Resolution for Sepsis?

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Charged with protecting the host from invading organisms, distinguishing self from nonself, and the repair of tissue injury, inflammation is no trivial event: Life depends on it. However, there are times when this most primordial of events fails to protect the host and, paradoxically, goes into disarray. This is abundantly evident in rheumatoid arthritis, asthma, and psoriasis, for example, in which a perfectly well-meaning innate immune response somehow fails to resolve and instead progresses, irresistibly, toward chronic inflammation. However, neither the complex activation of the adaptive immune system nor the characteristic mayhem of chronic inflammation is necessarily required to bring about Virchow’s 5th cardinal sign of inflammation: Loss of organ function. This can happen in a much more immediate manner with innate immunity and its response to tissue injury or infection in the form of sepsis. During sepsis, there is a rapid activation of the innate immune response and the release of soluble factors, including glucocorticoids, catecholamines, and proinflammatory cytokines (including tumor necrosis factor-α [TNF-α], interleukin-1β, and interleukin-6). Exaggerated cytokine production, along with that of inducible nitric oxide synthase (NOS)–derived nitric oxide, platelet activation factor, and eicosanoids, has been implicated in the endothelial cell dysfunction, hypotension, inadequate organ perfusion, and necrotic cell death associated with multiple organ failure.

Conventional treatment for septic shock has focused on source control, antimicrobials, vasopressors, and fluid resuscitation. Despite effective antibiotics, septic shock remains the most common cause of death in the intensive care unit, incurring a mortality rate of 30% to 50%. Although several therapies target the upregulated innate inflammatory pathways, it is generally thought that few such strategies are beneficial. Clinical trials aimed at neutralizing proinflammatory mediators with antibodies against endotoxin and TNF-α, antagonists of interleukin-1β, or platelet activating factor, for instance, have proved disappointing. Moreover, of those who survive the initial acute event, there is a predicted 26% mortality rate within 1 year, with many patients succumbing to lung complications. In search of a more effective treatment for sepsis, Witzenbichler and colleagues have shown a protective role for angioptoeitin-1 (Ang-1), a ligand for the endothelial cell-specific receptor tyrosine kinase Tie2, in an experimental model of lipopolysaccharide-induced septic shock in mice. In that article, the authors show that Ang-1 protected against lipopolysaccharide-induced hemodynamic changes, which resulted in enhanced survival and reduced leukocyte infiltration and edema in the lung, possibly resulting from decreased cell adhesion molecule expression. An endogenous factor that is antiedematous and anti-leukocyte trafficking and that reduces mortality deserves closer scrutiny.

Tie (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains) represents a novel class of receptor tyrosine kinases that are predominately expressed by vascular endothelial cells. There are 2 members in this class, Tie1 (also known as Tie) and Tie2 (also known as Tek). Like Ang-1, endogenous Ang-2 shows specific affinity to the Tie2 receptor; however, Ang-2 does not induce phosphorylation of Tie2 but instead blocks Ang-1–mediated Tie2 receptor activation. Virtually all endothelial cells during embryonic development express Tie1 and Tie2. Tie2 expression is initially detected in endothelial cells at embryonic day 7.5 and continues to be expressed in these cells throughout development. Tie1 expression is detected slightly later, from day 8. In addition to embryonic expression, Tie2 protein is present in quiescent endothelial cells in a range of adult tissues. Interestingly, this receptor is also tyrosine phosphorylated in adult tissues, which indicates constitutive activation of Tie2. Both Ang-1 and Tie 2 null-mutant mice embryos have abnormal vascular networks, with growth-retarded vascular smooth muscle and pericyte precursors. Until recently, there has been no conclusive evidence that Ang-1 could induce angiogenesis in vivo. In vitro studies have demonstrated that Ang-1 is a poor inducer of endothelial cell proliferation and tube formation compared with vascular endothelial growth factor; however, Ang-1 has now been shown to induce the formation of new blood vessels in vivo when transgenically overexpressed in the skin. In addition to direct effects on the endothelium, Ang-1 is also involved in normal interactions between endothelial cells and their underlying supporting cells and in the maintenance of the vascular stability. It has also been demonstrated that Ang-1 inhibits capillary permeability, which prevents plasma leakage in response to vascular endothelial growth factor and mustard oil. In addition, Ang-1 causes enhanced platelet and endothelial cell adhesion molecule-1 localization to the endothelial cell junctions, reduced TNF-α–stimulated polymorphonuclear leukocyte transmigration, and reduced expression of E-selectin, a cytokine associated with inflamma-
tion, proliferation, and angiogenesis. Collectively, it appears that Ang-1 may represent a worthy endogenous counterregulatory signal to an innate inflammatory response out of control.

The conundrum facing the treatment of sepsis seems blindingly simple: Given the wide availability of potent inhibitors of the innate immune response, including steroids and nonsteroidal antiinflammatories, why isn’t aggressive treatment of a systemic innate inflammatory response successful? Certainly, Witzenbichler and colleagues show enhanced life span with Ang-1 treatment, the benchmark of any successful treatment regimen. Some of the problems may be rooted in our understanding of septic shock, gleaned from experimental animal models, and the time of drug intervention. With many animal models of acute inflammation, antiinflammatory therapy is invoked prophylactically, ie, before the response initiates or very soon thereafter. In contrast, patients often present well into the disease process, when organ dysfunction has already begun. Moreover, although scientific habit determines that animal studies are performed in young healthy animals, the clinical setting is more likely to have a broader age range of patients bearing secondary complications, including diabetes, immune suppression, or cancer. In animal models, a well-defined bacterial strain or endotoxin challenge is often used to bring about the onset of sepsis. In human sepsis, the pathogenic bacteria are often not known, and mixed infections that involve both Gram-negative and Gram-positive bacteria are common. Moreover, the strategy of using antiinflammatory therapy may spare the bacteria, which is fine if antibiotic treatment is effective but harmful if it is not. Thus, an intervention in human sepsis is attempted at a later stage and under very different conditions than in animal models. Coupled with a prevailing skepticism that the inhibition of proinflammatory pathways has no overall benefit for treating sepsis, do the findings of Witzenbichler and colleagues provide new hope for the treatment of sepsis with Ang-1 or Ang-1 receptor agonists? These authors have shown that Ang-1 has antiinflammatory effects on the innate immune response; however, we need to be cautious at this point until further studies reveal the efficacy of Ang-1 in sepsis under more clinically relevant conditions such as those mentioned above. In particular, it would be important to determine that Ang-1 is protective in animals of various ages and at various stages of a disease process elicited by diverse sepsis-inducing modalities, including live organisms. This is not a criticism of Ang-1 in particular but of novel antiinflammatory therapeutics in general. On this theme, the present report by Witzenbichler and colleagues opens the debate on the role of the innate immune response in host defense and the wisdom of inhibiting acute inflammation during inflammatory disease processes.

It is generally held that innate inflammation is good for the host because it neutralizes infection and repairs damaged tissue. In rheumatoid arthritis, for example, acute swelling and pain occur in response to immune complex deposition or antigen recognition. This response manifests as pain and stiffness, which are often treated with steroidal and nonsteroidal antiinflammatories, in the first instance. Although the inhibition of such an acute inflammatory response ameliorates the symptoms of periodic flares in autoimmune joint disease, there may be a long-term price to pay. There is the increasing notion in inflammation research that just as the initiation of the response is under the control of “go signals” that drive cell trafficking and edema formation, the resolution or switching-off phase is equally well coordinated by endogenous proresoluction factors that mediate cell clearance, including apoptosis, phagocytosis, and lymphatic drainage. Some, but not all, of the factors intrinsic to resolution are triggered by soluble mediators that are active during onset. Thus, aggressively dampening the onset phase of acute inflammation may ultimately have an inhibitory effect on the resolution of inflammatory lesions, an event implicated in the development of chronic inflammation and autoimmunity. Consequently, in inflammation-driven disease processes, we need to be mindful that aggressive antiinflammatory therapy may have immediate protective effects but detrimental long-term effects.

Witzenbichler and colleagues show that Ang-1 has diverse modulatory effects on the innate immune system: It inhibited inflammatory cell adhesion molecule and inducible NO synthase expression but prevented the downregulation of protective endothelial NO that typically occurs during sepsis. Endothelial NO is central to the control of cell trafficking because of its ability to negatively regulate leukocyte/endothelial cell interaction through the inhibition of inflammatory cell adhesion molecule expression. It is interesting that during sepsis, there is a suppression of this protein, supposedly to facilitate leukocyte migration across the endothelium. Indeed, there is experimental and clinical evidence that during or soon after systemic infection or inflammation there is an increased incidence of cardiovascular events, possibly resulting from endothelial dysfunction. At this stage, it is not clear what causes this endothelial dysfunction, but perhaps a closer look at the level of endothelial NO expression and enzyme activity during these periods of vascular susceptibility is warranted.

So, where do we go from here? Although we call for more clinically relevant studies to determine the effectiveness of Ang-1 in sepsis and inflammation, the use of therapeutics based on the mode of action of endogenous antiinflammatories such as Ang-1 may reflect the sort of approach that needs to be borne in mind when novel antiinflammatories are being developed. The approach of inhibiting single proinflammatory mediators or pathways has provided the mainstay of conventional antiinflammatory therapy in the past, but it is not without its side effects. For instance, anti-TNF-α therapy is a highly effective treatment for rheumatoid arthritis but dampens the host’s ability to deal with infection. It has recently come to light that rofecoxib (Vioxx) causes an increased risk of stroke and myocardial infarction because of its inhibition of constitutively expressed cyclooxygenase-2, which appears to have a role in the vasculature of synthesizing cardioprotective prostacyclin. The principle of introducing back to an inflamed system an endogenous factor with inherent antiinflammatory counterregulatory properties provides an attractive alternative approach. In particular, endogenous factors expressed during the resolution of acute inflammation, including
the lipoxins, cyclopentenone prostaglandins, and heme-oxygenase, have beneficial effects when administered in the setting of chronic experimental inflammatory diseases. Like Ang-1, such proresolution factors do not abrogate a single pathway but have multiple diverse modulatory roles in the inflammatory response that culminate in its resolution. It is argued that novel compounds based on the mechanism of action of a given proresolving mediator will be modulatory in their action and likely to produce a lower burden of side effects. It may be this approach that ultimately gains recognition and success for the future treatment of inflammatory diseases.

References


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