of treatment in pulmonary TB patients is associated with TB recurrence (345). Finally, infection with helminths in TB patients results in decreased antigen-specific IFN γ and IL-17 responses, which are dependent on IL-10, because IL-10 blockade significantly increases frequencies of IFN γ -producing cells (346, 347).

Following mycobacterial stimulation, dendritic cells and macrophages both produce IL-10 (338, 348). In macrophages, IL-10 can block phagosome maturation and macrophage activation in a STAT3-dependent manner, thus allowing a niche for *M. tuberculosis* to replicate and survive within the phagosome (349). In addition, IL-10 can inhibit aspects of IFN γ -mediated macrophage activation (350). In dendritic cells, mycobacterially induced IL-10 production can inhibit antigen presentation through the downregulation of MHC class II molecules, decreased IL-12 production, and inhibition of dendritic cell trafficking to the lymph nodes for T-cell priming (351, 352). In keeping with this regulatory role for IL-10, studies have shown that IL-10 gene-deficient mice infected with *M. tuberculosis* exhibit increased T_H1 and T_H17 responses, and this coincides with improved *M. tuberculosis* control during chronic infection (336) (Fig. 2). The effect is not dramatic and indeed some challenge models fail to show an impact of IL-10 gene deficiency (299, 353, 354). Interestingly, CBA mice generate significant early macrophage IL-10 production correlating with increased susceptibility to *M. tuberculosis* infection (355). This increased susceptibility also coincides with reduced expression of TNF α and IFN γ in T cells and can be reversed by blocking IL-10R signaling very early in infection (355). In CBA IL-10 gene-deficient mice, *M. tuberculosis* infection results in development of fibrotic granulomas with similarity to lesions seen in humans (356). In vaccine models, blocking IL-10 at the time of BCG vaccination (336), or using IL-10 gene-deficient mice in BCG vaccination and *M. tuberculosis* challenge experiments (244), demonstrates that IL-10 limits IFN γ and IL-17 responses during priming and decreases vaccine-induced protection against *M. tuberculosis* challenge. Computational modeling also highlights the pleiotropic role for IL-10 (357). Importantly, there are differences in the role of specific cytokines depending on the nature of the *M. tuberculosis* strains being examined. Indeed, the W-Beijing HN878 strain induces robust IL-10 production to inhibit the induction of a Th1 response (98). In the future, therefore, addressing the role for IL-10 in the context of infection, a variety of *M. tuberculosis* strains will likely provide novel insights into the function of IL-10 in TB.

THE CHEMOKINES

Limiting bacterial spread and containment of inflammation within discrete sites are hallmarks of disease control in TB and dovetail with the establishment of the TB granuloma. The TB granuloma is a multicellular immune bolus consisting of a number of cell types including macrophages, neutrophils, lymphocytes, and B cells, among others (358). Formation of the TB granuloma is governed by coordinated expression of the chemotactic cytokines referred to as chemokines. Chemokine expression establishes a chemical gradient that drives mobilization and recruitment of cells from peripheral organs to the site of infection and within the granuloma. The importance of this coordination has recently emerged to be critical in disease control with proper localization of CD4 T cells in the lung parenchyma being paramount (80–82).

Since the discovery of the first chemokine, now known as CXCL8 (i.e., IL-8), numerous chemokines have been identified, resulting in the need for a uniform nomenclature currently based on primary sequences of chemokine ligands (359–361). These chemokine ligands modulate biological processes through interactions with seven transmembrane G protein-coupled receptors (360, 362). Chemokines are divided into four families (C, CC, CXC, CX3C) based on the presence of cysteine(s) and the presence or absence of nonconserved amino acids between those cysteines (360, 361). The CC chemokine receptors (CCR) are involved in the recruitment of monocytes, neutrophils, lymphocytes, and macrophages (34). During bacterial infection, signaling via pattern recognition receptors drives the expression of CC chemokine ligands (CCL) and the development of gradients that are responded to by specific cell surface chemokine receptors (34) with functional recruitment involving monomeric or dimeric forms in the respective chemokine ligands (363). CXC chemokine ligands, denoted as CXCL, contain a nonconserved amino acid between the two cysteines, unlike CCL chemokines (360, 361). The number of chemokine ligands outnumbers the chemokine receptors, suggesting redundant or highly refined roles for the receptors as in the case for CCR4 expression mediating the migration of both T_H1 and T_H2 responses (363). This is further exemplified by CXC receptors (CXCR), which are capable of binding multiple CXCLs to promote the migration of specific cells along a chemokine gradient (360). Because development of the granuloma and communication between the cells within the granuloma are so critical for control of disease, this section will explore the roles chemokines play in modulating TB disease outcome. In accordance with the most

recent chemokine nomenclature, CCRs and CCLs as well as CXCRs and their ligands, CXCLs, are numbered (e.g., CCR2, CCL2) in a manner that avoids the previous random naming system (364) (Table 2).

CC Receptors and Their Ligands

CCR1

CCR1 is expressed by T lymphocytes, neutrophils, dendritic cells, monocytes, and macrophages (365–369). Under normal conditions, CCR1 is constitutively expressed at low levels, but it is upregulated during stimulation of neutrophils with granulocyte-macrophage colony-stimulating factor (GM-CSF) and during the differentiation of monocytes to macrophages (369, 370).

In TB patients, CD4⁺ T lymphocytes expressing CCR1 are elevated in the pleural fluid (371), and, in the blood, increased levels of CCR1⁺ T lymphocytes, natural killer (NK) cells, and neutrophils are seen (372). *In vitro*, human neutrophils express both CCR1 and produce CCL3 upon infection with *M. tuberculosis* (373). Infection with *M. tuberculosis* induces the expression of the CCR1 ligands CCL3, CCL4, and CCL5 in the lung (374, 375); however, CCR1 deficiency in mice does not impact control or disease progression following *M. tuberculosis* infection (35). Thus, it is likely that, while CCR1 correlates with cellular activation during TB, it does not appear to play a strong role in protection.

CCR2

CCR2 has a similar distribution pattern as CCR1 on hematopoietic cells (376, 377). Expression of CCR2 on monocytes and its interaction with CCL2 and CCL7 are essential for mobilization of monocytes from the bone marrow into the circulation and into sites of inflammation (378). Increased levels of CCL2 in the serum of pulmonary TB and TB patients with disseminated disease have been reported (379) and are associated with the damaging influx of inflammatory cells during TB pleurisy (371, 372). At a minimum, the presence of CCR2 and its ligands is a potential indicator of disease severity in TB patients.

Low-dose aerosol *M. tuberculosis* infection of mice elicits increased expression of CCL2, CCL7, and CCL12 in the lung during the acute stages of *M. tuberculosis* infection (380). Accordingly, mice deficient in CCR2 or CCL2 are defective in macrophage and T-lymphocyte recruitment following *M. tuberculosis* infection (380–383) (Fig. 1). Consistent with defects in recruitment of immune cells, granuloma formation in CCR2 gene-deficient mice is delayed, and is associated with perivascular cuffing and loosely formed granulomas (380).

Similarly, *M. tuberculosis*-infected CCL2 gene-deficient mice also exhibit decreased granulomatous inflammation in *M. tuberculosis*-infected lungs (382, 383), despite these innate and adaptive immune defects, CCR2 gene-deficient mice are not more susceptible to low-dose *M. tuberculosis* infection using either the aerosol or intravenous route (380). When taken in the context of the role of the type I IFNs in recruiting just enough (102) but not too many phagocytes (101), it may be that using a simple gene deficiency model to dissect the role of each chemokine or chemokine receptor will not be informative (Fig. 1).

CCR4

CCR4 is expressed on T-cell subsets including T_H17, T_H2, and T_{REG} cells that mediate allergic responses and protection against extracellular pathogens (384–386). T lymphocytes expressing CCR4 are mobilized via a chemokine gradient established by dendritic cells in the context of both allergic and parasite-induced inflammation (387–392). In the context of *M. tuberculosis* infection, T_{REG} cells are increased in the peripheral blood of TB patients and inhibit production of IFN γ by *M. tuberculosis*-specific CD4⁺ T cells (393, 394), and CCR4 antagonists promote proliferation of T cells during MVA85A vaccination (395). The ligand for CCR4, CCL17, but not CCL22 has also been shown to be elevated in the serum of active TB patients (396). These data suggest that CCR4-mediated regulation of T-cell responses to *M. tuberculosis* antigens may occur during TB and that antagonism of CCR4 maybe a target for therapeutic use or as an adjuvant during vaccination. Mechanistic analysis of CCR4 function during mycobacterially induced granuloma responses demonstrates that, despite delivery of mycobacterial and helminth antigens inducing both CCL17 and CCL22 in mouse lungs, the absence of CCR4 results in reduced granuloma formation in following mycobacterial but not helminth antigen challenge (397). Further investigation of the role of CCR4 in the development of immunity and immunopathology is likely warranted.

CCR5

CCR5 is expressed on monocytes, macrophages, T lymphocytes, neutrophils, and dendritic cells (34, 376, 377, 398) and responds to CCL3, CCL4, and CCL5 (374, 375). CCR5 is most notable in the study of HIV infection, where CCR5 facilitates viral entry into T lymphocytes and macrophages (398, 399). HIV infection dramatically compromises immunity to TB, and this is thought to be largely as a result of compromised

T-cell function; however, blocking CCL5 in cultures of *M. tuberculosis*-infected alveolar macrophages from HIV patients results in enhanced *M. tuberculosis* growth (374), suggesting that CCL5 can directly promote bacterial killing by *M. tuberculosis*-infected macrophages. Interestingly, analysis of single-nucleotide polymorphisms in CCL5 has identified two risk haplotypes, A-C-T and G-C-C, that are associated with susceptibility to TB (400). What remains unclear is whether this haplotype is associated with increased or decreased CCL5 production.

In the mouse model of *M. tuberculosis* infection, all three CCR5 ligands are upregulated in the lungs, with CCL5 being induced to the highest level (375, 401). Upon *M. tuberculosis* infection, CCL5 gene-deficient mice exhibit transient early impairment in granuloma formation and delayed T-cell recruitment (401), while CCR5 deficiency results in increased inflammation in the lung (375) (Fig. 1). The observed delayed T-cell recruitment into the lungs of CCL5-deficient mice (401) is not entirely surprising, because CCR5-CCL5 are important for dendritic cell trafficking to the lymph nodes, facilitating T-cell activation and accumulation during TB (375, 401). The difference between the outcome for the CCR5- and CCL5-deficient mice in terms of inflammatory outcome may reflect the action of other CCR5 ligands acting in the absence of CCL5. The increased accumulation of CD4⁺ and CD8⁺ T lymphocytes, myeloid cells, neutrophils, and macrophages in the lungs of chronically infected CCR5-deficient mice suggests, however, that any compensating ligand is not optimal at limiting pathologic consequences (375). Whether the models are showing true redundancy in the chemokine or our failure to appreciate the subtle nature of the function of each chemokine is still an issue for debate (402).

CCR6

CCR6 has only one known ligand, CCL20 (403), and is expressed on effector and memory T cells, myeloid dendritic cells, and B cells. CCR6 is important for the recruitment of CCR6-expressing cells to mucosal surfaces and their localization at sites of inflammation in epithelial tissues (403, 404). While CCR6 plays a vital role under both homeostatic and inflammatory conditions, it has been implicated in pathologic conditions, particularly in cancer and rheumatoid arthritis models (405, 406). Although few studies have investigated the role of CCR6 in *M. tuberculosis* infections, emerging data support a protective role for CCR6 (407). Specifically, memory CD4⁺ T cells specific for *M. tuberculosis* antigens coexpress CXCR3 and CCR6 and these

CXCR3⁺CCR6⁺ CD4⁺ T cells are associated with an IFN γ response (386). Following *ex vivo* expansion, those CD4⁺ T cells that produced IL-17A in response to *M. tuberculosis* coexpressed CXCR3 and CCR6 (408). In a detailed analysis of reactivity to mycobacterial antigens it was found that CXCR3⁺CCR6⁺ IFN γ -producing CD4⁺ T cells from latently *M. tuberculosis*-infected individuals responded to three immunodominant antigenic islands within the *M. tuberculosis* genome that were all associated with bacterial secretion systems (409) (Fig. 2). The CCR6 ligand, CCL20, appears at high levels in peripheral blood mononuclear cells, myeloid-derived macrophages, and bronchoalveolar lavage samples from TB patients (410, 411) and increased CCL20 mRNA is seen in murine and NHP lung (412, 413). It is likely therefore that CCR6 mediates the localization of memory cells to sites of *M. tuberculosis*-induced inflammation. Mouse studies have identified a critical role for CCR6 in the innate immune-mediated control following acute BCG infection (407). Innate cell types, such as CD1b-restricted iNKT cells, are impacted by the absence of CCR6, in that they fail to accumulate effectively in the lung, and this is associated with poor bacterial control and increased susceptibility to *M. tuberculosis* infection (407). Collectively, the current literature suggests that there is a correlation between CCR6 expression and bacterial control; however, mechanistic studies investigating the function of CCR6 in innate immune responses as well as its role in directing memory T-cell migration are required.

CCR7

Correct localization of dendritic cells and T and B cells is critical for the function of secondary lymphoid tissues (414). CCR7 ligation by CCL19 and CCL21 is vital for the positioning of T cells and dendritic cells in the paracortical region of these secondary lymphoid organs (SLO) (415) (Figs. 1 and 2). CCL19 and CCL21 are constitutively expressed by SLO stromal cells, while CCL21, but not CCL19, is expressed on lymphatic endothelial and high endothelial venules (415–418). CCR7 has also been implicated in thymic function and development, as well as homeostatic and inflammation-induced migration of dendritic cells to draining lymph nodes via the afferent lymphatics. In *M. tuberculosis* infections, it is thought to be necessary for dendritic cells from the lungs to relocate in the SLOs, activate naive T cells, and elicit recruitment of T cells into the site of infection for bacterial control. Early migration of mature dendritic cells to the mediastinal lymph node is supported by CCR7 (419), and CCR7-deficient mice

exhibit impaired dendritic cell migration to this node (420) (Fig. 2). Similarly, *plt* mutant mice, which lack expression of CCL19 and CCL21-Ser in SLO, also have poor dendritic cell migration (421), and proliferation of adoptively transferred *M. tuberculosis*-specific CD4⁺ T cells is delayed in mice deficient of CCR7 (420) and *plt* mice (422). Interestingly, the CCR7 chemokine ligand, CCL19, is present within granulomas containing B-cell aggregates that resemble lymphoid structures, and in the absence of CCR7 these B-cell follicles are also absent (416). While these mice display disorganized B-cell aggregation, the enhanced lymphocytic infiltrations observed in the lungs of CCR7 gene-deficient mice are sufficient to control *M. tuberculosis* to levels comparable to CCR7-sufficient mice (416). Similarly to CCR7-deficient mice, *plt* mutant mice fail to develop B-cell follicles and have disorganized granulomas (422). However, unlike CCR7-deficient mice, *plt* mutant mice also have delayed accumulation of IFN γ -producing T cells and maintain higher bacterial burden (422). Thus, it seems that CCR7 plays an important role in the proper migration of dendritic cells to the draining lymph node for priming and activation of T cells, as well as the migration of CD4⁺ T cells into lymphoid follicles following *M. tuberculosis* infection.

CXC Receptors and Their Ligands

CXCR1 and CXCR2

CXCR1 and CXCR2 share the binding partners, CXCL6 and CXCL8, while CXCR2 can exclusively bind to CXCL1-3, CXCL5, and CXCL7 (423). All these CXCLs contain the ELR motif, corresponding to a Glu-Leu-Arg tripeptide motif at the amino terminus region, adjacent to their CXC sequence. The functional role of this ELR motif is to confer angiogenic activity to the ELR-containing chemokine (424) and this motif is important for ligand-receptor binding interactions on neutrophils (425, 426). Ligand binding to CXCR1 and CXCR2 causes degranulation, intracellular calcium mobilization, and phosphorylation of MAPK (427).

Although most notably expressed on neutrophils in TB patients, both CXCR1 and CXCR2 can also be expressed on NK cells, T cells, and monocytes (423, 428). Comparison of CXCR1 expression on peripheral blood from TB patients shows that individuals with pulmonary TB have increased CXCR1, whereas latent TB patients have increased CXCR2 in whole blood (429). Moreover, increased CXCR1 correlates with impaired oxidative function in leukocytes, suggesting a possible regulatory role for CXCR1 on oxidative stress

(429). CXCR2-deficient mice infected intraperitoneally with *Mycobacterium avium* have decreased neutrophil accumulation and increased bacterial burden (430). However, following pulmonary infection with *M. avium*, no difference in cellular infiltrate or bacterial burden is observed, which highlights the importance of route and dose on identifying the function of the highly redundant chemokines.

CXCL8 has been the most studied CXCR1/2 ligand in the context of TB and this important neutrophil chemoattractant is expressed by multiple cell types, including alveolar epithelial cells, monocytes, macrophages, and fibroblasts upon *M. tuberculosis* infection *in vitro* (431–434) (Fig. 1). Following *in vivo* *M. tuberculosis* infection, pulmonary granulomas containing fibroblasts are also capable of secreting CXCL8 (431), and TB sputum samples contain elevated CXCL8 levels (435). CXCL8 is present at high levels at positive tuberculin skin reaction sites and is associated with high levels of neutrophils at this site (436). Furthermore, neutrophils isolated from pulmonary TB patients have increased expression of CXCL8, which is further increased following *ex vivo* infection with H37Rv but not the clinical strains, S7 and S10, suggesting strain-specific regulation of CXCL8 production in neutrophils (373). Whether CXCL8 is associated with a protective or pathologic response remains controversial (437, 438). Serum CXCL8 levels from pulmonary TB patients following treatment with antibiotics decreased, suggesting that CXCL8 could be a marker for treatment efficacy (439). Whether disease improvement is directly correlated to reduced CXCL8 levels or simply a reflection of reduced neutrophil accumulation is unclear (Fig. 1).

CXCL5, which is also a CXCR2 ligand, plays an important role in host responses against *M. tuberculosis* (440), because both CXCR2 and CXCL5 gene-deficient mice display lower bacterial burden following *M. tuberculosis* infection, which correlates with reduced neutrophil accumulation to the lung (440). In this model, alveolar epithelial secretion of CXCL5, mediating the recruitment of neutrophils, is dependent on TLR2 engagement with *M. tuberculosis* and blocking of neutrophil recruitment improves outcome in the lung (440) (Fig. 1). It appears that CXCR2 plays an important role in the pathologic granulomatous response during TB, and this could be an important target for host-directed therapy.

CXCR3

CXCR3 binds to its chemokine ligand partners, CXCL9, CXCL10, and CXCL11, also known as MIG, IP-10, and

I-TAC, respectively (428, 441). It is expressed primarily by activated CD4⁺ and CD8⁺ T cells, and is detected on B cells and innate lymphocytes such as NK cells and NKT cells (428). CXCR3 expression is associated with supporting localization of cells to the site of infection (442, 443). Most notably, CXCR3 expression on effector T cells plays an important role in the migration of T cells both *in vitro* and *in vivo* (33, 441, 444–446) and the transcription factor T-bet transactivates CXCR3 on T cells to promote this migration (441) (Fig. 2). It is characterized as an inflammatory chemokine receptor on T cells and is significantly enhanced on T cells from inflamed tissues in human inflammatory reactions and has been implicated in various human and murine disease models, including idiopathic pulmonary fibrosis and asthma (441, 443, 447).

In response to *M. tuberculosis* infection, CXCR3-expressing T cells are found in the caseous, necrotic granulomas, and bronchoalveolar lavage in the NHP model, as well as in the lungs of infected mice (428). The presence of these cells correlates with elevated expression of CXCL9, CXCL10, and CXCL11 localized within granulomas (428), but CXCR3-deficient mice do not exhibit differences in bacterial burden following low-dose aerosol infection with *M. tuberculosis* (448, 449). Despite the absence of a bacterial phenotype, CXCR3-deficient mice do develop fewer granulomas of decreased size (448, 449), suggesting that CXCR3 is important for granuloma formation. The coexpression of CXCR3 with CCR6 on memory T cells in latently infected humans supports the importance of this receptor on the migration and function of human T cells during TB, but the precise role is not clear (Fig. 2). Human data support a protective role for CXCR3-binding chemokines because CXCL9 levels correlate with disease severity (379, 450), although the role of CXCL10 is unclear. CXCL10 has been proposed as a biomarker for improvement, because reduction of this chemokine in the serum relative to levels at recruitment is observed following TB treatment, and nonresponders do not show the same decrease (439, 451). Unfortunately, CXCL10 levels cannot distinguish between active and latent TB in children (452).

The mechanistic basis for CXCL10 activity in TB is not fully defined. In some cases, active TB can result in destruction of the lung parenchyma, leading to cavities. In AIDS-associated TB, increased CXCL10 is associated with noncavitary TB, whereas cavitary TB is associated with increased GM-CSF (114, 453). CXCL10 is important for modulating CXCL9 and CCL2, which promote disease, while CXCL10 is significantly increased

in patients with active pulmonary tuberculosis (100), and there may be a genetic association between a single-nucleotide polymorphism within the CXCL-10 promoter (135G/A) and TB susceptibility (454).

Additional studies are needed to confirm whether CXCR3 and its ligands are protective or harmful to disease outcome. It is also unclear how CXCL9-11 is induced and whether its induction is a direct result of *M. tuberculosis* infection or whether upregulated expression results from expression of cytokines capable of inducing CXCL9-11 expression (455–458). Still, animal models support CXCR3 and expression of its ligands as important regulators for granuloma formation (449, 459) (Fig. 2).

CXCR5

The B-cell chemoattractant, CXCL13, is the only known ligand for CXCR5. It is preferentially produced in B-cell follicles and, through its binding with CXCR5, is important for the development of lymphoid follicles. In lymphoid organs, the main source for CXCL13 is the follicular dendritic cell (460). However, IL-17-producing T cells have also been shown to express CXCL13 in a *Candida albicans* infection model as well as in synovial fluid from patients with rheumatoid arthritis (461). CXCL13 expression recruits CXCR5-expressing B cells and coordinates the correct position of these cells within SLO (462). A similar role has also been highlighted during *M. tuberculosis* infections. *M. tuberculosis* granulomas contain B cells, follicular dendritic cells, and high endothelial venules and thus provide important points of entry for trafficking lymphocytes (4, 428). CXCL13 is also elevated in *M. tuberculosis*-infected mice and is important for the localization of CXCR5⁺ T cells to the lung parenchyma as well as the activation of phagocytes and control of bacterial growth (422, 459) (Fig. 2). With the use of NHP and mouse models of *M. tuberculosis*, CXCR5⁺ T cells have been shown to traffic toward ectopic lymphoid follicles (bronchus-associated lymphoid tissues [iBALT]), adjacent to granulomas where CXCL13 is localized. In the absence of CXCR5, mice fail to develop iBALT and are more susceptible *M. tuberculosis* (459) with the impaired response being rescued through the adoptive transfer of CXCR5-sufficient T cells, suggesting that CXCR5 expression on T cells is important for both protection and the development of B-cell follicles. Furthermore, CXCR5 is required for the maintenance of *M. tuberculosis*-specific CD4⁺ T cells during chronic infection (81). B cells from *M. tuberculosis*-infected murine lungs are also able to migrate along a

CXCL13 chemotactic gradient *in vitro* via their expression of CXCR5 (463). IL-23- and IL-17R-dependent induction of CXCL13 within the *M. tuberculosis*-infected lungs appears to be important for control of this infection, and CXCL-13- and CXCR5-deficient mice are the only chemokine-deficient mice that show increased susceptibility upon *M. tuberculosis* infection, suggesting that this cytokine/chemokine axis is nonredundant in *M. tuberculosis* infection (Fig. 2).

CONCLUSION

Chemokines and cytokines are critical for initiating and coordinating the organized and sequential recruitment and activation of cells into *M. tuberculosis*-infected lungs (Figs. 1 and 2). Correct mononuclear cellular recruitment and localization are essential to ensure control of bacterial growth without the development of diffuse and damaging granulocytic inflammation. An important block to our understanding of TB pathogenesis lies in dissecting the critical aspects of the cytokine/chemokine interplay in light of the conditional role these molecules play throughout infection and disease development (Tables 1 and 2). Much of the data highlighted in this review appear at first glance to be contradictory, but it is the balance between the cytokines and chemokines that is critical, and the “goldilocks” (not too much and not too little) phenomenon is paramount in any discussion of the role of these molecules in TB. Determination of how the key chemokines/cytokines and their receptors are balanced and how the loss of that balance can promote disease is vital to understanding TB pathogenesis and to identifying novel therapies for effective eradication of this disease.

REFERENCES

1. Dinarello CA. 2007. Historical insights into cytokines. *Eur J Immunol* 37(Suppl 1):S34–S45 <http://dx.doi.org/10.1002/eji.200737772>.
2. Cooper AM. 2009. Cell-mediated immune responses in tuberculosis. *Annu Rev Immunol* 27:393–422 <http://dx.doi.org/10.1146/annurev.immunol.021908.132703>.
3. Flynn JL, Chan J. 2003. Immune evasion by *Mycobacterium tuberculosis*: living with the enemy. *Curr Opin Immunol* 15:450–455 [http://dx.doi.org/10.1016/S0952-7915\(03\)00075-X](http://dx.doi.org/10.1016/S0952-7915(03)00075-X).
4. Flynn JL, Chan J. 2001. Immunology of tuberculosis. *Annu Rev Immunol* 19:93–129 <http://dx.doi.org/10.1146/annurev.immunol.19.1.93>.
5. Brites D, Gagneux S. 2015. Co-evolution of *Mycobacterium tuberculosis* and *Homo sapiens*. *Immunol Rev* 264:6–24 <http://dx.doi.org/10.1111/imr.12264>.
6. Comas I, Coscolla M, Luo T, Borrell S, Holt KE, Kato-Maeda M, Parkhill J, Malla B, Berg S, Thwaites G, Yeboah-Manu D, Bothamley G, Mei J, Wei L, Bentley S, Harris SR, Niemann S, Diel R, Aseffa A, Gao Q, Young D, Gagneux S. 2013. Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nat Genet* 45:1176–1182 <http://dx.doi.org/10.1038/ng.2744>.

7. Orme IM, Robinson RT, Cooper AM. 2015. The balance between protective and pathogenic immune responses in the TB-infected lung. *Nat Immunol* 16:57–63 <http://dx.doi.org/10.1038/ni.3048>.
8. Dye C, Glaziou P, Floyd K, Raviglione M. 2013. Prospects for tuberculosis elimination. *Annu Rev Public Health* 34:271–286 <http://dx.doi.org/10.1146/annurev-publhealth-031912-114431>.
9. Robinson RT, Orme IM, Cooper AM. 2015. The onset of adaptive immunity in the mouse model of tuberculosis and the factors that compromise its expression. *Immunol Rev* 264:46–59 <http://dx.doi.org/10.1111/imr.12259>.
10. Wajant H, Pfizenmaier K, Scheurich P. 2003. Tumor necrosis factor signaling. *Cell Death Differ* 10:45–65 <http://dx.doi.org/10.1038/sj.cdd.4401189>.
11. Black RA, Rauch CT, Kozlosky CJ, Peschon JJ, Slack JL, Wolfson MF, Castner BJ, Stocking KL, Reddy P, Srinivasan S, Nelson N, Boiani N, Schooley KA, Gerhart M, Davis R, Fitzner JN, Johnson RS, Paxton RJ, March CJ, Cerretti DP. 1997. A metalloproteinase disintegrin that releases tumour-necrosis factor- α from cells. *Nature* 385:729–733 <http://dx.doi.org/10.1038/385729a0>.
12. Bazan JF. 1993. Emerging families of cytokines and receptors. *Curr Biol* 3:603–606 [http://dx.doi.org/10.1016/0960-9822\(93\)90009-D](http://dx.doi.org/10.1016/0960-9822(93)90009-D).
13. Devin A, Lin Y, Yamaoka S, Li Z, Karin M, Liu Zg. 2001. The α and β subunits of I κ B kinase (IKK) mediate TRAF2-dependent IKK recruitment to tumor necrosis factor (TNF) receptor 1 in response to TNF. *Mol Cell Biol* 21:3986–3994 <http://dx.doi.org/10.1128/MCB.21.12.3986-3994.2001>.
14. Hsu H, Huang J, Shu HB, Baichwal V, Goeddel DV. 1996. TNF-dependent recruitment of the protein kinase RIP to the TNF receptor-1 signaling complex. *Immunity* 4:387–396 [http://dx.doi.org/10.1016/S1074-7613\(00\)80252-6](http://dx.doi.org/10.1016/S1074-7613(00)80252-6).
15. Hsu H, Xiong J, Goeddel DV. 1995. The TNF receptor 1-associated protein TRADD signals cell death and NF- κ B activation. *Cell* 81:495–504 [http://dx.doi.org/10.1016/0092-8674\(95\)90070-5](http://dx.doi.org/10.1016/0092-8674(95)90070-5).
16. Jiang Y, Woronicz JD, Liu W, Goeddel DV. 1999. Prevention of constitutive TNF receptor 1 signaling by silencer of death domains. *Science* 283:543–546 <http://dx.doi.org/10.1126/science.283.5401.543>.
17. Naismith JH, Sprang SR. 1998. Modularity in the TNF-receptor family. *Trends Biochem Sci* 23:74–79 [http://dx.doi.org/10.1016/S0968-0004\(97\)01164-X](http://dx.doi.org/10.1016/S0968-0004(97)01164-X).
18. Banner DW, D'Arcy A, Janes W, Gentz R, Schoenfeld HJ, Broger C, Loetscher H, Lesslauer W. 1993. Crystal structure of the soluble human 55 kD TNF receptor-human TNF β complex: implications for TNF receptor activation. *Cell* 73:431–445 [http://dx.doi.org/10.1016/0092-8674\(93\)90132-A](http://dx.doi.org/10.1016/0092-8674(93)90132-A).
19. Chan FK, Chun HJ, Zheng L, Siegel RM, Bui KL, Lenardo MJ. 2000. A domain in TNF receptors that mediates ligand-independent receptor assembly and signaling. *Science* 288:2351–2354 <http://dx.doi.org/10.1126/science.288.5475.2351>.
20. Faustman DL, Davis M. 2013. TNF Receptor 2 and Disease: Autoimmunity and Regenerative Medicine. *Front Immunol* 4:478 <http://dx.doi.org/10.3389/fimmu.2013.00478>.
21. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. 1975. An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* 72:3666–3670 <http://dx.doi.org/10.1073/pnas.72.9.3666>.
22. Keane J, Balcewicz-Sablinska MK, Remold HG, Chupp GL, Meek BB, Fenton MJ, Kornfeld H. 1997. Infection by *Mycobacterium tuberculosis* promotes human alveolar macrophage apoptosis. *Infect Immun* 65:298–304.
23. Keane J, Remold HG, Kornfeld H. 2000. Virulent *Mycobacterium tuberculosis* strains evade apoptosis of infected alveolar macrophages. *J Immunol* 164:2016–2020 <http://dx.doi.org/10.4049/jimmunol.164.4.2016>.
24. Balcewicz-Sablinska MK, Keane J, Kornfeld H, Remold HG. 1998. Pathogenic *Mycobacterium tuberculosis* evades apoptosis of host macrophages by release of TNF-R2, resulting in inactivation of TNF- α . *J Immunol* 161:2636–2641.
25. Serbina NV, Flynn JL. 1999. Early emergence of CD8(+) T cells primed for production of type 1 cytokines in the lungs of *Mycobacterium tuberculosis*-infected mice. *Infect Immun* 67:3980–3988.
26. Flynn JL, Goldstein MM, Chan J, Triebold KJ, Pfeffer K, Lowenstein CJ, Schreiber R, Mak TW, Bloom BR. 1995. Tumor necrosis factor- α is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity* 2:561–572 [http://dx.doi.org/10.1016/1074-7613\(95\)90001-2](http://dx.doi.org/10.1016/1074-7613(95)90001-2).
27. Algood HM, Lin PL, Flynn JL. 2005. Tumor necrosis factor and chemokine interactions in the formation and maintenance of granulomas in tuberculosis. *Clin Infect Dis* 41(Suppl 3):S189–S193 <http://dx.doi.org/10.1086/429994>.
28. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. 2002. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 168:4620–4627 <http://dx.doi.org/10.4049/jimmunol.168.9.4620>.
29. Bean AG, Roach DR, Briscoe H, France MP, Korner H, Sedgwick JD, Britton WJ. 1999. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol *Mycobacterium tuberculosis* infection, which is not compensated for by lymphotoxin. *J Immunol* 162:3504–3511.
30. Lin PL, Plessner HL, Voitenok NN, Flynn JL. 2007. Tumor necrosis factor and tuberculosis. *J Invest Dermatol Symp Proc* 12:22–25 <http://dx.doi.org/10.1038/sj.jidsymp.5650027>.
31. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. 1989. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell* 56:731–740 [http://dx.doi.org/10.1016/0092-8674\(89\)90676-4](http://dx.doi.org/10.1016/0092-8674(89)90676-4).
32. Farber JM. 1997. Mig and IP-10: CXC chemokines that target lymphocytes. *J Leukoc Biol* 61:246–257.
33. Cole KE, Strick CA, Paradis TJ, Ogborne KT, Loetscher M, Gladue RP, Lin W, Boyd JG, Moser B, Wood DE, Sahagan BG, Neote K. 1998. Interferon-inducible T cell alpha chemoattractant (I-TAC): a novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. *J Exp Med* 187:2009–2021 <http://dx.doi.org/10.1084/jem.187.12.2009>.
34. Griffith JW, Sokol CL, Luster AD. 2014. Chemokines and chemokine receptors: positioning cells for host defense and immunity. *Annu Rev Immunol* 32:659–702 <http://dx.doi.org/10.1146/annurev-immunol-032713-120145>.
35. Saunders BM, Britton WJ. 2007. Life and death in the granuloma: immunopathology of tuberculosis. *Immunol Cell Biol* 85:103–111 <http://dx.doi.org/10.1038/sj.icb.7100027>.
36. Lynch K, Farrell M. 2010. Cerebral tuberculoma in a patient receiving anti-TNF α (adalimumab) treatment. *Clin Rheumatol* 29:1201–1204 <http://dx.doi.org/10.1007/s10067-010-1466-7>.
37. Seong SS, Choi CB, Woo JH, Bae KW, Joong CL, Uhm WS, Kim TH, Jun JB, Yoo DH, Lee JT, Bae SC. 2007. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. *J Rheumatol* 34:706–711.
38. Be NA, Kim KS, Bishai WR, Jain SK. 2009. Pathogenesis of central nervous system tuberculosis. *Curr Mol Med* 9:94–99 <http://dx.doi.org/10.2174/156652409787581655>.
39. Leonard JM, Des Prez RM. 1990. Tuberculous meningitis. *Infect Dis Clin North Am* 4:769–787.
40. Tsenova L, Bergtold A, Freedman VH, Young RA, Kaplan G. 1999. Tumor necrosis factor α is a determinant of pathogenesis and disease progression in mycobacterial infection in the central nervous system. *Proc Natl Acad Sci USA* 96:5657–5662 <http://dx.doi.org/10.1073/pnas.96.10.5657>.

41. Francisco NM, Hsu NJ, Keeton R, Randall P, Sebesho B, Allie N, Govender D, Quesniaux V, Ryffel B, Kellaway L, Jacobs M. 2015. TNF-dependent regulation and activation of innate immune cells are essential for host protection against cerebral tuberculosis. *J Neuroinflammation* 12:125 <http://dx.doi.org/10.1186/s12974-015-0345-1>.
42. Mohan VP, Scanga CA, Yu K, Scott HM, Tanaka KE, Tsang E, Tsai MM, Flynn JL, Chan J. 2001. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. *Infect Immun* 69:1847–1855 <http://dx.doi.org/10.1128/IAI.69.3.1847-1855.2001>.
43. Feldmann M. 2002. Development of anti-TNF therapy for rheumatoid arthritis. *Nat Rev Immunol* 2:364–371 <http://dx.doi.org/10.1038/nri802>.
44. Peyrin-Biroulet L. 2010. Anti-TNF therapy in inflammatory bowel diseases: a huge review. *Minerva Gastroenterol Dietol* 56:233–243.
45. Shaikha SA, Mansour K, Riad H. 2012. Reactivation of tuberculosis in three cases of psoriasis after initiation of anti-TNF therapy. *Case Rep Dermatol* 4:41–46 <http://dx.doi.org/10.1159/000337145>.
46. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Swieterman WD, Siegel JN, Braun MM. 2001. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 345:1098–1104 <http://dx.doi.org/10.1056/NEJMoa011110>.
47. Keane J. 2005. TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. *Rheumatology (Oxford)* 44:714–720 <http://dx.doi.org/10.1093/rheumatology/keh567>.
48. Raval A, Akhavan-Toyserkani G, Brinker A, Avigan M. 2007. Brief communication: characteristics of spontaneous cases of tuberculosis associated with infliximab. *Ann Intern Med* 147:699–702 <http://dx.doi.org/10.7326/0003-4819-147-10-200711200-00006>.
49. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, BIOBADASER Group. 2003. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 48:2122–2127 <http://dx.doi.org/10.1002/art.11137>.
50. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, British Society for Rheumatology Biologics Register. 2006. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 54:2368–2376 <http://dx.doi.org/10.1002/art.21978>.
51. Askling J, Foröd CM, Brandt L, Baecklund E, Bertiésson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Romanus V, Klareskog L, Feltelius N. 2005. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum* 52:1986–1992 <http://dx.doi.org/10.1002/art.21137>.
52. Tubach F, Salmon D, Ravaut P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lortholary O, Mariette X; Research Axed on Tolerance of Biotherapies Group. 2009. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 60:1884–1894. (Erratum 60:2540.) <http://dx.doi.org/10.1002/art.24632>.
53. Fallahi-Sichani M, Flynn JL, Linderman JJ, Kirschner DE. 2012. Differential risk of tuberculosis reactivation among anti-TNF therapies is due to drug binding kinetics and permeability. *J Immunol* 188:3169–3178 <http://dx.doi.org/10.4049/jimmunol.1103298>.
54. Bruns H, Meinken C, Schauenberg P, Härter G, Kern P, Modlin RL, Antoni C, Stenger S. 2009. Anti-TNF immunotherapy reduces CD8+ T cell-mediated antimicrobial activity against *Mycobacterium tuberculosis* in humans. *J Clin Invest* 119:1167–1177 <http://dx.doi.org/10.1172/JCI38482>.
55. Lin PL, Myers A, Smith LK, Bigbee C, Bigbee M, Fuhrman C, Grieser H, Chiosea I, Voitenek NN, Capuano SV, Klein E, Flynn JL. 2010. Tumor necrosis factor neutralization results in disseminated disease in acute and latent *Mycobacterium tuberculosis* infection with normal granuloma structure in a cynomolgus macaque model. *Arthritis Rheum* 62:340–350.
56. Clay H, Volkman HE, Ramakrishnan L. 2008. Tumor necrosis factor signaling mediates resistance to mycobacteria by inhibiting bacterial growth and macrophage death. *Immunity* 29:283–294 <http://dx.doi.org/10.1016/j.immuni.2008.06.011>.
57. Harari A, Rozot V, Bellutti Enders F, Perreau M, Stalder JM, Nicod LP, Cavassini M, Calandra T, Blanchet CL, Jaton K, Faouzi M, Day CL, Hanekom WA, Bart PA, Pantaleo G. 2011. Dominant TNF- α *Mycobacterium tuberculosis*-specific CD4+ T cell responses discriminate between latent infection and active disease. *Nat Med* 17:372–376 <http://dx.doi.org/10.1038/nm.2299>.
58. Schroder K, Hertzog PJ, Ravasi T, Hume DA. 2004. Interferon-gamma: an overview of signals, mechanisms and functions. *J Leukoc Biol* 75:163–189 <http://dx.doi.org/10.1189/jlb.0603252>.
59. Greenlund AC, Farrar MA, Viviano BL, Schreiber RD. 1994. Ligand-induced IFN gamma receptor tyrosine phosphorylation couples the receptor to its signal transduction system (p91). *EMBO J* 13:1591–1600.
60. Kovarik P, Stoiber D, Novy M, Decker T. 1998. Stat1 combines signals derived from IFN-gamma and LPS receptors during macrophage activation. *EMBO J* 17:3660–3668 <http://dx.doi.org/10.1093/emboj/17.13.3660>.
61. Frucht DM, Fukao T, Bogdan C, Schindler H, O'Shea JJ, Koyasu S. 2001. IFN-gamma production by antigen-presenting cells: mechanisms emerge. *Trends Immunol* 22:556–560 [http://dx.doi.org/10.1016/S1471-4906\(01\)02005-1](http://dx.doi.org/10.1016/S1471-4906(01)02005-1).
62. Reed JM, Branigan PJ, Bamezai A. 2008. Interferon gamma enhances clonal expansion and survival of CD4+ T cells. *J Interferon Cytokine Res* 28:611–622 <http://dx.doi.org/10.1089/jir.2007.0145>.
63. Munder M, Mallo M, Eichmann K, Modolell M. 1998. Murine macrophages secrete interferon gamma upon combined stimulation with interleukin (IL)-12 and IL-18: a novel pathway of autocrine macrophage activation. *J Exp Med* 187:2103–2108 <http://dx.doi.org/10.1084/jem.187.12.2103>.
64. Otani T, Nakamura S, Toki M, Motoda R, Kurimoto M, Orita K. 1999. Identification of IFN-gamma-producing cells in IL-12/IL-18-treated mice. *Cell Immunol* 198:111–119 <http://dx.doi.org/10.1006/cimm.1999.1589>.
65. Zhang SY, Boisson-Dupuis S, Chappier A, Yang K, Bustamante J, Puel A, Picard C, Abel L, Jouanguy E, Casanova JL. 2008. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense. *Immunol Rev* 226:29–40 <http://dx.doi.org/10.1111/j.1600-065X.2008.00698.x>.
66. Filipe-Santos O, Bustamante J, Chappier A, Vogt G, de Beaucoudrey L, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL. 2006. Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. *Semin Immunol* 18:347–361 <http://dx.doi.org/10.1016/j.smim.2006.07.010>.
67. Sologuren I, Boisson-Dupuis S, Pestano J, Vincent QB, Fernández-Pérez L, Chappier A, Cárdenas M, Feinberg J, García-Laorden MI, Picard C, Santiago E, Kong X, Jannié L, Colino E, Herrera-Ramos E, Francés A, Navarrete C, Blanche S, Faria E, Remiszewski P, Cordeiro A, Freeman A, Holland S, Abarca K, Valerón-Lemaun M, Gonçalves-Marques J, Silveira L, García-Castellano JM, Caminero J, Pérez-Arellano JL, Bustamante J, Abel L, Casanova J-L, Rodríguez-Gallego C. 2011. Partial recessive IFN- γ R1 deficiency: genetic, immunological and clinical features of 14 patients from 11 kindreds. *Hum Mol Genet* 20:1509–1523 <http://dx.doi.org/10.1093/hmg/ddr029>.
68. Vogt G, Chappier A, Yang K, Chuzhanova N, Feinberg J, Fieschi C, Boisson-Dupuis S, Alcais A, Filipe-Santos O, Bustamante J, de Beaucoudrey L, Al-Mohsen I, Al-Hajjar S, Al-Ghoniaim A, Adimi P, Mirsaeidi M,

- Khalilzadeh S, Rosenzweig S, de la Calle Martin O, Bauer TR, Puck JM, Ochs HD, Furthner D, Engelhorn C, Belohradsky B, Mansouri D, Holland SM, Schreiber RD, Abel L, Cooper DN, Soudais C, Casanova JL. 2005. Gains of glycosylation comprise an unexpectedly large group of pathogenic mutations. *Nat Genet* 37:692–700 <http://dx.doi.org/10.1038/ng1581>.
69. Dorman SE, Holland SM. 1998. Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. *J Clin Invest* 101:2364–2369 <http://dx.doi.org/10.1172/JCI2901>.
70. Cooper AM, Dalton DK, Stewart TA, Griffin JP, Russell DG, Orme IM. 1993. Disseminated tuberculosis in interferon gamma gene-disrupted mice. *J Exp Med* 178:2243–2247 <http://dx.doi.org/10.1084/jem.178.6.2243>.
71. Flynn JL, Chan J, Triebold KJ, Dalton DK, Stewart TA, Bloom BR. 1993. An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. *J Exp Med* 178:2249–2254 <http://dx.doi.org/10.1084/jem.178.6.2249>.
72. Dalton DK, Pitts-Meek S, Keshav S, Figari IS, Bradley A, Stewart TA. 1993. Multiple defects of immune cell function in mice with disrupted interferon-gamma genes. *Science* 259:1739–1742 <http://dx.doi.org/10.1126/science.8456300>.
73. Russell DG. 2001. *Mycobacterium tuberculosis*: here today, and here tomorrow. *Nat Rev Mol Cell Biol* 2:569–586 <http://dx.doi.org/10.1038/35085034>.
74. Mogues T, Goodrich ME, Ryan L, LaCourse R, North RJ. 2001. The relative importance of T cell subsets in immunity and immunopathology of airborne *Mycobacterium tuberculosis* infection in mice. *J Exp Med* 193:271–280 <http://dx.doi.org/10.1084/jem.193.3.271>.
75. Green AM, Difazio R, Flynn JL. 2013. IFN- γ from CD4 T cells is essential for host survival and enhances CD8 T cell function during *Mycobacterium tuberculosis* infection. *J Immunol* 190:270–277 <http://dx.doi.org/10.4049/jimmunol.1200061>.
76. Gallegos AM, van Heijst JW, Samstein M, Su X, Pamer EG, Glickman MS. 2011. A gamma interferon independent mechanism of CD4 T cell mediated control of *M. tuberculosis* infection in vivo. *PLoS Pathog* 7:e1002052 <http://dx.doi.org/10.1371/journal.ppat.1002052>.
77. Caruso AM, Serbina N, Klein E, Triebold K, Bloom BR, Flynn JL. 1999. Mice deficient in CD4 T cells have only transiently diminished levels of IFN-gamma, yet succumb to tuberculosis. *J Immunol* 162:5407–5416.
78. Saunders BM, Frank AA, Orme IM, Cooper AM. 2002. CD4 is required for the development of a protective granulomatous response to pulmonary tuberculosis. *Cell Immunol* 216:65–72 [http://dx.doi.org/10.1016/S0008-8749\(02\)00510-5](http://dx.doi.org/10.1016/S0008-8749(02)00510-5).
79. Serbina NV, Lazarevic V, Flynn JL. 2001. CD4(+) T cells are required for the development of cytotoxic CD8(+) T cells during *Mycobacterium tuberculosis* infection. *J Immunol* 167:6991–7000 <http://dx.doi.org/10.4049/jimmunol.167.12.6991>.
80. Sakai S, Kauffman KD, Schenkel JM, McBerry CC, Mayer-Barber KD, Masopust D, Barber DL. 2014. Cutting edge: control of *Mycobacterium tuberculosis* infection by a subset of lung parenchyma-homing CD4 T cells. *J Immunol* 192:2965–2969 <http://dx.doi.org/10.4049/jimmunol.1400019>.
81. Moguche AO, Shafiani S, Clemons C, Larson RP, Dinh C, Higdon LE, Cambier CJ, Sissons JR, Gallegos AM, Fink PJ, Urdahl KB. 2015. ICOS and Bcl6-dependent pathways maintain a CD4 T cell population with memory-like properties during tuberculosis. *J Exp Med* 212:715–728 <http://dx.doi.org/10.1084/jem.20141518>.
82. Torrado E, Fountain JJ, Liao M, Tighe M, Reiley WW, Lai RP, Meintjes G, Pearl JE, Chen X, Zak DE, Thompson EG, Aderem A, Ghilardi N, Solache A, McKinstry KK, Strutt TM, Wilkinson RJ, Swain SL, Cooper AM. 2015. Interleukin 27R regulates CD4+ T cell phenotype and impacts protective immunity during *Mycobacterium tuberculosis* infection. *J Exp Med* 212:1449–1463 <http://dx.doi.org/10.1084/jem.20141520>.
83. Keller C, Hoffmann R, Lang R, Brandau S, Hermann C, Ehlers S. 2006. Genetically determined susceptibility to tuberculosis in mice causally involves accelerated and enhanced recruitment of granulocytes. *Infect Immun* 74:4295–4309 <http://dx.doi.org/10.1128/IAI.00057-06>.
84. Eruslanov EB, Lyadova IV, Kondratieva TK, Majorov KB, Scheglov IV, Orlova MO, Apt AS. 2005. Neutrophil responses to *Mycobacterium tuberculosis* infection in genetically susceptible and resistant mice. *Infect Immun* 73:1744–1753 <http://dx.doi.org/10.1128/IAI.73.3.1744-1753.2005>.
85. Majorov KB, Eruslanov EB, Rubakova EI, Kondratieva TK, Apt AS. 2005. Analysis of cellular phenotypes that mediate genetic resistance to tuberculosis using a radiation bone marrow chimera approach. *Infect Immun* 73:6174–6178 <http://dx.doi.org/10.1128/IAI.73.9.6174-6178.2005>.
86. Mitsos LM, Cardon LR, Fortin A, Ryan L, LaCourse R, North RJ, Gros P. 2000. Genetic control of susceptibility to infection with *Mycobacterium tuberculosis* in mice. *Genes Immun* 1:467–477 <http://dx.doi.org/10.1038/sj.gene.6363712>.
87. Nandi B, Behar SM. 2011. Regulation of neutrophils by interferon- γ limits lung inflammation during tuberculosis infection. *J Exp Med* 208:2251–2262 <http://dx.doi.org/10.1084/jem.20110919>.
88. Desvignes L, Ernst JD. 2009. Interferon- γ -responsive nonhematopoietic cells regulate the immune response to *Mycobacterium tuberculosis*. *Immunity* 31:974–985 <http://dx.doi.org/10.1016/j.immuni.2009.10.007>.
89. Stefan DC, Dippenaar A, Detjen AK, Schaaf HS, Marais BJ, Kriel B, Loebenberg L, Walz G, Hesselink AC. 2010. Interferon-gamma release assays for the detection of *Mycobacterium tuberculosis* infection in children with cancer. *Int J Tuberc Lung Dis* 14:689–694.
90. Abu-Taleb AM, El-Sokkary RH, El Tarhouny SA. 2011. Interferon-gamma release assay for detection of latent tuberculosis infection in casual and close contacts of tuberculosis cases. *East Mediterr Health J* 17:749–753.
91. Ferrara G, Losi M, D'Amico R, Cagarelli R, Pezzi AM, Meacci M, Meccugni B, Marchetti Dori I, Rumpianesi F, Roversi P, Casali L, Fabbri LM, Richeldi L. 2009. Interferon-gamma-release assays detect recent tuberculosis re-infection in elderly contacts. *Int J Immunopathol Pharmacol* 22:669–677.
92. Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. 2011. Negative and positive predictive value of a whole-blood interferon- γ release assay for developing active tuberculosis: an update. *Am J Respir Crit Care Med* 183:88–95 <http://dx.doi.org/10.1164/rccm.201006-0974OC>.
93. Isaacs A, Lindenmann J. 1957. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci* 147:258–267 <http://dx.doi.org/10.1098/rspb.1957.0048>.
94. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. 2015. Type I interferons in infectious disease. *Nat Rev Immunol* 15:87–103 <http://dx.doi.org/10.1038/nri3787>.
95. Honda K, Takaoka A, Taniguchi T. 2006. Type I interferon [corrected] gene induction by the interferon regulatory factor family of transcription factors. *Immunity* 25:349–360 <http://dx.doi.org/10.1016/j.immuni.2006.08.009>.
96. Cooper AM, Pearl JE, Brooks JV, Ehlers S, Orme IM. 2000. Expression of the nitric oxide synthase 2 gene is not essential for early control of *Mycobacterium tuberculosis* in the murine lung. *Infect Immun* 68:6879–6882 <http://dx.doi.org/10.1128/IAI.68.12.6879-6882.2000>.
97. Manca C, Tsenova L, Bergtold A, Freeman S, Tovey M, Musser JM, Barry CE III, Freedman VH, Kaplan G. 2001. Virulence of a *Mycobacterium tuberculosis* clinical isolate in mice is determined by failure to induce Th1 type immunity and is associated with induction of IFN-alpha/beta. *Proc Natl Acad Sci USA* 98:5752–5757 <http://dx.doi.org/10.1073/pnas.091096998>.
98. Ordway D, Henao-Tamayo M, Harton M, Palanisamy G, Troudt J, Shanley C, Basaraba RJ, Orme IM. 2007. The hypervirulent *Mycobacterium tuberculosis* strain HN878 induces a potent TH1 response followed by rapid down-regulation. *J Immunol* 179:522–531 <http://dx.doi.org/10.4049/jimmunol.179.1.522>.

99. McNab FW, Ewbank J, Howes A, Moreira-Teixeira L, Martirosyan A, Ghilardi N, Saraiva M, O'Garra A. 2014. Type I IFN induces IL-10 production in an IL-27-independent manner and blocks responsiveness to IFN- γ for production of IL-12 and bacterial killing in *Mycobacterium tuberculosis*-infected macrophages. *J Immunol* 193:3600–3612 <http://dx.doi.org/10.4049/jimmunol.1401088>.
100. Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, Wilkinson KA, Banchereau R, Skinner J, Wilkinson RJ, Quinn C, Blankenship D, Dhawan R, Cush JJ, Mejias A, Ramilo O, Kon OM, Pascual V, Banchereau J, Chaussabel D, O'Garra A. 2010. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* 466:973–977 <http://dx.doi.org/10.1038/nature09247>.
101. Antonelli LR, Gigliotti Rothfuchs A, Gonçalves R, Roffé E, Cheever AW, Bafica A, Salazar AM, Feng CG, Sher A. 2010. Intranasal Poly-IC treatment exacerbates tuberculosis in mice through the pulmonary recruitment of a pathogen-permissive monocyte/macrophage population. *J Clin Invest* 120:1674–1682 <http://dx.doi.org/10.1172/JCI40817>.
102. Desvignes L, Wolf AJ, Ernst JD. 2012. Dynamic roles of type I and type II IFNs in early infection with *Mycobacterium tuberculosis*. *J Immunol* 188:6205–6215 <http://dx.doi.org/10.4049/jimmunol.1200255>.
103. Van Snick J. 1990. Interleukin-6: an overview. *Annu Rev Immunol* 8:253–278 <http://dx.doi.org/10.1146/annurev.iv.08.040190.001345>.
104. Shalaby MR, Waage A, Espevik T. 1989. Cytokine regulation of interleukin 6 production by human endothelial cells. *Cell Immunol* 121:372–382 [http://dx.doi.org/10.1016/0008-8749\(89\)90036-1](http://dx.doi.org/10.1016/0008-8749(89)90036-1).
105. Sanceau J, Beranger F, Gaudet C, Wietzerbin J. 1989. IFN- γ is an essential cosignal for triggering IFN- β 2/BSF-2/IL-6 gene expression in human monocytic cell lines. *Ann N Y Acad Sci* 557:130–143, discussion 141–143 <http://dx.doi.org/10.1111/j.1749-6632.1989.tb24006.x>.
106. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. 2003. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J* 374:1–20 <http://dx.doi.org/10.1042/bj20030407>.
107. Heinrich PC, Behrmann I, Müller-Newen G, Schaper F, Graeve L. 1998. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. *Biochem J* 334:297–314 <http://dx.doi.org/10.1042/bj3340297>.
108. Ladel CH, Blum C, Dreher A, Reifenberg K, Kopf M, Kaufmann SH. 1997. Lethal tuberculosis in interleukin-6-deficient mutant mice. *Infect Immun* 65:4843–4849.
109. Appelberg R, Castro AG, Pedrosa J, Minóprio P. 1994. Role of interleukin-6 in the induction of protective T cells during mycobacterial infections in mice. *Immunology* 82:361–364.
110. Saunders BM, Frank AA, Orme IM, Cooper AM. 2000. Interleukin-6 induces early gamma interferon production in the infected lung but is not required for generation of specific immunity to *Mycobacterium tuberculosis* infection. *Infect Immun* 68:3322–3326 <http://dx.doi.org/10.1128/IAI.68.6.3322-3326.2000>.
111. Leal IS, Smedegård B, Andersen P, Appelberg R. 1999. Interleukin-6 and interleukin-12 participate in induction of a type 1 protective T-cell response during vaccination with a tuberculosis subunit vaccine. *Infect Immun* 67:5747–5754.
112. Atreya R, Neurath MF. 2005. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. *Clin Rev Allergy Immunol* 28:187–196 <http://dx.doi.org/10.1385/CRIAI.28.3.187>.
113. Sodenkamp J, Waetzig GH, Scheller J, Seegert D, Grötzinger J, Rose-John S, Ehlers S, Hölscher C. 2012. Therapeutic targeting of interleukin-6 trans-signaling does not affect the outcome of experimental tuberculosis. *Immunobiology* 217:996–1004 <http://dx.doi.org/10.1016/j.imbio.2012.01.015>.
114. Nolan A, Condos R, Huie ML, Dawson R, Dheda K, Bateman E, Rom WN, Weiden MD. 2013. Elevated IP-10 and IL-6 from bronchoalveolar lavage cells are biomarkers of non-cavitary tuberculosis. *Int J Tuberc Lung Dis* 17:922–927 <http://dx.doi.org/10.5588/ijtld.12.0610>.
115. el-Ahmady O, Mansour M, Zoeir H, Mansour O. 1997. Elevated concentrations of interleukins and leukotriene in response to *Mycobacterium tuberculosis* infection. *Ann Clin Biochem* 34:160–164 <http://dx.doi.org/10.1177/000456329703400205>.
116. Dinarello CA. 1991. Interleukin-1 and interleukin-1 antagonism. *Blood* 77:1627–1652.
117. Menkin V. 1943. The effect of the leukocytosis-promoting factor on the growth of cells in the bone marrow. *Am J Pathol* 19:1021–1029.
118. Menkin V. 1943. Studies on the isolation of the factor responsible for tissue injury in inflammation. *Science* 97:165–167 <http://dx.doi.org/10.1126/science.97.2511.165>.
119. Menkin V. 1944. Chemical basis of fever. *Science* 100:337–338 <http://dx.doi.org/10.1126/science.100.2598.337>.
120. Gross O, Yazdi AS, Thomas CJ, Masin M, Heinz LX, Guarda G, Quadroni M, Drexler SK, Tschopp J. 2012. Inflammasome activators induce interleukin-1 α secretion via distinct pathways with differential requirement for the protease function of caspase-1. *Immunity* 36:388–400 <http://dx.doi.org/10.1016/j.immuni.2012.01.018>.
121. Sansonetti PJ, Phalipon A, Arondel J, Thirumalai K, Banerjee S, Akira S, Takeda K, Zychlinsky A. 2000. Caspase-1 activation of IL-1 β and IL-18 are essential for *Shigella flexneri*-induced inflammation. *Immunity* 12:581–590 [http://dx.doi.org/10.1016/S1074-7613\(00\)80209-5](http://dx.doi.org/10.1016/S1074-7613(00)80209-5).
122. Latz E, Xiao TS, Stutz A. 2013. Activation and regulation of the inflammasomes. *Nat Rev Immunol* 13:397–411 <http://dx.doi.org/10.1038/nri3452>.
123. Kayagaki N, Warming S, Lamkanfi M, Vande Walle L, Louie S, Dong J, Newton K, Qu Y, Liu J, Heldens S, Zhang J, Lee WP, Roose-Girma M, Dixit VM. 2011. Non-canonical inflammasome activation targets caspase-11. *Nature* 479:117–121 <http://dx.doi.org/10.1038/nature10558>.
124. Bossaller L, Chiang PI, Schmidt-Lauber C, Ganesan S, Kaiser WJ, Rathinam VA, Mocarski ES, Subramanian D, Green DR, Silverman N, Fitzgerald KA, Marshak-Rothstein A, Latz E. 2012. Cutting edge: FAS (CD95) mediates noncanonical IL-1 β and IL-18 maturation via caspase-8 in a RIP3-independent manner. *J Immunol* 189:5508–5512 <http://dx.doi.org/10.4049/jimmunol.1202121>.
125. Chen CJ, Kono H, Golenbock D, Reed G, Akira S, Rock KL. 2007. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. *Nat Med* 13:851–856 <http://dx.doi.org/10.1038/nm1603>.
126. Rider P, Carmi Y, Guttman O, Braiman A, Cohen I, Voronov E, White MR, Dinarello CA, Apte RN. 2011. IL-1 α and IL-1 β recruit different myeloid cells and promote different stages of sterile inflammation. *J Immunol* 187:4835–4843 <http://dx.doi.org/10.4049/jimmunol.1102048>.
127. Berda-Haddad Y, Robert S, Salers P, Zekraoui L, Farnarier C, Dinarello CA, Dignat-George F, Kaplanski G. 2011. Sterile inflammation of endothelial cell-derived apoptotic bodies is mediated by interleukin-1 α . *Proc Natl Acad Sci USA* 108:20684–20689 <http://dx.doi.org/10.1073/pnas.1116848108>.
128. Botelho FM, Bauer CM, Finch D, Nikota JK, Zavitz CC, Kelly A, Lambert KN, Piper S, Foster ML, Goldring JJ, Wedzicha JA, Bassett J, Bramson J, Iwakura Y, Sleeman M, Kolbeck R, Coyle AJ, Humbles AA, Stämpfli MR. 2011. IL-1 α /IL-1R1 expression in chronic obstructive pulmonary disease and mechanistic relevance to smoke-induced neutrophilia in mice. *PLoS One* 6:e28457 <http://dx.doi.org/10.1371/journal.pone.0028457>.
129. Freigang S, Ampenberger F, Weiss A, Kanneganti T-D, Iwakura Y, Hersberger M, Kopf M. 2013. Fatty acid-induced mitochondrial uncoupling elicits inflammasome-independent IL-1 α and sterile vascular inflammation in atherosclerosis. *Nat Immunol* 14:1045–1053 <http://dx.doi.org/10.1038/ni.2704>.
130. Barry KC, Fontana MF, Portman JL, Dugan AS, Vance RE. 2013. IL-1 α signaling initiates the inflammatory response to virulent *Legionella pneumophila* in vivo. *J Immunol* 190:6329–6339 <http://dx.doi.org/10.4049/jimmunol.1300100>.

131. Biondo C, Mancuso G, Midiri A, Signorino G, Domina M, Lanza Cariccio V, Mohammadi N, Venza M, Venza I, Teti G, Beninati C. 2014. The interleukin-1 β /CXCL12/neutrophil axis mediates host protection against group B streptococcal infection. *Infect Immun* 82:4508–4517 <http://dx.doi.org/10.1128/IAI.02104-14>.
132. Guo H, Gao J, Taxman DJ, Ting JP, Su L. 2014. HIV-1 infection induces interleukin-1 β production via TLR8 protein-dependent and NLRP3 inflammasome mechanisms in human monocytes. *J Biol Chem* 289:21716–21726 <http://dx.doi.org/10.1074/jbc.M114.566620>.
133. Rynko AE, Fryer AD, Jacoby DB. 2014. Interleukin-1 β mediates virus-induced m2 muscarinic receptor dysfunction and airway hyper-reactivity. *Am J Respir Cell Mol Biol* 51:494–501 <http://dx.doi.org/10.1165/rcmb.2014-0009OC>.
134. Shigematsu Y, Niwa T, Rehnberg E, Toyoda T, Yoshida S, Mori A, Wakabayashi M, Iwakura Y, Ichinose M, Kim YJ, Ushijima T. 2013. Interleukin-1 β induced by *Helicobacter pylori* infection enhances mouse gastric carcinogenesis. *Cancer Lett* 340:141–147 <http://dx.doi.org/10.1016/j.canlet.2013.07.034>.
135. Dinarello CA. 2011. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood* 117:3720–3732 <http://dx.doi.org/10.1182/blood-2010-07-273417>.
136. Konsman JP, Vignes S, Mackerlova L, Bristow A, Blomqvist A. 2004. Rat brain vascular distribution of interleukin-1 type-1 receptor immunoreactivity: relationship to patterns of inducible cyclooxygenase expression by peripheral inflammatory stimuli. *J Comp Neurol* 472:113–129 <http://dx.doi.org/10.1002/cne.20052>.
137. Marshall JD, Aste-Amézaga M, Chehimi SS, Murphy M, Olsen H, Trinchieri G. 1999. Regulation of human IL-18 mRNA expression. *Clin Immunol* 90:15–21 <http://dx.doi.org/10.1006/clim.1998.4633>.
138. Puren AJ, Fantuzzi G, Dinarello CA. 1999. Gene expression, synthesis, and secretion of interleukin 18 and interleukin 1 β are differentially regulated in human blood mononuclear cells and mouse spleen cells. *Proc Natl Acad Sci USA* 96:2256–2261 <http://dx.doi.org/10.1073/pnas.96.5.2256>.
139. Sugawara S, Uehara A, Nuchi T, Yamaguchi T, Ueda H, Sugiyama A, Hanzawa K, Kumagai K, Okamura H, Takada H. 2001. Neutrophil proteinase 3-mediated induction of bioactive IL-18 secretion by human oral epithelial cells. *J Immunol* 167:6568–6575 <http://dx.doi.org/10.4049/jimmunol.167.11.6568>.
140. Dinarello CA, Novick D, Kim S, Kaplanski G. 2013. Interleukin-18 and IL-18 binding protein. *Front Immunol* 4:289 <http://dx.doi.org/10.3389/fimmu.2013.00289>.
141. Hölscher C, Reiling N, Schaible UE, Hölscher A, Bathmann C, Korb D, Lenz I, Sonntag T, Kröger S, Akira S, Mossmann H, Kirschning CJ, Wagner H, Freudenberg M, Ehlers S. 2008. Containment of aerogenic *Mycobacterium tuberculosis* infection in mice does not require MyD88 adaptor function for TLR2, -4 and -9. *Eur J Immunol* 38:680–694 <http://dx.doi.org/10.1002/eji.200736458>.
142. O'Neill LA, Bowie AG. 2007. The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling. *Nat Rev Immunol* 7:353–364 <http://dx.doi.org/10.1038/nri2079>.
143. Fremont CM, Yermeev V, Nicolle DM, Jacobs M, Quesniaux VF, Ryffel B. 2004. Fatal *Mycobacterium tuberculosis* infection despite adaptive immune response in the absence of MyD88. *J Clin Invest* 114:1790–1799 <http://dx.doi.org/10.1172/JCI200421027>.
144. Fremont CM, Togbe D, Doz E, Rose S, Vasseur V, Maillet I, Jacobs M, Ryffel B, Quesniaux VF. 2007. IL-1 receptor-mediated signal is an essential component of MyD88-dependent innate response to *Mycobacterium tuberculosis* infection. *J Immunol* 179:1178–1189 <http://dx.doi.org/10.4049/jimmunol.179.2.1178>.
145. Mayer-Barber KD, Andrade BB, Barber DL, Hieny S, Feng CG, Caspar P, Oland S, Gordon S, Sher A. 2011. Innate and adaptive interferons suppress IL-1 α and IL-1 β production by distinct pulmonary myeloid subsets during *Mycobacterium tuberculosis* infection. *Immunity* 35:1023–1034 <http://dx.doi.org/10.1016/j.immuni.2011.12.002>.
146. Bourigault ML, Segueni N, Rose S, Court N, Vacher R, Vasseur V, Erard F, Le Bert M, Garcia I, Iwakura Y, Jacobs M, Ryffel B, Quesniaux VF. 2013. Relative contribution of IL-1 α , IL-1 β and TNF to the host response to *Mycobacterium tuberculosis* and attenuated *M. bovis* BCG. *Immun Inflamm Dis* 1:47–62 <http://dx.doi.org/10.1002/iid3.9>.
147. Di Paolo NC, Shafiani S, Day T, Papayannopoulou T, Russell DW, Iwakura Y, Sherman D, Urdahl K, Shayakhmetov DM. 2015. Interdependence between interleukin-1 and tumor necrosis factor regulates TNF-dependent control of *Mycobacterium tuberculosis* infection. *Immunity* 43:1125–1136. (Erratum: 44:438.) <http://dx.doi.org/10.1016/j.immuni.2015.11.016>.
148. Guler R, Parihar SP, Spohn G, Johansen P, Brombacher F, Bachmann MF. 2011. Blocking IL-1 α but not IL-1 β increases susceptibility to chronic *Mycobacterium tuberculosis* infection in mice. *Vaccine* 29:1339–1346 <http://dx.doi.org/10.1016/j.vaccine.2010.10.045>.
149. Gopal R, Monin L, Slight S, Uche U, Blanchard E, Fallert Junecko BA, Ramos-Payan R, Stallings CL, Reinhart TA, Kolls JK, Kaushal D, Nagarajan U, Rangel-Moreno J, Khader SA. 2014. Unexpected role for IL-17 in protective immunity against hypervirulent *Mycobacterium tuberculosis* HN878 infection. *PLoS Pathog* 10:e1004099 <http://dx.doi.org/10.1371/journal.ppat.1004099>.
150. Schneider BE, Korb D, Hagens K, Koch M, Raupach B, Enders J, Kaufmann SH, Mittrücker HW, Schaible UE. 2010. A role for IL-18 in protective immunity against *Mycobacterium tuberculosis*. *Eur J Immunol* 40:396–405 <http://dx.doi.org/10.1002/eji.200939583>.
151. Suwara MI, Green NJ, Borthwick LA, Mann J, Mayer-Barber KD, Barron L, Corris PA, Farrow SN, Wynn TA, Fisher AJ, Mann DA. 2014. IL-1 α released from damaged epithelial cells is sufficient and essential to trigger inflammatory responses in human lung fibroblasts. *Mucosal Immunol* 7:684–693 <http://dx.doi.org/10.1038/mi.2013.87>.
152. Fielding CA, McLoughlin RM, McLeod L, Colmont CS, Najdovska M, Grail D, Ernst M, Jones SA, Topley N, Jenkins BJ. 2008. IL-6 regulates neutrophil trafficking during acute inflammation via STAT3. *J Immunol* 181:2189–2195 <http://dx.doi.org/10.4049/jimmunol.181.3.2189>.
153. Lalor SJ, Dungan LS, Sutton CE, Basdeo SA, Fletcher JM, Mills KH. 2011. Caspase-1-processed cytokines IL-1 β and IL-18 promote IL-17 production by gammadelta and CD4 T cells that mediate autoimmunity. *J Immunol* 186:5738–5748 <http://dx.doi.org/10.4049/jimmunol.1003597>.
154. Dunne A, Ross PJ, Pospisilova E, Masin J, Meaney A, Sutton CE, Iwakura Y, Tschopp J, Sebo P, Mills KH. 2010. Inflammasome activation by adenylate cyclase toxin directs Th17 responses and protection against *Bordetella pertussis*. *J Immunol* 185:1711–1719 <http://dx.doi.org/10.4049/jimmunol.1000105>.
155. Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, Ma L, Watowich SS, Jetten AM, Tian Q, Dong C. 2009. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* 30:576–587 <http://dx.doi.org/10.1016/j.immuni.2009.02.007>.
156. Monin L, Griffiths KL, Slight S, Lin Y, Rangel-Moreno J, Khader SA. 2015. Immune requirements for protective Th17 recall responses to *Mycobacterium tuberculosis* challenge. *Mucosal Immunol* 8:1099–1109 <http://dx.doi.org/10.1038/mi.2014.136>.
157. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cilley GE, Shen F, Eaton SM, Gaffen SL, Swain SL, Locksley RM, Haynes L, Randall TD, Cooper AM. 2007. IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during *Mycobacterium tuberculosis* challenge. *Nat Immunol* 8:369–377 <http://dx.doi.org/10.1038/ni1449>.
158. Mayer-Barber KD, Andrade BB, Oland SD, Amaral EP, Barber DL, Gonzales J, Derrick SC, Shi R, Kumar NP, Wei W, Yuan X, Zhang G, Cai Y, Babu S, Catalfamo M, Salazar AM, Via LE, Barry CE III, Sher A. 2014. Host-directed therapy of tuberculosis based on interleukin-1 and type I interferon crosstalk. *Nature* 511:99–103 <http://dx.doi.org/10.1038/nature13489>.

159. Tominaga K, Yoshimoto T, Torigoe K, Kurimoto M, Matsui K, Hada T, Okamura H, Nakanishi K. 2000. IL-12 synergizes with IL-18 or IL-1beta for IFN-gamma production from human T cells. *Int Immunol* 12:151–160 <http://dx.doi.org/10.1093/intimm/12.2.151>.
160. Okamura H, Kashiwamura S, Tsutsui H, Yoshimoto T, Nakanishi K. 1998. Regulation of interferon-gamma production by IL-12 and IL-18. *Curr Opin Immunol* 10:259–264 [http://dx.doi.org/10.1016/S0952-7915\(98\)80163-5](http://dx.doi.org/10.1016/S0952-7915(98)80163-5).
161. Bohn E, Sing A, Zumbihl R, Bielfeldt C, Okamura H, Kurimoto M, Heesemann J, Autenrieth IB. 1998. IL-18 (IFN-gamma-inducing factor) regulates early cytokine production in, and promotes resolution of, bacterial infection in mice. *J Immunol* 160:299–307.
162. Sugawara I, Yamada H, Kaneko H, Mizuno S, Takeda K, Akira S. 1999. Role of interleukin-18 (IL-18) in mycobacterial infection in IL-18-gene-disrupted mice. *Infect Immun* 67:2585–2589.
163. Kinjo Y, Kawakami K, Uezu K, Yara S, Miyagi K, Koguchi Y, Hoshino T, Okamoto M, Kawase Y, Yokota K, Yoshino K, Takeda K, Akira S, Saito A. 2002. Contribution of IL-18 to Th1 response and host defense against infection by *Mycobacterium tuberculosis*: a comparative study with IL-12p40. *J Immunol* 169:323–329 <http://dx.doi.org/10.4049/jimmunol.169.1.323>.
164. Jones LL, Vignali DA. 2011. Molecular interactions within the IL-6/IL-12 cytokine/receptor superfamily. *Immunol Res* 51:5–14 <http://dx.doi.org/10.1007/s12026-011-8209-y>.
165. Collison LW, Vignali DA. 2008. Interleukin-35: odd one out or part of the family? *Immunol Rev* 226:248–262 <http://dx.doi.org/10.1111/j.1600-065X.2008.00704.x>.
166. Vignali DA, Kuchroo VK. 2012. IL-12 family cytokines: immunological playmakers. *Nat Immunol* 13:722–728 <http://dx.doi.org/10.1038/ni.2366>.
167. Méndez-Samperio P. 2010. Role of interleukin-12 family cytokines in the cellular response to mycobacterial disease. *Int J Infect Dis* 14:e366–e371 <http://dx.doi.org/10.1016/j.ijid.2009.06.022>.
168. Hunter CA. 2005. New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. *Nat Rev Immunol* 5:521–531 <http://dx.doi.org/10.1038/nri1648>.
169. Kobayashi M, Fitz L, Ryan M, Hewick RM, Clark SC, Chan S, Loudon R, Sherman F, Perussia B, Trinchieri G. 1989. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biologic effects on human lymphocytes. *J Exp Med* 170:827–845 <http://dx.doi.org/10.1084/jem.170.3.827>.
170. Gately MK, et al. 1991. Regulation of human lymphocyte proliferation by a heterodimeric cytokine, IL-12 (cytotoxic lymphocyte maturation factor). *J Immunol* 147:874–882.
171. Ma X, Trinchieri G. 2001. Regulation of interleukin-12 production in antigen-presenting cells. *Adv Immunol* 79:55–92 [http://dx.doi.org/10.1016/S0065-2776\(01\)79002-5](http://dx.doi.org/10.1016/S0065-2776(01)79002-5).
172. O'Shea JJ, Paul WE. 2002. Regulation of T(H)1 differentiation—controlling the controllers. *Nat Immunol* 3:506–508 <http://dx.doi.org/10.1038/ni0602-506>.
173. Ozbek N, Fieschi C, Yilmaz BT, de Beaucoudrey L, Demirhan B, Feinberg J, Bikmaz YE, Casanova JL. 2005. Interleukin-12 receptor beta 1 chain deficiency in a child with disseminated tuberculosis. *Clin Infect Dis* 40:e55–e58 <http://dx.doi.org/10.1086/427879>.
174. Dorman SE, Holland SM. 2000. Interferon-gamma and interleukin-12 pathway defects and human disease. *Cytokine Growth Factor Rev* 11:321–333 [http://dx.doi.org/10.1016/S1359-6101\(00\)00010-1](http://dx.doi.org/10.1016/S1359-6101(00)00010-1).
175. Picard C, Fieschi C, Altare F, Al-Jumaah S, Al-Hajjar S, Feinberg J, Dupuis S, Soudais C, Al-Mohsen IZ, Génin E, Lammas D, Kumararatne DS, Leclerc T, Rafi A, Frayha H, Murugasu B, Wah LB, Sinniah R, Loubser M, Okamoto E, Al-Ghonaia A, Tufenkeji H, Abel L, Casanova JL. 2002. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. *Am J Hum Genet* 70:336–348 <http://dx.doi.org/10.1086/338625>.
176. Altare F, Ensser A, Breiman A, Reichenbach J, Baghdadi JE, Fischer A, Emile JF, Gaillard JL, Meinel E, Casanova JL. 2001. Interleukin-12 receptor beta1 deficiency in a patient with abdominal tuberculosis. *J Infect Dis* 184:231–236 <http://dx.doi.org/10.1086/321999>.
177. Caragol I, Raspall M, Fieschi C, Feinberg J, Larrosa MN, Hernández M, Figueras C, Bertrán JM, Casanova JL, Español T. 2003. Clinical tuberculosis in 2 of 3 siblings with interleukin-12 receptor beta1 deficiency. *Clin Infect Dis* 37:302–306 <http://dx.doi.org/10.1086/375587>.
178. Casanova JL, Abel L. 2002. Genetic dissection of immunity to mycobacteria: the human model. *Annu Rev Immunol* 20:581–620 <http://dx.doi.org/10.1146/annurev.immunol.20.081501.125851>.
179. Bogunovic D, Byun M, Durfee LA, Abhyankar A, Sanal O, Mansouri D, Salem S, Radovanovic I, Grant AV, Adimi P, Mansouri N, Okada S, Bryant VL, Kong XF, Kreins A, Velez MM, Boisson B, Khalilzadeh S, Ozcelik U, Darazam IA, Schoggins JW, Rice CM, Al-Muhsen S, Behr M, Vogt G, Puel A, Bustamante J, Gros P, Huibregtse JM, Abel L, Boisson-Dupuis S, Casanova JL. 2012. Mycobacterial disease and impaired IFN-γ immunity in humans with inherited ISG15 deficiency. *Science* 337:1684–1688 <http://dx.doi.org/10.1126/science.1224026>.
180. Bustamante J, Arias AA, Vogt G, Picard C, Galicia LB, Prando C, Grant AV, Marchal CC, Hubeau M, Chappier A, de Beaucoudrey L, Puel A, Feinberg J, Valinetz E, Jannié L, Besse C, Boland A, Brisseau JM, Blanche S, Lortholary O, Fieschi C, Emile JF, Boisson-Dupuis S, Al-Muhsen S, Woda B, Newburger PE, Condino-Neto A, Dinuer MC, Abel L, Casanova JL. 2011. Germline CYBB mutations that selectively affect macrophages in kindreds with X-linked predisposition to tuberculous mycobacterial disease. *Nat Immunol* 12:213–221 <http://dx.doi.org/10.1038/ni.1992>.
181. Bustamante J, Picard C, Boisson-Dupuis S, Abel L, Casanova J-L. 2011. Genetic lessons learned from X-linked Mendelian susceptibility to mycobacterial diseases. *Ann N Y Acad Sci* 1246:92–101 <http://dx.doi.org/10.1111/j.1749-6632.2011.06273.x>.
182. Filipe-Santos O, Bustamante J, Haverkamp MH, Vinolo E, Ku CL, Puel A, Frucht DM, Christel K, von Bernuth H, Jouanguy E, Feinberg J, Durandy A, Senechal B, Chappier A, Vogt G, de Beaucoudrey L, Fieschi C, Picard C, Garfa M, Chemli J, Bejaoui M, Tsolia MN, Kutukculer N, Plebani A, Notarangelo L, Bodemer C, Geissmann F, Israël A, Véron M, Knackstedt M, Barbouche R, Abel L, Magdorf K, Gendrel D, Agou F, Holland SM, Casanova JL. 2006. X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. *J Exp Med* 203:1745–1759 <http://dx.doi.org/10.1084/jem.20060085>.
183. Zhang M, Gately MK, Wang E, Gong J, Wolf SF, Lu S, Modlin RL, Barnes PF. 1994. Interleukin 12 at the site of disease in tuberculosis. *J Clin Invest* 93:1733–1739 <http://dx.doi.org/10.1172/JCI117157>.
184. Cooper AM, Roberts AD, Rhoades ER, Callahan JE, Getzy DM, Orme IM. 1995. The role of interleukin-12 in acquired immunity to *Mycobacterium tuberculosis* infection. *Immunology* 84:423–432.
185. Cooper AM, Magram J, Ferrante J, Orme IM. 1997. Interleukin 12 (IL-12) is crucial to the development of protective immunity in mice intravenously infected with mycobacterium tuberculosis. *J Exp Med* 186:39–45 <http://dx.doi.org/10.1084/jem.186.1.39>.
186. Cooper AM, Kipnis A, Turner J, Magram J, Ferrante J, Orme IM. 2002. Mice lacking bioactive IL-12 can generate protective, antigen-specific cellular responses to mycobacterial infection only if the IL-12 p40 subunit is present. *J Immunol* 168:1322–1327 <http://dx.doi.org/10.4049/jimmunol.168.3.1322>.
187. Khader SA, Pearl JE, Sakamoto K, Gilmartin L, Bell GK, Jelley-Gibbs DM, Ghilardi N, deSavage F, Cooper AM. 2005. IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-gamma responses if IL-12p70 is available. *J Immunol* 175:788–795 <http://dx.doi.org/10.4049/jimmunol.175.2.788>.
188. Feng CG, Jankovic D, Kullberg M, Cheever A, Scanga CA, Hieny S, Caspar P, Yap GS, Sher A. 2005. Maintenance of pulmonary Th1 effector

- function in chronic tuberculosis requires persistent IL-12 production. *J Immunol* 174:4185–4192 <http://dx.doi.org/10.4049/jimmunol.174.7.4185>.
189. Cleary AM, Tu W, Enright A, Giffon T, Dewaal-Malefyt R, Gutierrez K, Lewis DB. 2003. Impaired accumulation and function of memory CD4 T cells in human IL-12 receptor beta 1 deficiency. *J Immunol* 170:597–603 <http://dx.doi.org/10.4049/jimmunol.170.1.597>.
 190. Bafica A, Scanga CA, Feng CG, Leifer C, Cheever A, Sher A. 2005. TLR9 regulates Th1 responses and cooperates with TLR2 in mediating optimal resistance to *Mycobacterium tuberculosis*. *J Exp Med* 202:1715–1724 <http://dx.doi.org/10.1084/jem.20051782>.
 191. Pathak SK, Basu S, Bhattacharyya A, Pathak S, Kundu M, Basu J. 2005. *Mycobacterium tuberculosis* lipoarabinomannan-mediated IRAK-M induction negatively regulates Toll-like receptor-dependent interleukin-12 p40 production in macrophages. *J Biol Chem* 280:42794–42800 <http://dx.doi.org/10.1074/jbc.M506471200>.
 192. Pecora ND, Gehring AJ, Canaday DH, Boom WH, Harding CV. 2006. *Mycobacterium tuberculosis* LprA is a lipoprotein agonist of TLR2 that regulates innate immunity and APC function. *J Immunol* 177:422–429 <http://dx.doi.org/10.4049/jimmunol.177.1.422>.
 193. Presky DH, Yang H, Minetti LJ, Chua AO, Nabavi N, Wu CY, Gately MK, Gubler U. 1996. A functional interleukin 12 receptor complex is composed of two beta-type cytokine receptor subunits. *Proc Natl Acad Sci USA* 93:14002–14007 <http://dx.doi.org/10.1073/pnas.93.24.14002>.
 194. Chua AO, et al. 1994. Expression cloning of a human IL-12 receptor component. A new member of the cytokine receptor superfamily with strong homology to gp130. *J Immunol* 153:128–136.
 195. Chua AO, Wilkinson VL, Presky DH, Gubler U. 1995. Cloning and characterization of a mouse IL-12 receptor-beta component. *J Immunol* 155:4286–4294.
 196. Gillesen S, Carvajal D, Ling P, Podlaski FJ, Stremlo DL, Familletti PC, Gubler U, Presky DH, Stern AS, Gately MK. 1995. Mouse interleukin-12 (IL-12) p40 homodimer: a potent IL-12 antagonist. *Eur J Immunol* 25:200–206 <http://dx.doi.org/10.1002/eji.1830250133>.
 197. Gately MK, Carvajal DM, Connaughton SE, Gillesen S, Warrior RR, Kolinsky KD, Wilkinson VL, Dwyer CM, Higgins GF Jr, Podlaski FJ, Faherty DA, Familletti PC, Stern AS, Presky DH. 1996. Interleukin-12 antagonist activity of mouse interleukin-12 p40 homodimer in vitro and in vivo. *Ann N Y Acad Sci* 795(1 Interleukin 1):1–12 <http://dx.doi.org/10.1111/j.1749-6632.1996.tb52650.x>.
 198. Mattner F, Fischer S, Guckes S, Jin S, Kaulen H, Schmitt E, Rude E, Germann T. 1993. The interleukin-12 subunit p40 specifically inhibits effects of the interleukin-12 heterodimer. *Eur J Immunol* 23:2202–2208 <http://dx.doi.org/10.1002/eji.1830230923>.
 199. Hölscher C, Atkinson RA, Arendse B, Brown N, Myburgh E, Alber G, Brombacher F. 2001. A protective and agonistic function of IL-12p40 in mycobacterial infection. *J Immunol* 167:6957–6966 <http://dx.doi.org/10.4049/jimmunol.167.12.6957>.
 200. Khader SA, Partida-Sanchez S, Bell G, Jelley-Gibbs DM, Swain S, Pearl JE, Ghilardi N, Desauvage FJ, Lund FE, Cooper AM. 2006. Interleukin 12p40 is required for dendritic cell migration and T cell priming after *Mycobacterium tuberculosis* infection. *J Exp Med* 203:1805–1815 <http://dx.doi.org/10.1084/jem.20052545>.
 201. Reinhardt RL, Hong S, Kang SJ, Wang ZE, Locksley RM. 2006. Visualization of IL-12/23p40 in vivo reveals immunostimulatory dendritic cell migrants that promote Th1 differentiation. *J Immunol* 177:1618–1627 <http://dx.doi.org/10.4049/jimmunol.177.3.1618>.
 202. Wolf AJ, Desvignes L, Linas B, Banaiee N, Tamura T, Takatsu K, Ernst JD. 2008. Initiation of the adaptive immune response to *Mycobacterium tuberculosis* depends on antigen production in the local lymph node, not the lungs. *J Exp Med* 205:105–115 <http://dx.doi.org/10.1084/jem.20071367>.
 203. Robinson RT, Khader SA, Martino CA, Fountain JJ, Teixeira-Coelho M, Pearl JE, Smiley ST, Winslow GM, Woodland DL, Walter MJ, Conejo-Garcia JR, Gubler U, Cooper AM. 2010. *Mycobacterium tuberculosis* infection induces il12rb1 splicing to generate a novel IL-12Rbeta1 isoform that enhances DC migration. *J Exp Med* 207:591–605. (Erratum: 207:897.) <http://dx.doi.org/10.1084/jem.20091085>.
 204. Keeton R, Allie N, Dambuza I, Abel B, Hsu NJ, Sebesho B, Randall P, Burger P, Fick E, Quesniaux VF, Ryffel B, Jacobs M. 2014. Soluble TNFRp75 regulates host protective immunity against *Mycobacterium tuberculosis*. *J Clin Invest* 124:1537–1551 <http://dx.doi.org/10.1172/JCI45005>.
 205. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, Vega F, Yu N, Wang J, Singh K, Zonin F, Vaisberg E, Churakova T, Liu M, Gorman D, Wagner J, Zurawski S, Liu Y, Abrams JS, Moore KW, Rennick D, de Waal-Malefyt R, Hannum C, Bazan JF, Kastelein RA. 2000. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 13:715–725 [http://dx.doi.org/10.1016/S1074-7613\(00\)00070-4](http://dx.doi.org/10.1016/S1074-7613(00)00070-4).
 206. Uhlig HH, McKenzie BS, Hue S, Thompson C, Joyce-Shaikh B, Stepankova R, Robinson N, Buonocore S, Tskaloova-Hogenova H, Cua DJ, Powrie F. 2006. Differential activity of IL-12 and IL-23 in mucosal and systemic innate immune pathology. *Immunity* 25:309–318 <http://dx.doi.org/10.1016/j.immuni.2006.05.017>.
 207. Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, Cua DJ. 2015. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat Med* 21:719–729 <http://dx.doi.org/10.1038/nm.3895>.
 208. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, Lucian L, To W, Kwan S, Churakova T, Zurawski S, Wiekowski M, Lira SA, Gorman D, Kastelein RA, Sedgwick JD. 2003. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 421:744–748 <http://dx.doi.org/10.1038/nature01355>.
 209. Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, Kastelein RA, Sedgwick JD, Cua DJ. 2003. Divergent pro- and anti-inflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med* 198:1951–1957 <http://dx.doi.org/10.1084/jem.20030896>.
 210. Kroenke MA, Carlson TJ, Andjelkovic AV, Segal BM. 2008. IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. *J Exp Med* 205:1535–1541 <http://dx.doi.org/10.1084/jem.20080159>.
 211. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelletier A, Lafaille JJ, Cua DJ, Littman DR. 2006. The orphan nuclear receptor RORgamma directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell* 126:1121–1133 <http://dx.doi.org/10.1016/j.cell.2006.07.035>.
 212. Hirota K, Duarte JH, Veldhoen M, Hornsby E, Li Y, Cua DJ, Ahlfors H, Wilhelm C, Tolaini M, Menzel U, Garefalaki A, Potocnik AJ, Stockinger B. 2011. Fate mapping of IL-17-producing T cells in inflammatory responses. *Nat Immunol* 12:255–263 <http://dx.doi.org/10.1038/ni.1993>.
 213. Weaver CT, Hatton RD, Mangan PR, Harrington LE. 2007. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 25:821–852 <http://dx.doi.org/10.1146/annurev.jimmunol.25.022106.141557>.
 214. Parham C, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, Pflanz S, Zhang R, Singh KP, Vega F, To W, Wagner J, O'Farrell AM, McClanahan T, Zurawski S, Hannum C, Gorman D, Rennick DM, Kastelein RA, de Waal Malefyt R, Moore KW. 2002. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. *J Immunol* 168:5699–5708 <http://dx.doi.org/10.4049/jimmunol.168.11.5699>.
 215. Watford WT, Hissong BD, Bream JH, Kanno Y, Muul L, O'Shea JJ. 2004. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. *Immunol Rev* 202:139–156 <http://dx.doi.org/10.1111/j.0105-2896.2004.00211.x>.
 216. Trinchieri G. 2003. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat Rev Immunol* 3:133–146 <http://dx.doi.org/10.1038/nri1001>.

217. Wozniak TM, Ryan AA, Triccas JA, Britton WJ. 2006. Plasmid interleukin-23 (IL-23), but not plasmid IL-27, enhances the protective efficacy of a DNA vaccine against *Mycobacterium tuberculosis* infection. *Infect Immun* 74:557–565 <http://dx.doi.org/10.1128/IAI.74.1.557-565.2006>.
218. Lockhart E, Green AM, Flynn JL. 2006. IL-17 production is dominated by gamma delta T cells rather than CD4 T cells during *Mycobacterium tuberculosis* infection. *J Immunol* 177:4662–4669 <http://dx.doi.org/10.4049/jimmunol.177.7.4662>.
219. Khader SA, Guglani L, Rangel-Moreno J, Gopal R, Junecko BA, Fountain JJ, Martino C, Pearl JE, Tighe M, Lin YY, Slight S, Kolls JK, Reinhart TA, Randall TD, Cooper AM. 2011. IL-23 is required for long-term control of *Mycobacterium tuberculosis* and B cell follicle formation in the infected lung. *J Immunol* 187:5402–5407 <http://dx.doi.org/10.4049/jimmunol.1101377>.
220. Happel KI, Lockhart EA, Mason CM, Porretta E, Keoshkerian E, Odden AR, Nelson S, Ramsay AJ. 2005. Pulmonary interleukin-23 gene delivery increases local T-cell immunity and controls growth of *Mycobacterium tuberculosis* in the lungs. *Infect Immun* 73:5782–5788 <http://dx.doi.org/10.1128/IAI.73.9.5782-5788.2005>.
221. Gopal R, Rangel-Moreno J, Slight S, Lin Y, Nawar HF, Fallert Junecko BA, Reinhart TA, Kolls J, Randall TD, Connell TD, Khader SA. 2013. Interleukin-17-dependent CXCL13 mediates mucosal vaccine-induced immunity against tuberculosis. *Mucosal Immunol* 6:972–984 <http://dx.doi.org/10.1038/mi.2012.135>.
222. Lindenstrøm T, Woodworth J, Dietrich J, Aagaard C, Andersen P, Agger EM. 2012. Vaccine-induced th17 cells are maintained long-term postvaccination as a distinct and phenotypically stable memory subset. *Infect Immun* 80:3533–3544 <http://dx.doi.org/10.1128/IAI.00550-12>.
223. Desel C, Dorhoi A, Bandermann S, Grode L, Eisele B, Kaufmann SH. 2011. Recombinant BCG ΔureC hly+ induces superior protection over parental BCG by stimulating a balanced combination of type 1 and type 17 cytokine responses. *J Infect Dis* 204:1573–1584 <http://dx.doi.org/10.1093/infdis/jir592>.
224. Kastelein RA, Hunter CA, Cua DJ. 2007. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu Rev Immunol* 25:221–242 <http://dx.doi.org/10.1146/annurev.immunol.22.012703.104758>.
225. Langrish CL, McKenzie BS, Wilson NJ, de Waal Malefyt R, Kastelein RA, Cua DJ. 2004. IL-12 and IL-23: master regulators of innate and adaptive immunity. *Immunol Rev* 202:96–105 <http://dx.doi.org/10.1111/j.0105-2896.2004.00214.x>.
226. Cox JH, Kljavin NM, Ramamoorthi N, Diehl L, Batten M, Ghilardi N. 2011. IL-27 promotes T cell-dependent colitis through multiple mechanisms. *J Exp Med* 208:115–123 <http://dx.doi.org/10.1084/jem.20100410>.
227. Shimizu S, Sugiyama N, Masutani K, Sadanaga A, Miyazaki Y, Inoue Y, Akahoshi M, Katafuchi R, Hirakata H, Harada M, Hamano S, Nakashima H, Yoshida H. 2005. Membranous glomerulonephritis development with Th2-type immune deviations in MRL/lpr mice deficient for IL-27 receptor (WSX-1). *J Immunol* 175:7185–7192 <http://dx.doi.org/10.4049/jimmunol.175.11.7185>.
228. Cao Y, Doodles PD, Glant TT, Finnegan A. 2008. IL-27 induces a Th1 immune response and susceptibility to experimental arthritis. *J Immunol* 180:922–930 <http://dx.doi.org/10.4049/jimmunol.180.2.922>.
229. Pflanz S, Timans JC, Cheung J, Rosales R, Kanzler H, Gilbert J, Hibbert L, Churakova T, Travis M, Vaisberg E, Blumenschein WM, Mattson JD, Wagner JL, To W, Zurawski S, McClanahan TK, Gorman DM, Bazan JF, de Waal Malefyt R, Rennick D, Kastelein RA. 2002. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4+ T cells. *Immunity* 16:779–790 [http://dx.doi.org/10.1016/S1074-7613\(02\)00324-2](http://dx.doi.org/10.1016/S1074-7613(02)00324-2).
230. Pflanz S, Hibbert L, Mattson J, Rosales R, Vaisberg E, Bazan JF, Phillips JH, McClanahan TK, de Waal Malefyt R, Kastelein RA. 2004. WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. *J Immunol* 172:2225–2231 <http://dx.doi.org/10.4049/jimmunol.172.4.2225>.
231. Batten M, Li J, Yi S, Kljavin NM, Danilenko DM, Lucas S, Lee J, de Sauvage FJ, Ghilardi N. 2006. Interleukin 27 limits autoimmune encephalomyelitis by suppressing the development of interleukin 17-producing T cells. *Nat Immunol* 7:929–936 <http://dx.doi.org/10.1038/ni1375>.
232. Neufert C, Becker C, Wirtz S, Fantini MC, Weigmann B, Galle PR, Neurath MF. 2007. IL-27 controls the development of inducible regulatory T cells and Th17 cells via differential effects on STAT1. *Eur J Immunol* 37:1809–1816 <http://dx.doi.org/10.1002/eji.200636896>.
233. Takeda A, Hamano S, Yamanaka A, Hanada T, Ishibashi T, Mak TW, Yoshimura A, Yoshida H. 2003. Cutting edge: role of IL-27/WSX-1 signaling for induction of T-bet through activation of STAT1 during initial Th1 commitment. *J Immunol* 170:4886–4890 <http://dx.doi.org/10.4049/jimmunol.170.10.4886>.
234. Pearl JE, Khader SA, Solache A, Gilmartin L, Ghilardi N, deSauvage F, Cooper AM. 2004. IL-27 signaling compromises control of bacterial growth in mycobacteria-infected mice. *J Immunol* 173:7490–7496 <http://dx.doi.org/10.4049/jimmunol.173.12.7490>.
235. Hölscher C, Hölscher A, Rückerl D, Yoshimoto T, Yoshida H, Mak T, Saris C, Ehlers S. 2005. The IL-27 receptor chain WSX-1 differentially regulates antibacterial immunity and survival during experimental tuberculosis. *J Immunol* 174:3534–3544 <http://dx.doi.org/10.4049/jimmunol.174.6.3534>.
236. Sodenkamp J, Behrends J, Förster I, Müller W, Ehlers S, Hölscher C. 2011. gp130 on macrophages/granulocytes modulates inflammation during experimental tuberculosis. *Eur J Cell Biol* 90:505–514 <http://dx.doi.org/10.1016/j.ejcb.2010.10.010>.
237. Neurath MF. 2008. IL-12 family members in experimental colitis. *Mucosal Immunol* 1(Suppl 1):S28–S30 <http://dx.doi.org/10.1038/mi.2008.45>.
238. Vignali DA, Collison LW, Workman CJ. 2008. How regulatory T cells work. *Nat Rev Immunol* 8:523–532 <http://dx.doi.org/10.1038/nri2343>.
239. Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, Cross R, Sehy D, Blumberg RS, Vignali DA. 2007. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature* 450:566–569 <http://dx.doi.org/10.1038/nature06306>.
240. Jin W, Dong C. 2013. IL-17 cytokines in immunity and inflammation. *Emerg Microbes Infect* 2:e60 <http://dx.doi.org/10.1038/emi.2013.58>.
241. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, Fujikado N, Tanahashi Y, Akitsu A, Kotaki H, Sudo K, Nakae S, Sasakawa C, Iwakura Y. 2009. Differential roles of interleukin-17A and -17F in host defense against mucocutaneous bacterial infection and allergic responses. *Immunity* 30:108–119 <http://dx.doi.org/10.1016/j.immuni.2008.11.009>.
242. Yang XO, Chang SH, Park H, Nurieva R, Shah B, Acero L, Wang YH, Schluns KS, Broaddus RR, Zhu Z, Dong C. 2008. Regulation of inflammatory responses by IL-17F. *J Exp Med* 205:1063–1075 <http://dx.doi.org/10.1084/jem.20071978>.
243. Umemura M, Yahagi A, Hamada S, Begum MD, Watanabe H, Kawakami K, Suda T, Sudo K, Nakae S, Iwakura Y, Matsuzaki G. 2007. IL-17-mediated regulation of innate and acquired immune response against pulmonary *Mycobacterium bovis* bacille Calmette-Guérin infection. *J Immunol* 178:3786–3796 <http://dx.doi.org/10.4049/jimmunol.178.6.3786>.
244. Gopal R, Lin Y, Obermajer N, Slight S, Nuthalapati N, Ahmed M, Kalinski P, Khader SA. 2012. IL-23-dependent IL-17 drives Th1-cell responses following *Mycobacterium bovis* BCG vaccination. *Eur J Immunol* 42:364–373 <http://dx.doi.org/10.1002/eji.201141569>.
245. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK. 2008. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat Med* 14:275–281 <http://dx.doi.org/10.1038/nm1710>.

246. Aguilo N, Alvarez-Arguedas S, Uranga S, Marinova D, Monzón M, Badiola J, Martin C. 2016. Pulmonary but not subcutaneous delivery of BCG vaccine confers protection to tuberculosis-susceptible mice by an interleukin 17-dependent mechanism. *J Infect Dis* 213:831–839 <http://dx.doi.org/10.1093/infdis/jiv503>.
247. Cruz A, Torrado E, Carmona J, Fraga AG, Costa P, Rodrigues F, Appelberg R, Correia-Neves M, Cooper AM, Saraiva M, Pedrosa J, Castro AG. 2015. BCG vaccination-induced long-lasting control of *Mycobacterium tuberculosis* correlates with the accumulation of a novel population of CD4⁺IL-17⁺TNF⁺IL-2⁺ T cells. *Vaccine* 33:85–91 <http://dx.doi.org/10.1016/j.vaccine.2014.11.013>.
248. Cruz A, Fraga AG, Fountain JJ, Rangel-Moreno J, Torrado E, Saraiva M, Pereira DR, Randall TD, Pedrosa J, Cooper AM, Castro AG. 2010. Pathological role of interleukin 17 in mice subjected to repeated BCG vaccination after infection with *Mycobacterium tuberculosis*. *J Exp Med* 207:1609–1616 <http://dx.doi.org/10.1084/jem.20100265>.
249. Gopal R, Monin L, Torres D, Slight S, Mehra S, McKenna KC, Fallert Junecko BA, Reinhardt TA, Kolls J, Báez-Saldaña R, Cruz-Lagunas A, Rodríguez-Reyna TS, Kumar NP, Tessier P, Roth J, Selman M, Becerril-Villanueva E, Baquera-Heredia J, Cumming B, Kasprovicz VO, Steyn AJ, Babu S, Kaushal D, Zúñiga J, Vogt T, Rangel-Moreno J, Khader SA. 2013. S100A8/A9 proteins mediate neutrophilic inflammation and lung pathology during tuberculosis. *Am J Respir Crit Care Med* 188:1137–1146 <http://dx.doi.org/10.1164/rccm.201304-0803OC>.
250. McAleer JP, Kolls JK. 2014. Directing traffic: IL-17 and IL-22 coordinate pulmonary immune defense. *Immunol Rev* 260:129–144 <http://dx.doi.org/10.1111/imr.12183>.
251. Sonnenberg GF, Nair MG, Kirn TJ, Zaph C, Fouser LA, Artis D. 2010. Pathological versus protective functions of IL-22 in airway inflammation are regulated by IL-17A. *J Exp Med* 207:1293–1305 <http://dx.doi.org/10.1084/jem.20092054>.
252. Kolls JK, McCray PB Jr, Chan YR. 2008. Cytokine-mediated regulation of antimicrobial proteins. *Nat Rev Immunol* 8:829–835 <http://dx.doi.org/10.1038/nri2433>.
253. Matthews K, Wilkinson KA, Kalsdorf B, Roberts T, Diacon A, Walzl G, Wolske J, Ntsekhe M, Syed F, Russell J, Mayosi BM, Dawson R, Dheda K, Wilkinson RJ, Hanekom WA, Scriba TJ. 2011. Predominance of interleukin-22 over interleukin-17 at the site of disease in human tuberculosis. *Tuberculosis (Edinb)* 91:587–593 <http://dx.doi.org/10.1016/j.tube.2011.06.009>.
254. Yao S, Huang D, Chen CY, Halliday L, Zeng G, Wang RC, Chen ZW. 2010. Differentiation, distribution and gamma delta T cell-driven regulation of IL-22-producing T cells in tuberculosis. *PLoS Pathog* 6:e1000789 <http://dx.doi.org/10.1371/journal.ppat.1000789>.
255. Zeng G, Chen CY, Huang D, Yao S, Wang RC, Chen ZW. 2011. Membrane-bound IL-22 after de novo production in tuberculosis and anti-*Mycobacterium tuberculosis* effector function of IL-22+ CD4+ T cells. *J Immunol* 187:190–199 <http://dx.doi.org/10.4049/jimmunol.1004129>.
256. Dhiman R, Venkatasubramanian S, Paidipally P, Barnes PF, Tvinnereim A, Vankayalapati R. 2014. Interleukin 22 inhibits intracellular growth of *Mycobacterium tuberculosis* by enhancing calgranulin A expression. *J Infect Dis* 209:578–587 <http://dx.doi.org/10.1093/infdis/jit495>.
257. Dhiman R, Indramohan M, Barnes PF, Nayak RC, Paidipally P, Rao LV, Vankayalapati R. 2009. IL-22 produced by human NK cells inhibits growth of *Mycobacterium tuberculosis* by enhancing phagolysosomal fusion. *J Immunol* 183:6639–6645 <http://dx.doi.org/10.4049/jimmunol.0902587>.
258. Zhang M, Zeng G, Yang Q, Zhang J, Zhu X, Chen Q, Suthakaran P, Zhang Y, Deng Q, Liu H, Zhou B, Chen X. 2014. Anti-tuberculosis treatment enhances the production of IL-22 through reducing the frequencies of regulatory B cell. *Tuberculosis (Edinb)* 94:238–244 <http://dx.doi.org/10.1016/j.tube.2013.12.003>.
259. Behrends J, Renaud JC, Ehlers S, Hölscher C. 2013. IL-22 is mainly produced by IFN γ -secreting cells but is dispensable for host protection against *Mycobacterium tuberculosis* infection. *PLoS One* 8:e57379 <http://dx.doi.org/10.1371/journal.pone.0057379>.
260. Wilson MS, Feng CG, Barber DL, Yarovinsky F, Cheever AW, Sher A, Grigg M, Collins M, Fouser L, Wynn TA. 2010. Redundant and pathogenic roles for IL-22 in mycobacterial, protozoan, and helminth infections. *J Immunol* 184:4378–4390 <http://dx.doi.org/10.4049/jimmunol.0903416>.
261. Dhiman R, Periasamy S, Barnes PF, Jaiswal AG, Paidipally P, Barnes AB, Tvinnereim A, Vankayalapati R. 2012. NK1.1+ cells and IL-22 regulate vaccine-induced protective immunity against challenge with *Mycobacterium tuberculosis*. *J Immunol* 189:897–905 <http://dx.doi.org/10.4049/jimmunol.1102833>.
262. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. 1986. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 136:2348–2357.
263. Killar L, MacDonald G, West J, Woods A, Bottomly K. 1987. Cloned, Ia-restricted T cells that do not produce interleukin 4 (IL 4)/B cell stimulatory factor 1 (BSF-1) fail to help antigen-specific B cells. *J Immunol* 138:1674–1679.
264. Powrie F, Menon S, Coffman RL. 1993. Interleukin-4 and interleukin-10 synergize to inhibit cell-mediated immunity in vivo. *Eur J Immunol* 23:3043–3049 <http://dx.doi.org/10.1002/eji.1830231147>.
265. Appelberg R, Orme IM, Pinto de Sousa MI, Silva MT. 1992. In vitro effects of interleukin-4 on interferon-gamma-induced macrophage activation. *Immunology* 76:553–559.
266. Ferber IA, Lee HJ, Zonin F, Heath V, Mui A, Arai N, O'Garra A. 1999. GATA-3 significantly downregulates IFN-gamma production from developing Th1 cells in addition to inducing IL-4 and IL-5 levels. *Clin Immunol* 91:134–144 <http://dx.doi.org/10.1006/clim.1999.4718>.
267. Steinke JW, Borish L. 2001. Th2 cytokines and asthma. Interleukin-4: its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. *Respir Res* 2:66–70 <http://dx.doi.org/10.1186/rr40>.
268. Stone KD, Prussin C, Metcalfe DD. 2010. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 125(Suppl 2):S73–S80 <http://dx.doi.org/10.1016/j.jaci.2009.11.017>.
269. MacDonald AS, Araujo MI, Pearce EJ. 2002. Immunology of parasitic helminth infections. *Infect Immun* 70:427–433 <http://dx.doi.org/10.1128/IAI.70.2.427-433.2002>.
270. Zhu J, Paul WE. 2008. CD4 T cells: fates, functions, and faults. *Blood* 112:1557–1569 <http://dx.doi.org/10.1182/blood-2008-05-078154>.
271. Nelms K, Keegan AD, Zamorano J, Ryan JJ, Paul WE. 1999. The IL-4 receptor: signaling mechanisms and biologic functions. *Annu Rev Immunol* 17:701–738 <http://dx.doi.org/10.1146/annurev.immunol.17.1.701>.
272. Zheng W, Flavell RA. 1997. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. *Cell* 89:587–596 [http://dx.doi.org/10.1016/S0092-8674\(00\)80240-8](http://dx.doi.org/10.1016/S0092-8674(00)80240-8).
273. Zhang DH, Cohn L, Ray P, Bottomly K, Ray A. 1997. Transcription factor GATA-3 is differentially expressed in murine Th1 and Th2 cells and controls Th2-specific expression of the interleukin-5 gene. *J Biol Chem* 272:21597–21603 <http://dx.doi.org/10.1074/jbc.272.34.21597>.
274. Kaplan MH, Schindler U, Smiley ST, Grusby MJ. 1996. Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity* 4:313–319 [http://dx.doi.org/10.1016/S1074-7613\(00\)80439-2](http://dx.doi.org/10.1016/S1074-7613(00)80439-2).
275. Shimoda K, van Deursen J, Sangster MY, Sarawar SR, Carson RT, Tripp RA, Chu C, Quelle FW, Nosaka T, Vignali DA, Doherty PC, Grosveld G, Paul WE, Ihle JN. 1996. Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. *Nature* 380:630–633 <http://dx.doi.org/10.1038/380630a0>.
276. Swain SL, Weinberg AD, English M, Huston G. 1990. IL-4 directs the development of Th2-like helper effectors. *J Immunol* 145:3796–3806.

277. Le Gros G, Ben-Sasson SZ, Seder R, Finkelman FD, Paul WE. 1990. Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. *J Exp Med* 172:921–929 <http://dx.doi.org/10.1084/jem.172.3.921>.
278. Lowenthal JW, Castle BE, Christiansen J, Schreurs J, Rennick D, Arai N, Hoy P, Takebe Y, Howard M. 1988. Expression of high affinity receptors for murine interleukin 4 (BSF-1) on hemopoietic and nonhemopoietic cells. *J Immunol* 140:456–464.
279. Ohara J, Paul WE. 1987. Receptors for B-cell stimulatory factor-1 expressed on cells of haematopoietic lineage. *Nature* 325:537–540 <http://dx.doi.org/10.1038/325537a0>.
280. Coffman RL, Seymour BW, Hudak S, Jackson J, Rennick D. 1989. Antibody to interleukin-5 inhibits helminth-induced eosinophilia in mice. *Science* 245:308–310 <http://dx.doi.org/10.1126/science.2787531>.
281. Phillips C, Coward WR, Pritchard DI, Hewitt CR. 2003. Basophils express a type 2 cytokine profile on exposure to proteases from helminths and house dust mites. *J Leukoc Biol* 73:165–171 <http://dx.doi.org/10.1189/jlb.0702356>.
282. Hitoshi Y, Yamaguchi N, Mita S, Sonoda E, Takaki S, Tominaga A, Takatsu K. 1990. Distribution of IL-5 receptor-positive B cells. Expression of IL-5 receptor on Ly-1(CD5)+ B cells. *J Immunol* 144:4218–4225.
283. Rolink AG, Thalmann P, Kikuchi Y, Erdei A. 1990. Characterization of the interleukin 5-reactive splenic B cell population. *Eur J Immunol* 20:1949–1956 <http://dx.doi.org/10.1002/eji.1830200912>.
284. Takatsu K. 2011. Interleukin-5 and IL-5 receptor in health and diseases. *Proc Jpn Acad, Ser B, Phys Biol Sci* 87:463–485 <http://dx.doi.org/10.2183/pjab.87.463>.
285. Schauf V, Rom WN, Smith KA, Sampaio EP, Meyn PA, Tramontana JM, Cohn ZA, Kaplan G. 1993. Cytokine gene activation and modified responsiveness to interleukin-2 in the blood of tuberculosis patients. *J Infect Dis* 168:1056–1059 <http://dx.doi.org/10.1093/infdis/168.4.1056>.
286. Surcel HM, Troye-Blomberg M, Paulie S, Andersson G, Moreno C, Pasvol G, Ivanyi J. 1994. Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. *Immunology* 81:171–176.
287. Zhang M, Gong J, Iyer DV, Jones BE, Modlin RL, Barnes PF. 1994. T cell cytokine responses in persons with tuberculosis and human immunodeficiency virus infection. *J Clin Invest* 94:2435–2442 <http://dx.doi.org/10.1172/JCI117611>.
288. Lin Y, Zhang M, Hofman FM, Gong J, Barnes PF. 1996. Absence of a prominent Th2 cytokine response in human tuberculosis. *Infect Immun* 64:1351–1356.
289. Lai CK, Ho S, Chan CH, Chan J, Choy D, Leung R, Lai KN. 1997. Cytokine gene expression profile of circulating CD4+ T cells in active pulmonary tuberculosis. *Chest* 111:606–611 <http://dx.doi.org/10.1378/chest.111.3.606>.
290. Mihret A, Bekele Y, Bobosha K, Kidd M, Aseffa A, Howe R, Walzl G. 2013. Plasma cytokines and chemokines differentiate between active disease and non-active tuberculosis infection. *J Infect* 66:357–365 <http://dx.doi.org/10.1016/j.jinf.2012.11.005>.
291. Mihret A, Abebe M, Bekele Y, Aseffa A, Walzl G, Howe R. 2014. Impact of HIV co-infection on plasma level of cytokines and chemokines of pulmonary tuberculosis patients. *BMC Infect Dis* 14:125 <http://dx.doi.org/10.1186/1471-2334-14-125>.
292. Bezuidenhout J, Roberts T, Muller L, van Helden P, Walzl G. 2009. Pleural tuberculosis in patients with early HIV infection is associated with increased TNF-alpha expression and necrosis in granulomas. *PLoS One* 4:e4228 <http://dx.doi.org/10.1371/journal.pone.0004228>.
293. Mazzarella G, Bianco A, Perna F, D'Auria D, Grella E, Moscardello E, Sanduzzi A. 2003. T lymphocyte phenotypic profile in lung segments affected by cavitary and non-cavitary tuberculosis. *Clin Exp Immunol* 132:283–288 <http://dx.doi.org/10.1046/j.1365-2249.2003.02121.x>.
294. Mattila JT, Diedrich CR, Lin PL, Phuah J, Flynn JL. 2011. Simian immunodeficiency virus-induced changes in T cell cytokine responses in cynomolgus macaques with latent *Mycobacterium tuberculosis* infection are associated with timing of reactivation. *J Immunol* 186:3527–3537 <http://dx.doi.org/10.4049/jimmunol.1003773>.
295. Wassie L, Demissie A, Aseffa A, Abebe M, Yamaue L, Tilahun H, Petros B, Rook G, Zumla A, Andersen P, Doherty TM. 2008. Ex vivo cytokine mRNA levels correlate with changing clinical status of Ethiopian TB patients and their contacts over time. *PLoS One* 3:e1522. [doi:10.1371/journal.pone.0001522](http://dx.doi.org/10.1371/journal.pone.0001522).
296. Fletcher HA, Owiafe P, Jeffries D, Hill P, Rook GA, Zumla A, Doherty TM, Brookes RH, Vacsell Study Group. 2004. Increased expression of mRNA encoding interleukin (IL)-4 and its splice variant IL-4delta2 in cells from contacts of *Mycobacterium tuberculosis*, in the absence of in vitro stimulation. *Immunology* 112:669–673 <http://dx.doi.org/10.1111/j.1365-2567.2004.01922.x>.
297. Demissie A, Abebe M, Aseffa A, Rook G, Fletcher H, Zumla A, Weldingh K, Brock I, Andersen P, Doherty TM, VACSEL Study Group. 2004. Healthy individuals that control a latent infection with *Mycobacterium tuberculosis* express high levels of Th1 cytokines and the IL-4 antagonist IL-4delta2. *J Immunol* 172:6938–6943 <http://dx.doi.org/10.4049/jimmunol.172.11.6938>.
298. Jung YJ, LaCourse R, Ryan L, North RJ. 2002. Evidence inconsistent with a negative influence of T helper 2 cells on protection afforded by a dominant T helper 1 response against *Mycobacterium tuberculosis* lung infection in mice. *Infect Immun* 70:6436–6443 <http://dx.doi.org/10.1128/IAI.70.11.6436-6443.2002>.
299. North RJ. 1998. Mice incapable of making IL-4 or IL-10 display normal resistance to infection with *Mycobacterium tuberculosis*. *Clin Exp Immunol* 113:55–58 <http://dx.doi.org/10.1046/j.1365-2249.1998.00636.x>.
300. Lukacs NW, Addison CL, Gaudie J, Graham F, Simpson K, Strieter RM, Warmington K, Chensue SW, Kunkel SL. 1997. Transgene-induced production of IL-4 alters the development and collagen expression of T helper cell 1-type pulmonary granulomas. *J Immunol* 158:4478–4484.
301. Ramakrishnan L. 2012. Revisiting the role of the granuloma in tuberculosis. *Nat Rev Immunol* 12:352–366.
302. Erb KJ, Kirman J, Delahunt B, Chen W, Le Gros G. 1998. IL-4, IL-5 and IL-10 are not required for the control of *M. bovis*-BCG infection in mice. *Immunol Cell Biol* 76:41–46 <http://dx.doi.org/10.1046/j.1440-1711.1998.00719.x>.
303. Diedrich CR, Mattila JT, Flynn JL. 2013. Monocyte-derived IL-5 reduces TNF production by *Mycobacterium tuberculosis*-specific CD4 T cells during SIV/M. tuberculosis coinfection. *J Immunol* 190:6320–6328 <http://dx.doi.org/10.4049/jimmunol.1202043>.
304. Minty A, Chalou P, Derocq J-M, Dumont X, Guillemot J-C, Kaghad M, Labit C, Leplatois P, Liauzun P, Miloux B, Minty C, Casellas P, Loison G, Lupker J, Shire D, Ferrara P, Caput D. 1993. Interleukin-13 is a new human lymphokine regulating inflammatory and immune responses. *Nature* 362:248–250 <http://dx.doi.org/10.1038/362248a0>.
305. McKenzie AN, Culpepper JA, de Waal Malefyt R, Briere F, Punnonen J, Aversa G, Sato A, Dang W, Cocks BG, Menon S. 1993. Interleukin 13, a T-cell-derived cytokine that regulates human monocyte and B-cell function. *Proc Natl Acad Sci USA* 90:3735–3739 <http://dx.doi.org/10.1073/pnas.90.8.3735>.
306. Wynn TA. 2003. IL-13 effector functions. *Annu Rev Immunol* 21:425–456 <http://dx.doi.org/10.1146/annurev.immunol.21.120601.141142>.
307. Zhu Z, Homer RJ, Wang Z, Chen Q, Geba GP, Wang J, Zhang Y, Elias JA. 1999. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest* 103:779–788 <http://dx.doi.org/10.1172/JCI5909>.
308. Wynn TA, Eltoum I, Oswald IP, Cheever AW, Sher A. 1994. Endogenous interleukin 12 (IL-12) regulates granuloma formation induced by eggs of *Schistosoma mansoni* and exogenous IL-12 both inhibits and prophylactically immunizes against egg pathology. *J Exp Med* 179:1551–1561 <http://dx.doi.org/10.1084/jem.179.5.1551>.

309. Gessner A, Mohrs K, Mohrs M. 2005. Mast cells, basophils, and eosinophils acquire constitutive IL-4 and IL-13 transcripts during lineage differentiation that are sufficient for rapid cytokine production. *J Immunol* 174:1063–1072 <http://dx.doi.org/10.4049/jimmunol.174.2.1063>.
310. Ying S, Humbert M, Barkans J, Corrigan CJ, Pfister R, Menz G, Larché M, Robinson DS, Durham SR, Kay AB. 1997. Expression of IL-4 and IL-5 mRNA and protein product by CD4+ and CD8+ T cells, eosinophils, and mast cells in bronchial biopsies obtained from atopic and nonatopic (intrinsic) asthmatics. *J Immunol* 158:3539–3544.
311. O'Brien TF, Bao K, Dell'Aringa M, Ang WX, Abraham S, Reinhardt RL. 2016. Cytokine expression by invariant natural killer T cells is tightly regulated throughout development and settings of type-2 inflammation. *Mucosal Immunol* 9:597–609. [doi:10.1038/mi.2015.78](http://dx.doi.org/10.1038/mi.2015.78).
312. Bao K, Reinhardt RL. 2015. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. *Cytokine* 75:25–37 <http://dx.doi.org/10.1016/j.cyto.2015.05.008>.
313. McCormick SM, Heller NM. 2015. Commentary: IL-4 and IL-13 receptors and signaling. *Cytokine* 75:38–50 <http://dx.doi.org/10.1016/j.cyto.2015.05.023>.
314. Dhanasekaran S, Jenum S, Stavrum R, Ritz C, Faurholt-Jepsen D, Kenneth J, Vaz M, Grewal HM, Doherty TM, Doherty M, Grewal HMS, Hesseling AC, Jacob A, Jahnsen F, Kenneth J, Kurpad AV, Lindtjorn B, Macaden R, Nelson J, Sumithra S, Vaz M, Walker R, TB Trials Study Group. 2013. Identification of biomarkers for *Mycobacterium tuberculosis* infection and disease in BCG-vaccinated young children in Southern India. *Genes Immun* 14:356–364 <http://dx.doi.org/10.1038/gene.2013.26>.
315. Gutierrez MG, Master SS, Singh SB, Taylor GA, Colombo MI, Deretic V. 2004. Autophagy is a defense mechanism inhibiting BCG and *Mycobacterium tuberculosis* survival in infected macrophages. *Cell* 119:753–766 <http://dx.doi.org/10.1016/j.cell.2004.11.038>.
316. Singh SB, Davis AS, Taylor GA, Deretic V. 2006. Human IRGM induces autophagy to eliminate intracellular mycobacteria. *Science* 313:1438–1441 <http://dx.doi.org/10.1126/science.1129577>.
317. Harris J, De Haro SA, Master SS, Keane J, Roberts EA, Delgado M, Deretic V. 2007. T helper 2 cytokines inhibit autophagic control of intracellular *Mycobacterium tuberculosis*. *Immunity* 27:505–517 <http://dx.doi.org/10.1016/j.immuni.2007.07.022>.
318. Heitmann L, Abad Dar M, Schreiber T, Erdmann H, Behrends J, McKenzie ANJ, Brombacher F, Ehlers S, Hölscher C. 2014. The IL-13/IL-4R α axis is involved in tuberculosis-associated pathology. *J Pathol* 234:338–350 <http://dx.doi.org/10.1002/path.4399>.
319. Massagué J. 2012. TGF β signalling in context. *Nat Rev Mol Cell Biol* 13:616–630 <http://dx.doi.org/10.1038/nrm3434>.
320. Feng XH, Derynck R. 2005. Specificity and versatility in TGF- β signaling through Smads. *Annu Rev Cell Dev Biol* 21:659–693 <http://dx.doi.org/10.1146/annurev.cellbio.21.022404.142018>.
321. Massagué J, Seoane J, Wotton D. 2005. Smad transcription factors. *Genes Dev* 19:2783–2810 <http://dx.doi.org/10.1101/gad.1350705>.
322. Trompouki E, Bowman TV, Lawton LN, Fan ZP, Wu DC, DiBiase A, Martin CS, Cech JN, Sessa AK, Leblanc JL, Li P, Durand EM, Mosimann C, Heffner GC, Daley GQ, Paulson RF, Young RA, Zon LI. 2011. Lineage regulators direct BMP and Wnt pathways to cell-specific programs during differentiation and regeneration. *Cell* 147:577–589 <http://dx.doi.org/10.1016/j.cell.2011.09.044>.
323. Taylor AW. 2009. Review of the activation of TGF- β in immunity. *J Leukoc Biol* 85:29–33 <http://dx.doi.org/10.1189/jlb.0708415>.
324. Roberts AB, Sporn MB. 1988. Transforming growth factor beta. *Adv Cancer Res* 51:107–145 [http://dx.doi.org/10.1016/S0065-230X\(08\)60221-3](http://dx.doi.org/10.1016/S0065-230X(08)60221-3).
325. Massagué J. 1990. The transforming growth factor-beta family. *Annu Rev Cell Biol* 6:597–641 <http://dx.doi.org/10.1146/annurev.cb.06.110190.003121>.
326. Letterio JJ, Roberts AB. 1998. Regulation of immune responses by TGF- β . *Annu Rev Immunol* 16:137–161 <http://dx.doi.org/10.1146/annurev.immunol.16.1.137>.
327. Sporn MB, Roberts AB. 1992. Autocrine secretion—10 years later. *Ann Intern Med* 117:408–414 <http://dx.doi.org/10.7326/0003-4819-117-5-408>.
328. Toossi Z, Gogate P, Shiratsuchi H, Young T, Ellner JJ. 1995. Enhanced production of TGF- β by blood monocytes from patients with active tuberculosis and presence of TGF- β in tuberculous granulomatous lung lesions. *J Immunol* 154:465–473.
329. Dahl KE, Shiratsuchi H, Hamilton BD, Ellner JJ, Toossi Z. 1996. Selective induction of transforming growth factor beta in human monocytes by lipoarabinomannan of *Mycobacterium tuberculosis*. *Infect Immun* 64:399–405.
330. Hirsch CS, Yoneda T, Averill L, Ellner JJ, Toossi Z. 1994. Enhancement of intracellular growth of *Mycobacterium tuberculosis* in human monocytes by transforming growth factor-beta 1. *J Infect Dis* 170:1229–1237 <http://dx.doi.org/10.1093/infdis/170.5.1229>.
331. Hirsch CS, Ellner JJ, Blinkhorn R, Toossi Z. 1997. In vitro restoration of T cell responses in tuberculosis and augmentation of monocyte effector function against *Mycobacterium tuberculosis* by natural inhibitors of transforming growth factor beta. *Proc Natl Acad Sci USA* 94:3926–3931 <http://dx.doi.org/10.1073/pnas.94.8.3926>.
332. Othieno C, Hirsch CS, Hamilton BD, Wilkinson K, Ellner JJ, Toossi Z. 1999. Interaction of *Mycobacterium tuberculosis*-induced transforming growth factor beta1 and interleukin-10. *Infect Immun* 67:5730–5735.
333. Sivangala R, Ponnana M, Thada S, Joshi L, Ansari S, Hussain H, Valluri V, Gaddam S. 2014. Association of cytokine gene polymorphisms in patients with tuberculosis and their household contacts. *Scand J Immunol* 79:197–205 <http://dx.doi.org/10.1111/sji.12136>.
334. Mak JC, Leung HC, Sham AS, Mok TY, Poon YN, Ling SO, Wong KC, Chan-Yeung M. 2007. Genetic polymorphisms and plasma levels of transforming growth factor-beta(1) in Chinese patients with tuberculosis in Hong Kong. *Cytokine* 40:177–182 <http://dx.doi.org/10.1016/j.cyto.2007.09.006>.
335. Vieira P, de Waal-Malefyt R, Dang MN, Johnson KE, Kastelein R, Fiorentino DF, deVries JE, Roncarolo MG, Mosmann TR, Moore KW. 1991. Isolation and expression of human cytokine synthesis inhibitory factor cDNA clones: homology to Epstein-Barr virus open reading frame BCRF1. *Proc Natl Acad Sci USA* 88:1172–1176 <http://dx.doi.org/10.1073/pnas.88.4.1172>.
336. Redford PS, Murray PJ, O'Garra A. 2011. The role of IL-10 in immune regulation during *M. tuberculosis* infection. *Mucosal Immunol* 4:261–270 <http://dx.doi.org/10.1038/mi.2011.7>.
337. Liu Y, Wei SH, Ho AS, de Waal Malefyt R, Moore KW. 1994. Expression cloning and characterization of a human IL-10 receptor. *J Immunol* 152:1821–1829.
338. Jang S, Uematsu S, Akira S, Salgame P. 2004. IL-6 and IL-10 induction from dendritic cells in response to *Mycobacterium tuberculosis* is predominantly dependent on TLR2-mediated recognition. *J Immunol* 173:3392–3397 <http://dx.doi.org/10.4049/jimmunol.173.5.3392>.
339. Rogers NC, Slack EC, Edwards AD, Nolte MA, Schulz O, Schweighoffer E, Williams DL, Gordon S, Tybulewicz VL, Brown GD, Reis e Sousa C. 2005. Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. *Immunity* 22:507–517 <http://dx.doi.org/10.1016/j.immuni.2005.03.004>.
340. Ke Z, Yuan L, Ma J, Zhang X, Guo Y, Xiong H. 2015. IL-10 polymorphisms and tuberculosis susceptibility: an updated meta-analysis. *Yonsei Med J* 56:1274–1287 <http://dx.doi.org/10.3349/ymj.2015.56.5.1274>.
341. Jeong YH, Hur YG, Lee H, Kim S, Cho JE, Chang J, Shin SJ, Lee H, Kang YA, Cho SN, Ha SJ. 2015. Discrimination between active and latent tuberculosis based on ratio of antigen-specific to mitogen-induced IP-10 production. *J Clin Microbiol* 53:504–510 <http://dx.doi.org/10.1128/JCM.02758-14>.
342. Tebruegge M, Dutta B, Donath S, Ritz N, Forbes B, Camacho-Badilla K, Clifford V, Zufferey C, Robins-Browne R, Hanekom W, Graham SM, Connell T, Curtis N. 2015. Mycobacteria-specific cytokine

- responses detect tuberculosis infection and distinguish latent from active tuberculosis. *Am J Respir Crit Care Med* 192:485–499 <http://dx.doi.org/10.1164/rccm.201501-0059OC>.
343. Kumar NP, Moideen K, Banurekha VV, Nair D, Sridhar R, Nutman TB, Babu S. 2015. IL-27 and TGF β mediated expansion of Th1 and adaptive regulatory T cells expressing IL-10 correlates with bacterial burden and disease severity in pulmonary tuberculosis. *Immun Inflamm Dis* 3:289–299 <http://dx.doi.org/10.1002/iid3.68>.
344. Eum SY, Jeon BY, Min JH, Kim SC, Cho S, Park SK, Cho SN. 2008. Tumor necrosis factor- α and interleukin-10 in whole blood is associated with disease progression in pulmonary multidrug-resistant tuberculosis patients. *Respiration* 76:331–337 <http://dx.doi.org/10.1159/000113932>.
345. Lago PM, Bochat N, Migueis DP, Almeida AS, Lazzarini LC, Saldanha MM, Kritski AL, Ho JL, Lapa e Silva JR. 2012. Interleukin-10 and interferon- γ patterns during tuberculosis treatment: possible association with recurrence. *Int J Tuberc Lung Dis* 16:656–659.
346. George PJ, Pavan Kumar N, Jaganathan J, Dolla C, Kumaran P, Nair D, Banurekha VV, Shen K, Nutman TB, Babu S. 2015. Modulation of pro- and anti-inflammatory cytokines in active and latent tuberculosis by coexistent *Strongyloides stercoralis* infection. *Tuberculosis (Edinb)* 95:822–828 <http://dx.doi.org/10.1016/j.tube.2015.09.009>.
347. George PJ, Anuradha R, Kumar NP, Sridhar R, Banurekha VV, Nutman TB, Babu S. 2014. Helminth infections coincident with active pulmonary tuberculosis inhibit mono- and multifunctional CD4+ and CD8+ T cell responses in a process dependent on IL-10. *PLoS Pathog* 10: e1004375 <http://dx.doi.org/10.1371/journal.ppat.1004375>.
348. Verreck FA, de Boer T, Langenberg DM, Hoeve MA, Kramer M, Vaisberg E, Kastelein R, Kolk A, de Waal-Malefyt R, Ottenhoff TH. 2004. Human IL-23-producing type 1 macrophages promote but IL-10-producing type 2 macrophages subvert immunity to (myco)bacteria. *Proc Natl Acad Sci USA* 101:4560–4565 <http://dx.doi.org/10.1073/pnas.0400983101>.
349. O'Leary S, O'Sullivan MP, Keane J. 2011. IL-10 blocks phagosome maturation in *Mycobacterium tuberculosis*-infected human macrophages. *Am J Respir Cell Mol Biol* 45:172–180 <http://dx.doi.org/10.1165/rcmb.2010-0319OC>.
350. Oswald IP, Wynn TA, Sher A, James SL. 1992. Interleukin 10 inhibits macrophage microbicidal activity by blocking the endogenous production of tumor necrosis factor α required as a costimulatory factor for interferon γ -induced activation. *Proc Natl Acad Sci USA* 89:8676–8680 <http://dx.doi.org/10.1073/pnas.89.18.8676>.
351. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. 2001. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 19:683–765 <http://dx.doi.org/10.1146/annurev.immunol.19.1.683>.
352. Richardson ET, Shukla S, Sweet DR, Wearsch PA, Tschlis PN, Boom WH, Harding CV. 2015. Toll-like receptor 2-dependent extracellular signal-regulated kinase signaling in *Mycobacterium tuberculosis*-infected macrophages drives anti-inflammatory responses and inhibits Th1 polarization of responding T cells. *Infect Immun* 83:2242–2254 <http://dx.doi.org/10.1128/IAI.00135-15>.
353. Jung YJ, Ryan L, LaCourse R, North RJ. 2003. Increased interleukin-10 expression is not responsible for failure of T helper 1 immunity to resolve airborne *Mycobacterium tuberculosis* infection in mice. *Immunology* 109:295–299 <http://dx.doi.org/10.1046/j.1365-2567.2003.01645.x>.
354. Higgins DM, Sanchez-Campillo J, Rosas-Taraco AG, Lee EJ, Orme IM, Gonzalez-Juarrero M. 2009. Lack of IL-10 alters inflammatory and immune responses during pulmonary *Mycobacterium tuberculosis* infection. *Tuberculosis (Edinb)* 89:149–157 <http://dx.doi.org/10.1016/j.tube.2009.01.001>.
355. Beamer GL, Flaherty DK, Assogba BD, Stromberg P, Gonzalez-Juarrero M, de Waal Malefyt R, Vesosky B, Turner J. 2008. Interleukin-10 promotes *Mycobacterium tuberculosis* disease progression in CBA/J mice. *J Immunol* 181:5545–5550 <http://dx.doi.org/10.4049/jimmunol.181.8.5545>.
356. Cyktor JC, Carruthers B, Kominsky RA, Beamer GL, Stromberg P, Turner J. 2013. IL-10 inhibits mature fibrotic granuloma formation during *Mycobacterium tuberculosis* infection. *J Immunol* 190:2778–2790 <http://dx.doi.org/10.4049/jimmunol.1202722>.
357. Cilfone NA, Ford CB, Marino S, Mattila JT, Gideon HP, Flynn JL, Kirschner DE, Linderman JJ. 2015. Computational modeling predicts IL-10 control of lesion sterilization by balancing early host immunity-mediated antimicrobial responses with caseation during *Mycobacterium tuberculosis* infection. *J Immunol* 194:664–677 <http://dx.doi.org/10.4049/jimmunol.1400734>.
358. Dorhoi A, Kaufmann SH. 2016. Pathology and immune reactivity: understanding multidimensionality in pulmonary tuberculosis. *Semin Immunopathol* 38:153–166. doi:10.1007/s00281-015-0531-3.
359. Yoshimura T. 2015. Discovery of IL-8/CXCL8 (The Story from Frederick). *Front Immunol* 6:278 <http://dx.doi.org/10.3389/fimmu.2015.00278>.
360. Murphy PM, Baggiolini M, Charo IF, Hbert CA, Horuk R, Matsushima K, Miller LH, Oppenheim JJ, Power CA. 2000. International union of pharmacology. XXII. Nomenclature for chemokine receptors. *Pharmacol Rev* 52:145–176.
361. Murphy PM. 2002. International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. *Pharmacol Rev* 54:227–229 <http://dx.doi.org/10.1124/pr.54.2.227>.
362. Bacon K, Baggiolini M, Broxmeyer H, Horuk R, Lindley I, Mantovani A, Maysushima K, Murphy P, Nomiyama H, Oppenheim J, Rot A, Schall T, Tsang M, Thorpe R, Van Damme J, Wadhwa M, Yoshie O, Zlotnik A, Zoon K, IUIS/WHO Subcommittee on Chemokine Nomenclature. 2002. Chemokine/chemokine receptor nomenclature. *J Interferon Cytokine Res* 22:1067–1068 <http://dx.doi.org/10.1089/107999002760624305>.
363. Zlotnik A, Yoshie O. 2012. The chemokine superfamily revisited. *Immunity* 36:705–716 <http://dx.doi.org/10.1016/j.immuni.2012.05.008>.
364. Zlotnik A, Yoshie O. 2000. Chemokines: a new classification system and their role in immunity. *Immunity* 12:121–127 [http://dx.doi.org/10.1016/S1074-7613\(00\)80165-X](http://dx.doi.org/10.1016/S1074-7613(00)80165-X).
365. Su SB, Mukaida N, Wang J, Nomura H, Matsushima K. 1996. Preparation of specific polyclonal antibodies to a C-C chemokine receptor, CCR1, and determination of CCR1 expression on various types of leukocytes. *J Leukoc Biol* 60:658–666.
366. Neote K, DiGregorio D, Mak JY, Horuk R, Schall TJ. 1993. Molecular cloning, functional expression, and signaling characteristics of a C-C chemokine receptor. *Cell* 72:415–425 [http://dx.doi.org/10.1016/0092-8674\(93\)90118-A](http://dx.doi.org/10.1016/0092-8674(93)90118-A).
367. Gao JL, Kuhns DB, Tiffany HL, McDermott D, Li X, Francke U, Murphy PM. 1993. Structure and functional expression of the human macrophage inflammatory protein 1 α /RANTES receptor. *J Exp Med* 177:1421–1427 <http://dx.doi.org/10.1084/jem.177.5.1421>.
368. Gao JL, Murphy PM. 1995. Cloning and differential tissue-specific expression of three mouse beta chemokine receptor-like genes, including the gene for a functional macrophage inflammatory protein-1 α receptor. *J Biol Chem* 270:17494–17501 <http://dx.doi.org/10.1074/jbc.270.29.17494>.
369. Kaufmann A, Salentin R, Gerns D, Sprenger H. 2001. Increase of CCR1 and CCR5 expression and enhanced functional response to MIP-1 α during differentiation of human monocytes to macrophages. *J Leukoc Biol* 69:248–252.
370. Cheng SS, Lai JJ, Lukacs NW, Kunkel SL. 2001. Granulocyte-macrophage colony stimulating factor up-regulates CCR1 in human neutrophils. *J Immunol* 166:1178–1184 <http://dx.doi.org/10.4049/jimmunol.166.2.1178>.
371. Pokkali S, Das SD, Logamurthy R. 2008. Expression of CXC and CC type of chemokines and its receptors in tuberculous and non-tuberculous effusions. *Cytokine* 41:307–314 <http://dx.doi.org/10.1016/j.cyto.2007.12.009>.

372. Pokkali S, Das SD. 2009. Augmented chemokine levels and chemokine receptor expression on immune cells during pulmonary tuberculosis. *Hum Immunol* 70:110–115 <http://dx.doi.org/10.1016/j.humimm.2008.11.003>.
373. Hilda JN, Narasimhan M, Das SD. 2014. Neutrophils from pulmonary tuberculosis patients show augmented levels of chemokines MIP-1 α , IL-8 and MCP-1 which further increase upon in vitro infection with mycobacterial strains. *Hum Immunol* 75:914–922 <http://dx.doi.org/10.1016/j.humimm.2014.06.020>.
374. Saukkonen JJ, Bazydlo B, Thomas M, Strieter RM, Keane J, Kornfeld H. 2002. Beta-chemokines are induced by *Mycobacterium tuberculosis* and inhibit its growth. *Infect Immun* 70:1684–1693 <http://dx.doi.org/10.1128/IAI.70.4.1684-1693.2002>.
375. Algood HM, Flynn JL. 2004. CCR5-deficient mice control *Mycobacterium tuberculosis* infection despite increased pulmonary lymphocytic infiltration. *J Immunol* 173:3287–3296 <http://dx.doi.org/10.4049/jimmunol.173.5.3287>.
376. Randolph GJ, Ochando J, Partida-Sánchez S. 2008. Migration of dendritic cell subsets and their precursors. *Annu Rev Immunol* 26:293–316 <http://dx.doi.org/10.1146/annurev.immunol.26.021607.090254>.
377. Glatzel A, Wesch D, Schiemann F, Brandt E, Janssen O, Kabelitz D. 2002. Patterns of chemokine receptor expression on peripheral blood gamma delta T lymphocytes: strong expression of CCR5 is a selective feature of V delta 2/V gamma 9 gamma delta T cells. *J Immunol* 168:4920–4929 <http://dx.doi.org/10.4049/jimmunol.168.10.4920>.
378. Tsou CL, Peters W, Si Y, Slaymaker S, Aslanian AM, Weisberg SP, Mack M, Charo IF. 2007. Critical roles for CCR2 and MCP-3 in monocyte mobilization from bone marrow and recruitment to inflammatory sites. *J Clin Invest* 117:902–909 <http://dx.doi.org/10.1172/JCI29919>.
379. Hasan Z, Jamil B, Khan J, Ali R, Khan MA, Nasir N, Yusuf MS, Jamil S, Irfan M, Hussain R. 2009. Relationship between circulating levels of IFN-gamma, IL-10, CXCL9 and CCL2 in pulmonary and extra-pulmonary tuberculosis is dependent on disease severity. *Scand J Immunol* 69:259–267 <http://dx.doi.org/10.1111/j.1365-3083.2008.02217.x>.
380. Scott HM, Flynn JL. 2002. *Mycobacterium tuberculosis* in chemokine receptor 2-deficient mice: influence of dose on disease progression. *Infect Immun* 70:5946–5954 <http://dx.doi.org/10.1128/IAI.70.11.5946-5954.2002>.
381. Peters W, Scott HM, Chambers HF, Flynn JL, Charo IF, Ernst JD. 2001. Chemokine receptor 2 serves an early and essential role in resistance to *Mycobacterium tuberculosis*. *Proc Natl Acad Sci USA* 98:7958–7963 <http://dx.doi.org/10.1073/pnas.131207398>.
382. Lu B, Rutledge BJ, Gu L, Fiorillo J, Lukacs NW, Kunkel SL, North R, Gerard C, Rollins BJ. 1998. Abnormalities in monocyte recruitment and cytokine expression in monocyte chemoattractant protein 1-deficient mice. *J Exp Med* 187:601–608 <http://dx.doi.org/10.1084/jem.187.4.601>.
383. Kipnis A, Basaraba RJ, Orme IM, Cooper AM. 2003. Role of chemokine ligand 2 in the protective response to early murine pulmonary tuberculosis. *Immunology* 109:547–551 <http://dx.doi.org/10.1046/j.1365-2567.2003.01680.x>.
384. Iellem A, Mariani M, Lang R, Recalde H, Panina-Bordignon P, Sinigaglia F, D'Ambrosio D. 2001. Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by CD4(+)CD25(+) regulatory T cells. *J Exp Med* 194:847–854 <http://dx.doi.org/10.1084/jem.194.6.847>.
385. Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, Evdemon-Hogan M, Conejo-Garcia JR, Zhang L, Burow M, Zhu Y, Wei S, Kryczek I, Daniel B, Gordon A, Myers L, Lackner A, Disis ML, Knutson KL, Chen L, Zou W. 2004. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med* 10:942–949 <http://dx.doi.org/10.1038/nm1093>.
386. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, Sallusto F, Napolitani G. 2007. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol* 8:639–646 <http://dx.doi.org/10.1038/ni1467>.
387. Kunkel EJ, Boisvert J, Murphy K, Vierra MA, Genovese MC, Wardlaw AJ, Greenberg HB, Hodge MR, Wu L, Butcher EC, Campbell JJ. 2002. Expression of the chemokine receptors CCR4, CCR5, and CXCR3 by human tissue-infiltrating lymphocytes. *Am J Pathol* 160:347–355 [http://dx.doi.org/10.1016/S0002-9440\(10\)64378-7](http://dx.doi.org/10.1016/S0002-9440(10)64378-7).
388. Hu Z, Lancaster JN, Sasiponganan C, Ehrlich LI. 2015. CCR4 promotes medullary entry and thymocyte-dendritic cell interactions required for central tolerance. *J Exp Med* 212:1947–1965 <http://dx.doi.org/10.1084/jem.20150178>.
389. Cowan JE, McCarthy NI, Parnell SM, White AJ, Bacon A, Serge A, Irla M, Lane PJ, Jenkinson EJ, Jenkinson WE, Anderson G. 2014. Differential requirement for CCR4 and CCR7 during the development of innate and adaptive $\alpha\beta$ T cells in the adult thymus. *J Immunol* 193:1204–1212 <http://dx.doi.org/10.4049/jimmunol.1400993>.
390. Andrew DP, Ruffing N, Kim CH, Miao W, Heath H, Li Y, Murphy K, Campbell JJ, Butcher EC, Wu L. 2001. C-C chemokine receptor 4 expression defines a major subset of circulating nonintestinal memory T cells of both Th1 and Th2 potential. *J Immunol* 166:103–111 <http://dx.doi.org/10.4049/jimmunol.166.1.103>.
391. Paul WE, Zhu J. 2010. How are T(H)2-type immune responses initiated and amplified? *Nat Rev Immunol* 10:225–235 <http://dx.doi.org/10.1038/nri2735>.
392. Oliphant CJ, Barlow JL, McKenzie AN. 2011. Insights into the initiation of type 2 immune responses. *Immunology* 134:378–385 <http://dx.doi.org/10.1111/j.1365-2567.2011.03499.x>.
393. Li L, Lao SH, Wu CY. 2007. Increased frequency of CD4(+)CD25 (high) Treg cells inhibit BCG-specific induction of IFN-gamma by CD4(+) T cells from TB patients. *Tuberculosis (Edinb)* 87:526–534 <http://dx.doi.org/10.1016/j.tube.2007.07.004>.
394. Roberts T, Beyers N, Aguirre A, Walzl G. 2007. Immunosuppression during active tuberculosis is characterized by decreased interferon- gamma production and CD25 expression with elevated forkhead box P3, transforming growth factor- beta, and interleukin-4 mRNA levels. *J Infect Dis* 195:870–878 <http://dx.doi.org/10.1086/511277>.
395. Bayry J, Tchilian EZ, Davies MN, Forbes EK, Draper SJ, Kaveri SV, Hill AV, Kazatchkine MD, Beverley PC, Flower DR, Tough DF. 2008. In silico identified CCR4 antagonists target regulatory T cells and exert adjuvant activity in vaccination. *Proc Natl Acad Sci USA* 105:10221–10226 <http://dx.doi.org/10.1073/pnas.0803453105>.
396. Feng Y, Yin H, Mai G, Mao L, Yue J, Xiao H, Hu Z. 2011. Elevated serum levels of CCL17 correlate with increased peripheral blood platelet count in patients with active tuberculosis in China. *Clin Vaccine Immunol* 18:629–632 <http://dx.doi.org/10.1128/CVI.00493-10>.
397. Freeman CM, Stolberg VR, Chiu BC, Lukacs NW, Kunkel SL, Chensue SW. 2006. CCR4 participation in Th type 1 (mycobacterial) and Th type 2 (schistosomal) anamnestic pulmonary granulomatous responses. *J Immunol* 177:4149–4158 <http://dx.doi.org/10.4049/jimmunol.177.6.4149>.
398. Dragic T, Litwin V, Allaway GP, Martin SR, Huang Y, Nagashima KA, Cayanan C, Maddon PJ, Koup RA, Moore JP, Paxton WA. 1996. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* 381:667–673 <http://dx.doi.org/10.1038/381667a0>.
399. Deng H, Liu R, Ellmeier W, Choe S, Unutmaz D, Burkhardt M, Di Marzio P, Marmor S, Sutton RE, Hill CM, Davis CB, Peiper SC, Schall TJ, Littman DR, Landau NR. 1996. Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 381:661–666 <http://dx.doi.org/10.1038/381661a0>.
400. Chu SF, Tam CM, Wong HS, Kam KM, Lau YL, Chiang AK. 2007. Association between RANTES functional polymorphisms and tuberculosis in Hong Kong Chinese. *Genes Immun* 8:475–479 <http://dx.doi.org/10.1038/sj.gene.6364412>.
401. Vesosky B, Rottinghaus EK, Stromberg P, Turner J, Beamer G. 2010. CCL5 participates in early protection against *Mycobacterium tuberculosis*. *J Leukoc Biol* 87:1153–1165 <http://dx.doi.org/10.1189/jlb.1109742>.

402. Mantovani A. 1999. The chemokine system: redundancy for robust outputs. *Immunol Today* 20:254–257 [http://dx.doi.org/10.1016/S0167-5699\(99\)01469-3](http://dx.doi.org/10.1016/S0167-5699(99)01469-3).
403. Schutysse E, Struyf S, Van Damme J. 2003. The CC chemokine CCL20 and its receptor CCR6. *Cytokine Growth Factor Rev* 14:409–426 [http://dx.doi.org/10.1016/S1359-6101\(03\)00049-2](http://dx.doi.org/10.1016/S1359-6101(03)00049-2).
404. Ito T, Carson WF 4th, Cavassani KA, Connett JM, Kunkel SL. 2011. CCR6 as a mediator of immunity in the lung and gut. *Exp Cell Res* 317:613–619 <http://dx.doi.org/10.1016/j.yexcr.2010.12.018>.
405. Nandi B, Pai C, Huang Q, Prabhala RH, Munshi NC, Gold JS. 2014. CCR6, the sole receptor for the chemokine CCL20, promotes spontaneous intestinal tumorigenesis. *PLoS One* 9:e97566 <http://dx.doi.org/10.1371/journal.pone.0097566>.
406. Lee AY, Körner H. 2014. CCR6 and CCL20: emerging players in the pathogenesis of rheumatoid arthritis. *Immunol Cell Biol* 92:354–358 <http://dx.doi.org/10.1038/icb.2013.97>.
407. Stolberg VR, Chiu BC, Martin BE, Shah SA, Sandor M, Chensue SW. 2011. Cysteine-cysteinyll chemokine receptor 6 mediates invariant natural killer T cell airway recruitment and innate stage resistance during mycobacterial infection. *J Innate Immun* 3:99–108 <http://dx.doi.org/10.1159/000321156>.
408. Perreau M, Rozot V, Welles HC, Belluti-Enders F, Vigano S, Maillard M, Dorta G, Mazza-Stalder J, Bart PA, Roger T, Calandra T, Nicod L, Harari A. 2013. Lack of *Mycobacterium tuberculosis*-specific interleukin-17A-producing CD4+ T cells in active disease. *Eur J Immunol* 43:939–948 <http://dx.doi.org/10.1002/eji.201243090>.
409. Lindestam Arlehamn CS, Gerasimova A, Mele F, Henderson R, Swann J, Greenbaum JA, Kim Y, Sidney J, James EA, Taplitz R, McKinney DM, Kwok WW, Grey H, Sallusto F, Peters B, Sette A. 2013. Memory T cells in latent *Mycobacterium tuberculosis* infection are directed against three antigenic islands and largely contained in a CXCR3+CCR6+ Th1 subset. *PLoS Pathog* 9:e1003130 <http://dx.doi.org/10.1371/journal.ppat.1003130>.
410. Rivero-Lezcano OM, González-Cortés C, Reyes-Ruvalcaba D, Díez-Tascón C. 2010. CCL20 is overexpressed in *Mycobacterium tuberculosis*-infected monocytes and inhibits the production of reactive oxygen species (ROS). *Clin Exp Immunol* 162:289–297 <http://dx.doi.org/10.1111/j.1365-2249.2010.04168.x>.
411. Lee JS, Lee JY, Son JW, Oh JH, Shin DM, Yuk JM, Song CH, Paik TH, Jo EK. 2008. Expression and regulation of the CC-chemokine ligand 20 during human tuberculosis. *Scand J Immunol* 67:77–85 <http://dx.doi.org/10.1111/j.1365-3083.2007.02040.x>.
412. Kang DD, Lin Y, Moreno JR, Randall TD, Khader SA. 2011. Profiling early lung immune responses in the mouse model of tuberculosis. *PLoS One* 6:e16161 <http://dx.doi.org/10.1371/journal.pone.0016161>.
413. Mehra S, Pahar B, Dutta NK, Conerly CN, Philippi-Falkenstein K, Alvarez X, Kaushal D. 2010. Transcriptional reprogramming in non-human primate (rhesus macaque) tuberculosis granulomas. *PLoS One* 5:e12266 <http://dx.doi.org/10.1371/journal.pone.0012266>.
414. Förster R, Davalos-Misslitz AC, Rot A. 2008. CCR7 and its ligands: balancing immunity and tolerance. *Nat Rev Immunol* 8:362–371 <http://dx.doi.org/10.1038/nri2297>.
415. Gunn MD, Kyuwa S, Tam C, Kakiuchi T, Matsuzawa A, Williams LT, Nakano H. 1999. Mice lacking expression of secondary lymphoid organ chemokine have defects in lymphocyte homing and dendritic cell localization. *J Exp Med* 189:451–460 <http://dx.doi.org/10.1084/jem.189.3.451>.
416. Kahnert A, Höpken UE, Stein M, Bandermann S, Lipp M, Kaufmann SH. 2007. *Mycobacterium tuberculosis* triggers formation of lymphoid structure in murine lungs. *J Infect Dis* 195:46–54 <http://dx.doi.org/10.1086/508894>.
417. Gunn MD, Tangemann K, Tam C, Cyster JG, Rosen SD, Williams LT. 1998. A chemokine expressed in lymphoid high endothelial venules promotes the adhesion and chemotaxis of naive T lymphocytes. *Proc Natl Acad Sci USA* 95:258–263 <http://dx.doi.org/10.1073/pnas.95.1.258>.
418. Sacki H, Moore AM, Brown MJ, Hwang ST. 1999. Cutting edge: secondary lymphoid-tissue chemokine (SLC) and CC chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes. *J Immunol* 162:2472–2475.
419. Bhatt K, Hickman SP, Salgame P. 2004. Cutting edge: a new approach to modeling early lung immunity in murine tuberculosis. *J Immunol* 172:2748–2751 <http://dx.doi.org/10.4049/jimmunol.172.5.2748>.
420. Olmos S, Stukes S, Ernst JD. 2010. Ectopic activation of *Mycobacterium tuberculosis*-specific CD4+ T cells in lungs of CCR7-/- mice. *J Immunol* 184:895–901 <http://dx.doi.org/10.4049/jimmunol.0901230>.
421. Nakano H, Gunn MD. 2001. Gene duplications at the chemokine locus on mouse chromosome 4: multiple strain-specific haplotypes and the deletion of secondary lymphoid-organ chemokine and EBI-1 ligand chemokine genes in the plt mutation. *J Immunol* 166:361–369 <http://dx.doi.org/10.4049/jimmunol.166.1.361>.
422. Khader SA, Rangel-Moreno J, Fountain JJ, Martino CA, Reiley WW, Pearl JE, Winslow GM, Woodland DL, Randall TD, Cooper AM. 2009. In a murine tuberculosis model, the absence of homeostatic chemokines delays granuloma formation and protective immunity. *J Immunol* 183:8004–8014 <http://dx.doi.org/10.4049/jimmunol.0901937>.
423. Allen SJ, Crown SE, Handel TM. 2007. Chemokine: receptor structure, interactions, and antagonism. *Annu Rev Immunol* 25:787–820 <http://dx.doi.org/10.1146/annurev.immunol.24.021605.090529>.
424. Strieter RM, Polverini PJ, Kunkel SL, Arenberg DA, Burdick MD, Kasper J, Dzuiba J, Van Damme J, Walz A, Marriott D, Chan S-Y, Roczniak S, Shanafelt AB. 1995. The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem* 270:27348–27357 <http://dx.doi.org/10.1074/jbc.270.45.27348>.
425. Hébert CA, Vitangcol RV, Baker JB. 1991. Scanning mutagenesis of interleukin-8 identifies a cluster of residues required for receptor binding. *J Biol Chem* 266:18989–18994.
426. Clark-Lewis I, Dewald B, Geiser T, Moser B, Baggiolini M. 1993. Platelet factor 4 binds to interleukin 8 receptors and activates neutrophils when its N terminus is modified with Glu-Leu-Arg. *Proc Natl Acad Sci USA* 90:3574–3577 <http://dx.doi.org/10.1073/pnas.90.8.3574>.
427. Jones SA, Moser B, Thelen M. 1995. A comparison of post-receptor signal transduction events in Jurkat cells transfected with either IL-8R1 or IL-8R2. Chemokine mediated activation of p42/p44 MAP-kinase (ERK-2). *FEBS Lett* 364:211–214 [http://dx.doi.org/10.1016/0014-5793\(95\)00397-R](http://dx.doi.org/10.1016/0014-5793(95)00397-R).
428. Slight SR, Khader SA. 2013. Chemokines shape the immune responses to tuberculosis. *Cytokine Growth Factor Rev* 24:105–113 <http://dx.doi.org/10.1016/j.cytogfr.2012.10.002>.
429. Alaridah N, Winqvist N, Håkansson G, Tenland E, Rönnholm A, Sturegård E, Björkman P, Godaly G. 2015. Impaired CXCR1-dependent oxidative defence in active tuberculosis patients. *Tuberculosis (Edinb)* 95:744–750 <http://dx.doi.org/10.1016/j.tube.2015.07.008>.
430. Gonçalves AS, Appelberg R. 2002. The involvement of the chemokine receptor CXCR2 in neutrophil recruitment in LPS-induced inflammation and in *Mycobacterium avium* infection. *Scand J Immunol* 55:585–591 <http://dx.doi.org/10.1046/j.1365-3083.2002.01097.x>.
431. O'Kane CM, Boyle JJ, Horncastle DE, Elkington PT, Friedland JS. 2007. Monocyte-dependent fibroblast CXCL8 secretion occurs in tuberculosis and limits survival of mycobacteria within macrophages. *J Immunol* 178:3767–3776 <http://dx.doi.org/10.4049/jimmunol.178.6.3767>.
432. Friedland JS, Remick DG, Shattock R, Griffin GE. 1992. Secretion of interleukin-8 following phagocytosis of *Mycobacterium tuberculosis* by human monocyte cell lines. *Eur J Immunol* 22:1373–1378 <http://dx.doi.org/10.1002/eji.1830220607>.
433. Zhang Y, Broser M, Cohen H, Bodkin M, Law K, Reibman J, Rom WN. 1995. Enhanced interleukin-8 release and gene expression in macrophages after exposure to *Mycobacterium tuberculosis* and its components. *J Clin Invest* 95:586–592 <http://dx.doi.org/10.1172/JCI117702>.

434. Lin Y, Zhang M, Barnes PF. 1998. Chemokine production by a human alveolar epithelial cell line in response to *Mycobacterium tuberculosis*. *Infect Immun* 66:1121–1126.
435. Kurashima K, Mukaida N, Fujimura M, Yasui M, Nakazumi Y, Matsuda T, Matsushima K. 1997. Elevated chemokine levels in bronchoalveolar lavage fluid of tuberculosis patients. *Am J Respir Crit Care Med* 155:1474–1477 <http://dx.doi.org/10.1164/ajrccm.155.4.9105097>.
436. Larsen CG, et al. 1995. The delayed-type hypersensitivity reaction is dependent on IL-8. Inhibition of a tuberculin skin reaction by an anti-IL-8 monoclonal antibody. *J Immunol* 155:2151–2157.
437. Ma X, Reich RA, Wright JA, Tooker HR, Teeter LD, Musser JM, Graviss EA. 2003. Association between interleukin-8 gene alleles and human susceptibility to tuberculosis disease. *J Infect Dis* 188:349–355 <http://dx.doi.org/10.1086/376559>.
438. Cooke GS, Campbell SJ, Fielding K, Sillah J, Manneh K, Sirugo G, Bennett S, McAdam KP, Lienhardt C, Hill AV. 2004. Interleukin-8 polymorphism is not associated with pulmonary tuberculosis in the gambia. *J Infect Dis* 189:1545–1546, author reply 1546 <http://dx.doi.org/10.1086/382489>.
439. Almeida CS, Abramo C, Alves CC, Mazzocchi L, Ferreira AP, Teixeira HC. 2009. Anti-mycobacterial treatment reduces high plasma levels of CXCL-chemokines detected in active tuberculosis by cytometric bead array. *Mem Inst Oswaldo Cruz* 104:1039–1041 <http://dx.doi.org/10.1590/S0074-02762009000700018>.
440. Nouailles G, Dorhoi A, Koch M, Zerrahn J, Weiner J III, Faé KC, Arrey F, Kuhlmann S, Banderhann S, Loewe D, Mollenkopf HJ, Vogelzang A, Meyer-Schwesinger C, Mittrücker HW, McEwen G, Kaufmann SH. 2014. CXCL5-secreting pulmonary epithelial cells drive destructive neutrophilic inflammation in tuberculosis. *J Clin Invest* 124:1268–1282 <http://dx.doi.org/10.1172/JCI72030>.
441. Groom JR, Luster AD. 2011. CXCR3 in T cell function. *Exp Cell Res* 317:620–631 <http://dx.doi.org/10.1016/j.yexcr.2010.12.017>.
442. Thomas SY, Hou R, Boyson JE, Means TK, Hess C, Olson DP, Strominger JL, Brenner MB, Gumperz JE, Wilson SB, Luster AD. 2003. CD1d-restricted NKT cells express a chemokine receptor profile indicative of Th1-type inflammatory homing cells. *J Immunol* 171:2571–2580 <http://dx.doi.org/10.4049/jimmunol.171.5.2571>.
443. Qin S, Rottman JB, Myers P, Kassam N, Weinblatt M, Loetscher M, Koch AE, Moser B, Mackay CR. 1998. The chemokine receptors CXCR3 and CCR5 mark subsets of T cells associated with certain inflammatory reactions. *J Clin Invest* 101:746–754 <http://dx.doi.org/10.1172/JCI1422>.
444. Lu B, Humbles A, Bota D, Gerard C, Moser B, Soler D, Luster AD, Gerard NP. 1999. Structure and function of the murine chemokine receptor CXCR3. *Eur J Immunol* 29:3804–3812 [http://dx.doi.org/10.1002/\(SICI\)1521-4141\(199911\)29:11<3804::AID-IMMU3804>3.0.CO;2-9](http://dx.doi.org/10.1002/(SICI)1521-4141(199911)29:11<3804::AID-IMMU3804>3.0.CO;2-9).
445. Campanella GS, Grimm J, Manice LA, Colvin RA, Medoff BD, Wojtkiewicz GR, Weissleder R, Luster AD. 2006. Oligomerization of CXCL10 is necessary for endothelial cell presentation and in vivo activity. *J Immunol* 177:6991–6998 <http://dx.doi.org/10.4049/jimmunol.177.10.6991>.
446. Loetscher M, Loetscher P, Brass N, Meese E, Moser B. 1998. Lymphocyte-specific chemokine receptor CXCR3: regulation, chemokine binding and gene localization. *Eur J Immunol* 28:3696–3705 [http://dx.doi.org/10.1002/\(SICI\)1521-4141\(199811\)28:11<3699::AID-IMMU3399>3.0.CO;2-W](http://dx.doi.org/10.1002/(SICI)1521-4141(199811)28:11<3699::AID-IMMU3399>3.0.CO;2-W).
447. Shields PL, Morland CM, Salmon M, Qin S, Hubscher SG, Adams DH. 1999. Chemokine and chemokine receptor interactions provide a mechanism for selective T cell recruitment to specific liver compartments within hepatitis C-infected liver. *J Immunol* 163:6236–6243.
448. Seiler P, Aichele P, Banderhann S, Hauser AE, Lu B, Gerard NP, Gerard C, Ehlers S, Mollenkopf HJ, Kaufmann SH. 2003. Early granuloma formation after aerosol *Mycobacterium tuberculosis* infection is regulated by neutrophils via CXCR3-signaling chemokines. *Eur J Immunol* 33:2676–2686 <http://dx.doi.org/10.1002/eji.200323956>.
449. Chakravarty SD, Xu J, Lu B, Gerard C, Flynn J, Chan J. 2007. The chemokine receptor CXCR3 attenuates the control of chronic *Mycobacterium tuberculosis* infection in BALB/c mice. *J Immunol* 178:1723–1735 <http://dx.doi.org/10.4049/jimmunol.178.3.1723>.
450. Hasan Z, Jamil B, Ashraf M, Islam M, Dojki M, Irfan M, Hussain R. 2009. Differential live *Mycobacterium tuberculosis*-, *M. bovis* BCG-, recombinant ESAT6-, and culture filtrate protein 10-induced immunity in tuberculosis. *Clin Vaccine Immunol* 16:991–998 <http://dx.doi.org/10.1128/CVI.00091-09>.
451. Azzurri A, Sow OY, Amedei A, Bah B, Diallo S, Peri G, Benagiano M, D'Elia MM, Mantovani A, Del Prete G. 2005. IFN-gamma-inducible protein 10 and pentraxin 3 plasma levels are tools for monitoring inflammation and disease activity in *Mycobacterium tuberculosis* infection. *Microbes Infect* 7:1–8 <http://dx.doi.org/10.1016/j.micinf.2004.09.004>.
452. Whittaker E, Gordon A, Kampmann B. 2008. Is IP-10 a better biomarker for active and latent tuberculosis in children than IFNgamma? *PLoS One* 3:e3901 <http://dx.doi.org/10.1371/journal.pone.0003901>.
453. Kibiki GS, Myers LC, Kalombo CF, Hoang SB, Stoler MH, Stroup SE, Houpt ER. 2007. Bronchoalveolar neutrophils, interferon gamma-inducible protein 10 and interleukin-7 in AIDS-associated tuberculosis. *Clin Exp Immunol* 148:254–259 <http://dx.doi.org/10.1111/j.1365-2249.2007.03330.x>.
454. Tang NL, Fan HP, Chang KC, Ching JK, Kong KP, Yew WW, Kam KM, Leung CC, Tam CM, Blackwell J, Chan CY. 2009. Genetic association between a chemokine gene CXCL-10 (IP-10), interferon gamma inducible protein 10) and susceptibility to tuberculosis. *Clin Chim Acta* 406:98–102 <http://dx.doi.org/10.1016/j.cca.2009.06.006>.
455. Loos T, Dekeyser L, Struyf S, Schutyser E, Gijssels K, Gouwy M, Fraeyman A, Put W, Ronsse I, Grillet B, Opdenakker G, Van Damme J, Proost P. 2006. TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: enhanced CXCL9 in autoimmune arthritis. *Lab Invest* 86:902–916 <http://dx.doi.org/10.1038/labinvest.3700453>.
456. Kanda N, Shimizu T, Tada Y, Watanabe S. 2007. IL-18 enhances IFN-gamma-induced production of CXCL9, CXCL10, and CXCL11 in human keratinocytes. *Eur J Immunol* 37:338–350 <http://dx.doi.org/10.1002/eji.200636420>.
457. Basset L, Chevalier S, Danger Y, Arshad MI, Piquet-Pellorce C, Gascan H, Samson M. 2015. Interleukin-27 and IFN γ regulate the expression of CXCL9, CXCL10, and CXCL11 in hepatitis. *J Mol Med (Berl)* 93:1355–1367 <http://dx.doi.org/10.1007/s00109-015-1319-6>.
458. Oo YH, Banz V, Kavanagh D, Liaskou E, Withers DR, Humphreys E, Reynolds GM, Lee-Turner L, Kalia N, Hubscher SG, Klenerman P, Eksteen B, Adams DH. 2012. CXCR3-dependent recruitment and CCR6-mediated positioning of Th-17 cells in the inflamed liver. *J Hepatol* 57:1044–1051 <http://dx.doi.org/10.1016/j.jhep.2012.07.008>.
459. Slight SR, Rangel-Moreno J, Gopal R, Lin Y, Fallert Junecko BA, Mehra S, Selman M, Becerril-Villanueva E, Baquera-Heredia J, Pavon L, Kaushal D, Reinhart TA, Randall TD, Khader SA. 2013. CXCR5⁺ T helper cells mediate protective immunity against tuberculosis. *J Clin Invest* 123:712–726.
460. Vermi W, Lonardi S, Bosisio D, Uguccioni M, Danelon G, Pileri S, Fletcher C, Sozzani S, Zorzi F, Arrighi G, Doglioni C, Ponzoni M, Facchetti F. 2008. Identification of CXCL13 as a new marker for follicular dendritic cell sarcoma. *J Pathol* 216:356–364 <http://dx.doi.org/10.1002/path.2420>.
461. Takagi R, Higashi T, Hashimoto K, Nakano K, Mizuno Y, Okazaki Y, Matsushita S. 2008. B cell chemoattractant CXCL13 is preferentially expressed by human Th17 cell clones. *J Immunol* 181:186–189 <http://dx.doi.org/10.4049/jimmunol.181.1.186>.
462. Gunn MD, Ngo VN, Ansel KM, Eklund EH, Cyster JG, Williams LT. 1998. A B-cell-homing chemokine made in lymphoid follicles activates Burkitt's lymphoma receptor-1. *Nature* 391:799–803 <http://dx.doi.org/10.1038/35876>.
463. Maglione PJ, Xu J, Chan J. 2007. B cells moderate inflammatory progression and enhance bacterial containment upon pulmonary challenge with *Mycobacterium tuberculosis*. *J Immunol* 178:7222–7234 <http://dx.doi.org/10.4049/jimmunol.178.11.7222>.