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Editorial

Editorial: **PD-1, a new target for sepsis treatment: better late than never**

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The high cost of sepsis/septic shock in terms of morbidity, mortality (>750,00 cases/year with >200,000 deaths), and dollars ($17 billion) makes it a prime target for the development of new therapies [1, 2]. However, numerous clinical trials targeting proinflammatory products, including cytokines (TNF, IL-1), NO, coagulation factors, and bacterial products (such as LPS) [3] have been disappointing failures. The only U.S. Food and Drug Administration-approved treatment, activated protein C, a molecule that functions in the degradation of clotting factors Va and VIIIa and provides antithrombotic activity, has only a modest effect on survival [4]. Thus, there is a constant quest for new and improved therapies. It is likely that the failure of previous trials is a reflection of the enormous heterogeneity of a syndrome that has many pathways to its final outcome. This heterogeneity is reflected in variation in the ability to identify infectious foci and the differing phases (acute or early vs. chronic or late) of the disease.

Indeed, studies by Remick and co-workers [5, 6] have shown that there are dramatic differences in the early and late phases of sepsis/septic shock in mice; mice that die in the early stages express high levels of the proinflammatory cytokines IL-6 and TNF-α, as well as the anti-inflammatory cytokines IL-1R antagonist and IL-10, as if there is an attempt to suppress the overly active immune system. In contrast, mice that survive the early stages and die at later stages, or survive, do not display this early cytokine storm [5, 6]. Thus, although the prevailing theory has been that sepsis represents an uncontrolled, inflammatory response with patients dying from inflammation-induced organ injury, there is increasing evidence that in contrast to the early phase, characterized by the "cytokine storm," the late phase of sepsis/septic shock is characterized by immunosuppression. This immunosuppression very likely reflects an attempt by the immune system to down-regulate an overactive immune response.

Immunosuppression in sepsis, sometimes referred to as "immunoparalysis", is characterized by a number of factors, including monocyte deactivation, tolerance to endotoxin, impairment of neutrophil function, lymphocyte dysfunction, and apoptosis [7]. More recently, it has been observed that the PD-1 receptor, which down-regulates T and B cell responses [8–10], is inducibly expressed in macrophages in the CLP model of sepsis [11]. Ayala's group [11] showed for the first time a role for PD-1 in bacterial infection and that sepsis-induced expression of PD-1 by macrophages contributes to inhibition of macrophage function. Furthermore, they observed that mice deficient in PD-1 show enhanced survival following CLP and suggested that PD-1 might be an important therapeutic target for sepsis [11].

Brahmamdam et al. [12] have extended this key observation to show that an antibody directed to the PD-1 receptor can restore much of that immune responsiveness by inhibiting apoptosis and restoring generalized immune functions such as delayed-type hypersensitivity. More importantly, they show that such an antibody increases survival of mice subjected to CLP, even when given during relatively late stages of the disease. The observations in this paper parallel in many ways recent observations by this group, where they showed that IL-7 and IL-15 also promote T cell viability by preventing apoptosis and result in improved survival in sepsis [13, 14].

Other examples where bacterial activation of normal host proteins of the immune system lead to a state of immunosuppression and poor outcome in CLP sepsis include TLR9 and CD16, both of which induce immunosuppression via different mechanisms. CLP-induced activation via TLR9 results in a delayed influx of dendritic cells and neutrophils and leads to death, and inhibition of TLR9 function with inhibitory CpG, given up to 12 h after CLP, restores the ability of mice to survive and clear the infection [15]. Similarly, CLP-induced activation of CD16 down-regulates phagocytosis and killing of bacteria in CLP sepsis by a mechanism that is driven by the FcRγ ITAM chain; elimination of this immunosuppressed state by deleting FcRγ promotes bacterial clearance and survival [16].

Abbreviations: CLP=cecal ligation and puncture, PD-1=programmed death -1

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It should be noted that in contrast to these and other observations supporting the case for immune intervention designed to correct the immunosuppressed state in sepsis patients, there are a number of other observations, indicating that suppression is beneficial. These include the observation that an antibody that neutralizes CD137 (a member of the TNFR superfamily that acts as an activating T cell costimulatory molecule) blocks cytokine and chemokine induction in a CLP model of sepsis and promotes survival [17], although it can be argued that this represents rescue at the early proinflammatory stage of the disease. An example where suppression of the immune system was therapeutic at a late stage (24 h after CLP) was shown with JAK2 inhibitors that rescued mice from polymicrobial sepsis [18]. Similar to CD137 in CLP sepsis, inactivation of CB2 cannabinoid receptors also promotes survival [19]. It should be noted, however, that although deficiency in the CB2 cannabinoid receptors is protective by suppressing proinflammatory cytokines and chemokines, it also prevents apoptosis in lymphoid organs, providing a common link with the observations of Brahmamdam et al. [12] and PD-1.

In contrast to the example above, where inhibition of CD137 is beneficial in polymicrobial sepsis, studies of infection by a single infectious agent, Listeria, require CD137 for rapid bacterial clearance [20], indicating that inactivation of a particular pathway is beneficial in resolving infection by some microorganisms but is harmful and leads to increased mortality by others [17, 20].

Thus, it may be that neither generalized activation nor suppression of the immune system can be the panacea for all sepsis patients but rather, the restoration of the delicate balance that normally exists between the active and suppressor arms of the immune system. The precise nature of the imbalance in sepsis patients may depend on the pathogenic organism responsible for the infection, its location, and the amount of time passed since onset of infection, as well as other individual parameters. In these circumstances, the correct choice of tools in our armamentarium may well depend on the specific immune status or deficit of each individual patient and will become another example of personalized medicine.

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