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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Immunotherapy for Sepsis — A New Approach against an Ancient Foe

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

Septic shock is traditionally viewed as an excessive systemic inflammatory reaction to invasive microbial pathogens, yet efforts to improve the outcome of patients with sepsis by means of inhibitors of proinflammatory cytokines and mediators have been unsuccessful. Occasionally, patients present with an exaggerated systemic inflammatory response to highly virulent pathogens (such as in cases of meningococemia) and rapidly succumb. However, the vast majority of patients with sepsis survive the initial insult, only to end up in the intensive care unit with sepsis-induced multiorgan dysfunction days or weeks later. Sepsis-induced immunosuppression is increasingly recognized as the overriding immune dysfunction in these vulnerable patients.¹

The clinical relevance of this immunosuppressed state is evidenced by the frequent occurrence of infection with relatively avirulent and often multidrug-resistant bacterial, viral, or fungal pathogens such as species of *Stenotrophomonas*, *Acinetobacter*, *Candida*, *Pseudomonas*, *Enterococcus*, and cytomegalovirus. In light of progressive antimicrobial resistance and the paucity of new antimicrobial agents entering the developmental pipeline, the care of patients with sepsis is increasingly challenging.² Sepsis can be considered to represent a race between the pathogens and the host immune response; pathogens seek an advantage by incapacitating various aspects of host defenses. For example, they induce the apoptotic depletion of immune effector cells, suppress the expression of major-histocompatibility-complex class II molecules, increase expression of negative costimulatory molecules, increase anti-inflammatory cytokines, and augment levels of regulatory T cells and myeloid-derived suppressor cells (Fig. 1). The prevention of sepsis-induced immunosuppression, or its treatment if it occurs, is a research priority.

A recent study by Said and colleagues³ pro-

vides insights into the molecular mechanisms that underlie immune depression following sustained inflammation, such as occurs in patients with either chronic viral infections or protracted sepsis. These investigators studied a critical monocyte–macrophage protein known as programmed death 1 (PD-1), which is found in patients infected with the human immunodeficiency virus (HIV). PD-1, a negative costimulatory molecule expressed on immune effector cells, is up-regulated along with its cognate ligand PD-L1 (also expressed on effector cells) during chronic HIV infection. Said and colleagues found that microbial mediators translocate across the intestinal epithelium in chronic HIV-induced inflammation and are recognized by toll-like receptors. Persistent activation of the innate immune system by these intestinally derived microbial products up-regulates the expression of PD-1 and PD-L1 on various immune cells.

PD-1 impairs immunity by inducing apoptosis, increasing production of interleukin-10 (a key anti-inflammatory cytokine increased in sepsis), preventing T-cell proliferation, and causing T cells to become nonresponsive (“exhausted”). Said and colleagues described a new mechanism by which the interaction between PD-1 and PD-L1 induces immunosuppression in patients with HIV. They found that PD-1 activation results in the increased production of interleukin-10 by monocytes from persons infected with HIV. Moreover, the PD-1–induced inhibition of CD4 T cells was itself inhibited by the blocking of the interleukin-10 receptor. Thus, PD-1 affects immunosuppression through its effect on interleukin-10 expression. These results suggest that blocking PD-1 may improve the prognosis of patients with any of a variety of chronic infections. These findings are consistent with the improved survival in mice with fungal infections, and in mice with bacterial sepsis, in which PD-1 was inhibited.⁴

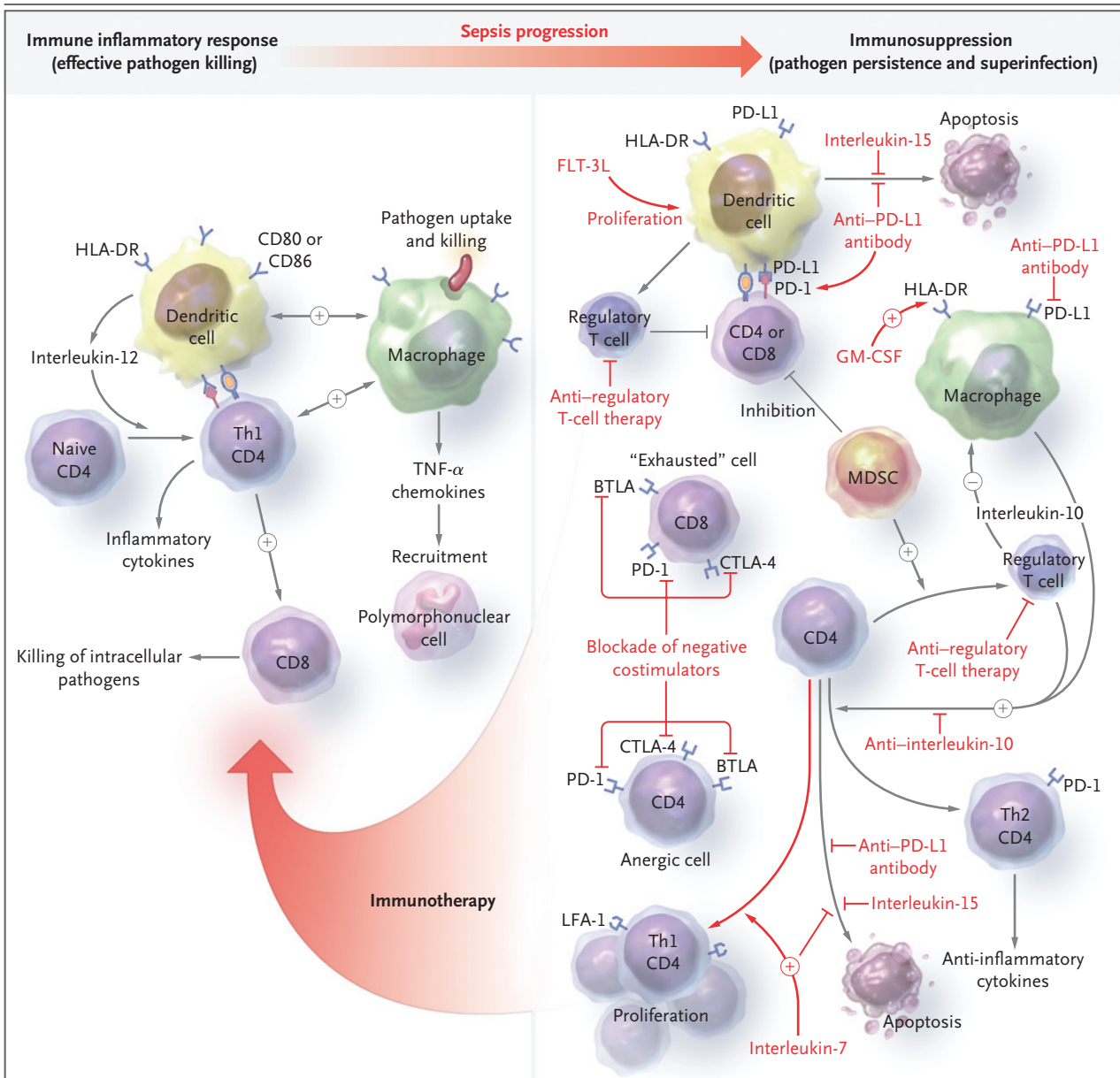


Figure 1. Reversal of Immunosuppression in Sepsis.

In many cases of sepsis, the immune system fails to eradicate the infectious pathogens, and a prolonged phase of sepsis-induced immunosuppression begins, characterized by a failure to eradicate the primary infection and by development of secondary nosocomial infections. This immunosuppression is mediated by multiple mechanisms, including massive apoptosis-induced depletion of lymphocytes and dendritic cells, decreased expression of the cell-surface antigen-presenting complex HLA-DR, and increased expression of the negative costimulatory molecules programmed death 1 (PD-1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and B- and T-lymphocyte attenuator (BTLA) and their corresponding ligands (e.g., PD-1 ligand [PD-L1]). Furthermore, the numbers of regulatory T cells and myeloid-derived suppressor cells (MDSCs) are increased, and there is a shift from a phenotype of inflammatory type 1 helper T (Th1) cells to an antiinflammatory phenotype of type 2 helper T (Th2) cells characterized by the production of interleukin-10. The net result is a severely compromised innate and adaptive immune system with poorly functional "exhausted" CD8 and anergic CD4 T cells. Targets of potential immunotherapeutic approaches (shown in red) include agents that block apoptosis, block negative costimulatory molecules, decrease the level of antiinflammatory cytokines, increase HLA-DR expression, and reactivate "exhausted" or anergic T cells. FLT-3L denotes Fms-related tyrosine kinase 3 ligand, GM-CSF granulocyte-macrophage colony-stimulating factor, LFA-1 lymphocyte function-associated antigen 1, and TNF- α tumor necrosis factor α .

Although it is possible that immunostimulatory therapy exacerbates the hyperinflammatory phase of sepsis or induces autoimmunity, clinical trials of interferon- γ , a potent immunostimulatory agent, and granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with various systemic inflammatory states did not elicit unbridled inflammatory reactions. Most patients with refractory sepsis are so severely immunosuppressed that the development of hyperinflammation or autoimmunity is unlikely.

To prevent the extensive apoptosis-induced depletion of immune effector cells in patients with sepsis, one potential strategy is use of the antiapoptotic, immunostimulatory cytokines interleukin-7 and interleukin-15; both agents have shown efficacy in models of infection, including sepsis. These cytokines, in preventing cell death, diminish the immunosuppressive effect on phagocytic cells (which are relieved from disposing of increased numbers of apoptotic cells). Interleukin-7 also restores the effector function of lymphocytes and improves lymphocyte migration by increasing the activity of integrins. Interleukin-7 is currently in clinical trials to treat cancer and infection with hepatitis C virus and HIV.

In the future, immunotherapy will probably be tailored to the individual patient on the basis of specific laboratory or clinical findings. For example, a recent trial of GM-CSF to treat sepsis tested the effect only on patients in whom monocyte HLA-DR expression was significantly depressed.⁵ Flow-cytometric studies quantitating the level of expression of negative costimulatory molecules (such as PD-1 and PD-L1) on leukocytes, or rapid whole-blood stimulation assays of cytokine secretion, could be used to guide

immunotherapeutic decisions. Patients with cytomegalovirus infection or reactivation of herpes simplex virus type 1 and those with sepsis due to infection with opportunistic pathogens (such as *Stenotrophomonas* or *Acinetobacter*) are good candidates for immunoenhancing therapy.

An old saying goes, "Desperate diseases are cured by desperate means or not at all." Trials of immunostimulatory agents should be undertaken, with close monitoring of innate and adaptive immune function, in patients with demonstrable immunosuppression. Many potentially beneficial immunomodulatory agents (Fig. 1) are currently in clinical trials for other indications and have reasonable safety profiles. We speculate that such approaches will have wide-ranging effects and could represent a major advance in the field of infectious disease.

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

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