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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Activating Immunity to Fight a Foe — A New Path**

Richard S. Hotchkiss, M.D., and Steven M. Opal, M.D.

The discovery of antibiotics is perhaps the single most important advance in medicine in the past century. However, the emergence of multidrug-resistant pathogens has rendered many antibiotics ineffective and is fueling a crisis: a dramatically increased incidence of infections refractory to treatment, resulting in more than 35,000 deaths in the United States in 2019. Fortuitously, knowledge of cellular mechanisms of immunity, including those undergirded by subclasses of T cells, is also growing.¹ Recent reports by Amezcua Vesely et al.¹ and Zander et al.² augment this knowledge and provide support for the development of drugs that boost immunity in patients with life-threatening infections.^{3,4}

Death in the context of sepsis has until relatively recently been considered to be the result of hyperinflammation mediated by cytokine storm, but subsequent work revealed this to be an inadequate explanation.^{3,4} Advances in supportive therapies have markedly decreased deaths during the early phases of septic shock; a protracted immunosuppression after the initial inflammatory phase occurs in the large majority of surviving patients.^{3,4} Multiple mechanisms drive immunosuppression, including apoptosis-induced lymphocyte depletion, increased numbers of myeloid-derived suppressor cells and regulatory T cells, and T-cell exhaustion. The effect of immunosuppression is manifested by the incidence of new secondary infections, often due to weakly virulent pathogens, that occur in 30 to 40% of patients with protracted sepsis.^{3,4} Further evidence of the critical role of host immunity in surviving sepsis is suggested by the characteristics of patients who die: older patients, in whom immunosenescence is known to be prevalent, and patients who have alcoholism, are malnourished, or have cancer or serious coexisting conditions that impair the immune system. The reactivation of multiple latent viruses that occurs in 50% of patients with protracted sepsis further illustrates their severe immunosuppression.⁴

Mucosal-associated invariant T (MAIT) cells and $\gamma\delta$ T cells are innate-like lymphocytes that line bronchial mucosa and respond rapidly to pathogen invasion by secreting cytokines essential for microbial killing: interferon- γ and interleukin-17. Amezcua Vesely et al. have added CD4 tissue-resident memory T (CD4 T_{RM}) cells to this group: they found that these cells are present in the lung and are derived from effector T_H17 cells (which secrete interleukin-17) and that they eliminate bacteria, including carbapenem-resistant *Klebsiella pneumoniae*, in mouse models of

Figure 1 (facing page). New Therapeutic Paradigm in Infectious Disease.

The current general strategy to treat infectious disease (Panel A) involves the rapid administration of antimicrobial drugs that target the pathogens. In the future (Panel B), immunoadjuvants that activate early-responding immune effector cells (green arrows) or that alleviate immunosuppressive mechanisms (red lines) are likely to be used in addition to antimicrobial agents. Mucosal-associated invariant T (MAIT) cells and $\gamma\delta$ T cells respond rapidly to eliminate invading pathogens. Recent studies identified additional new classes of early-responding immune effector cells, including CD4 and CD8 tissue-resident memory T (CD4 T_{RM} and CD8 T_{RM}) cells that play key roles in host defense.^{1,2} T-cell exhaustion, myeloid-derived suppressor cells (MDSCs), and regulatory T (Treg) cells are important sources of immunosuppression in patients with protracted infections, including sepsis. Interleukin-7, anti-programmed death 1 (PD-1), interferon- γ , and granulocyte-macrophage colony-stimulating factor (GM-CSF) are immunoadjuvants that have been used on a compassionate basis in patients with life-threatening bacterial, fungal, and viral infections and in small clinical trials involving patients with sepsis (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Interleukin-7 and anti-PD-1 activate $\gamma\delta$ T cells and MAIT cells. Interleukin-7 sustains CD4 T_{RM} cells. Anti-PD-1 blocks PD-1 to reverse T-cell exhaustion. APC denotes antigen-presenting cell, IL-7R interleukin-7 receptor, IL-12R interleukin-12 receptor, MHC-I major histocompatibility complex class I, MHC-II major histocompatibility complex class II, MR1 major histocompatibility complex class I-related protein, and TCR T-cell receptor.

infection.¹ They further determined that interleukin-7 was required for maintenance of these CD4 T_{RM} cells in the lung. Zander et al. reported

a new supportive role for CD4 T cells that produce interleukin-21: they stimulate the generation of a subset of CD8 T cells that eliminated

virus-infected cells in a mouse model of latent viral infection.

These studies have implications for the development of experimental immunoadjuvant therapies (Fig. 1). In the past several years, phase 1 and 2 trials of granulocyte-macrophage colony-stimulating factor, interferon- γ , anti-programmed death 1 (PD-1), anti-programmed death ligand 1 (PD-L1), and interleukin-7 were conducted in patients with sepsis. Although the trials were small, the results suggested that the drugs had satisfactory safety profiles, did not induce cytokine storm, and improved indexes of patient immunity.³⁻⁵ Furthermore, there are increasing numbers of case reports documenting clinical improvements in patients receiving immunoadjuvant agents for the treatment of life-threatening infection by pathogens, including JC virus (the causative agent in progressive multifocal leukoencephalopathy), hepatitis C virus, *Staphylococcus aureus*, disseminated candidiasis, and mucormycosis (see the Supplementary Appendix). Several of these immunoadjuvants activate rapidly responding immune cells, including CD4 T_{RM} cells, MAIT cells, and $\gamma\delta$ T cells. Collectively, these studies suggest that immunoadjuvant therapies could be tested experimentally as treatment for otherwise intractable infections, including those occurring in the context of sepsis.

Until recently, most trials that studied ways to boost immunity in patients with sepsis targeted neutrophils and monocytes but not T cells. The immune system is like an orchestra that functions best when all components work harmoniously; by this analogy, the CD4 helper T cell is the conductor. The importance of targeting T cells for an effective immune response is demonstrated in oncology: checkpoint inhibitors that reverse T-cell exhaustion are the current oncologic “superstars” and are included in most ongoing immunotherapy trials. The remarkable power of T cells is underscored by approval of anti-PD-1 and anti-PD-L1 drugs to treat more than 10 highly diverse types of tumor. Interleukin-7, which is currently being tested in several oncology trials, activates not only CD4 and CD8

T cells but also MAIT cells and $\gamma\delta$ T cells. We predict that combination drug therapies will ultimately become the standard for sepsis as well.

What needs to be done? There are more than 1700 immunotherapy trials under way in oncology, whereas almost no trials involving patients with sepsis are under way. Most important, pharmaceutical and National Institutes of Health leaders need vision and courage to support trials that boost host immunity in infectious diseases, including sepsis. The failures of drugs that were tested in previous sepsis trials, almost all of which were designed to block cytokine-mediated hyperinflammation, probably rested on misconceptions of the mechanisms underlying the disorder. Similar intense skepticism regarding immunotherapy pervaded the oncology field until the dramatic success of checkpoint inhibitors. Ideal candidates for immunoadjuvant therapies are patients with hospital-acquired infections, infections with multidrug-resistant bacteria, or fungal infections. These patients almost always have immunosuppression, and mortality among such patients is high. Should immunotherapy prove to be an effective treatment, it could serve as a weapon against increasingly lethal foes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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