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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. Recent reports by Amezcue Vesely et al. and Zander et al. augment this knowledge and provide support for the development of drugs that boost immunity in patients with life-threatening infections.

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. 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. 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 secondary infections, often due to weakly virulent pathogens, that occur in 30 to 40% of patients with protracted sepsis. 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.

Mucosal-associated invariant T (MAIT) cells and γδ 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. Amezcue 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_{17} cells (which secrete interleukin-17) and that they eliminate bacteria, including carbapenem-resistant Klebsiella pneumoniae, in mouse models of...
They further determined that interleukin-7 was required for maintenance of these CD4 $^{+}$ TRM 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 Tamiflu

Current Strategy: Target Is the Pathogen

- **Antibiotics**
- **Antivirals**
- **Antifungals**

Proposed Strategy (in Addition to Antimicrobial Therapy): Target Is Host Immunity

- **GM-CSF**
  - Promotes the production of macrophages, eosinophils, neutrophils, basophils, and monocytes
- **Interferon-γ**
  - Activates macrophages, increases MHC-II expression on APCs, and inhibits viral replication
- **Interleukin-7**
  - Improves maintenance
- **Anti–PD-1**
  - Enhances effector function of T cells

Enhances effector function of T cells

- **Exhausted T cell**
  - Diminishes inhibition of effectors by MDSCs
  - Diminishes immunosuppressor activity of Treg cells

Rapid responder with innate and adaptive immune functions

- **CD4 $^{+}$ T cell**
  - Has cytolytic activity and protects against chronic infection
  - Eliminates bacteria, including carbapenem-resistant strains
  - Produces pro-inflammatory cytokines and lyses infected cells
  - Activates macrophages, assists in dendritic-cell maturation, and promotes expression of MHC-I on APCs

- **CD8 $^{+}$ T cell**
  - Has cytolytic activity and protects against chronic infection

- **Macrophage**
  - Promotes the production of macrophages, eosinophils, neutrophils, basophils, and monocytes
  - Activates macrophages, increases MHC-II expression on APCs, and inhibits viral replication
  - Enhances effector function of T cells
  - Diminishes inhibition of effectors by MDSCs
  - Diminishes immunosuppressor activity of Treg cells
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.2-5 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 γδ 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 γδ 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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