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Editorial

The Fight Against Sepsis: Is Endothelial Barrier Enhancement the Answer?

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Editorial

Sepsis is the host's systemic inflammatory response to infection. Although improvements in supportive care of patients with sepsis (eg, mechanical ventilation, fluid resuscitation, and broad-spectrum antibiotics) have improved survival rates, sepsis remains a medical condition with high morbidity and mortality. Over decades of research, progress has been made in our understanding of the mechanisms of sepsis. Accumulating evidence suggest that sepsis is characterized by initial hyper-inflammatory stage (cytokine storm), followed by hypo-inflammation (immune-paralysis), leading to increased host susceptibility to secondary infections, although this notion is also challenged by others. The acute phase of sepsis is marked by an abrupt rise in the secretion of pro-inflammatory cytokines. This response is an important component of the innate immune response for countering against invading pathogens. An inflammatory response for a short duration can be beneficial because it helps to clear the infectious agent. However, prolonged inflammation can be detrimental because it may cause host toxicity, tissue damage, organ dysfunction and death.

The prominent role of cytokines in acute phase of sepsis has led to the testing of agents that reduce cytokine signaling as possible therapeutics. There have been over 100 failed clinical trials of biological response modifiers aimed at single therapeutic targets, mostly to suppress the early pro-inflammatory responses. Despite these clinical trials, to date no FDA-approved drug is available for use in sepsis. The containment of a hyper-inflammatory response is difficult, because of the multitude of proinflammatory mediators and receptors that have overlapping functions. This dilemma reflects our poor understanding of the responses in sepsis and the pressing need for new therapeutic approaches.

Over the past several decades of advances in basic research, the concept that endothelium is an organ system has emerged. Although cytokine storm is a critical predictor of morbidity and mortality, yet the cellular sources and signaling mechanisms that are important in initiating cytokine storm remain not completely defined. A recent important research demonstrated that endothelial cells are central orchestrators of cytokine amplification during influenza virus infection [1]. In addition to its innate immune function providing a first line of defense against invading pathogens by releasing multiple inflammatory cytokines, endothelial cells function as a barrier. Endothelial hyperpermeability is an important event in sepsis, leading to capillary leakage, microcirculatory dysfunction and multi-organ dysfunction syndrome (MODS). This "barrier failure" hypothesis is supported by the evidence from clinical and animal studies of severe sepsis. Therefore, apart from the immune-pathologic mechanism of sepsis, other researchers explored an alternative approach to combat sepsis: strengthening the vascular barrier, diminishing deleterious aspects of the host's response to the pathogen-induced cytokine storm.

Blood vessel leakiness is an early, transient event in acute inflammation but can also persist as vessels undergo remodeling in sustained inflammation. This underlies that angiogenesis and inflammation are closely integrated processes and may affect disease progression. Angiogenesis is a complex multistep process controlled by a wide range of positive and negative regulatory factors. Findings from angiogenesis research have shed some light on the research on acute inflammation such as sepsis. The angiogenic factors such as vascular endothelial growth factor (VEGF) and the angiopoietins have received great attention in critically ill patients because of their pivotal roles in both angiogenesis and microvascular permeability. Recent abundant evidence showed that excess circulating angiopoietin-2 may contribute to vascular leak, organ dysfunction and mortality in human sepsis [2-5]. Importantly, angiopoietin-2 neutralizing antibody treatment attenuated hemodynamic alterations and reduced the mortality rate in experimental sepsis model [6]. Research also shows that sepsis is associated with significant circulating levels of VEGF in animal and human models of sepsis [7,8]. Furthermore, FDA-approved anti-VEGF antibody Bevacizumab attenuated inflammation and decreased sepsis mortality [9]. Recent evidence also suggest more complex crosstalk between angiopoietin axis and VEGF axis [10], providing more opportunities for agents like a bispecific antibody recognizing VEGF-A with one arm and the other arm recognizing angiopoietin-2 [11]. Interestingly, London et al. reported that activating with the soluble ligand slit an endothelium-specific, Robo4-dependent signaling pathway that strengthens the vascular barrier, diminished deleterious aspects of the host's response to the pathogen-induced cytokine storm and increased survival in multiple relevant sepsis models [12]. However, the observed beneficial effects was not due to an alteration in inflammatory cytokine and chemokines, because there was no reduction in plasma concentrations of a panel of cytokines and chemokines, demonstrating that promotion of vascular stability was sufficient to mute the vascular hyperpermeability induced by multiple different cytokines and the subsequent mortality in sepsis.

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Thus, as discussed here, recent advance suggest that enhancing the resilience of the host vascular integrity to the host's innate immune response may present a therapeutic strategy for treating sepsis.

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