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EDITORIAL

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Dear SIRS, the concept of "alarmins" makes a lot of sense!

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The late Roger Bone [1, 2] coined the term "systemic inflammatory response syndrome, SIRS" more than 15 years ago to describe a clinical entity highly prevalent in our intensive care units (ICUs) [3, 4]. Patients with SIRS usually present with fever and leukocytosis in addition to tachychardia and tachypnea. Sepsis was defined as patients with a documented bacterial infection and at least two SIRS criteria [5]. It was also recognized by Bone and others that many patients without infection have SIRS, later defined as "aseptic SIRS" or "sterile shock" [6, 7]. Examples of such conditions include acute respiratory distress syndrome, trauma, pancreatitis, major surgery, and ischemia-reperfusion injury in patients recovering from shock.

The search for host molecules mediating SIRS has been fruitless for a long period of time. It was initially believed that SIRS is mediated by circulating proinflammatory mediators, such as tumor necrosis factor α and interleukin 1β. This concept served as a basis for conducting anticytokine clinical trials in a series of conditions with SIRS—including sepsis—which systematically failed. This led to a reappraisal of the SIRS concept [8, 9]. It was shown that the systemic compartment of critically ill patients with SIRS is already profoundly anti-inflammatory [10–12]. This state is due to the presence of high concentrations of natural soluble inhibitors of proinflammatory cytokines, and monocyte deactivating cytokines such as interleukin 10 [10, 12–14], leading to systemic immune suppression [15]. In addition, ICU therapies such as catecholamines, antimicrobials, and sedatives have frequently unsuspected anti-inflammatory effects [16]. Finally, a certain degree of inflammation is necessary for neutralizing pathogens and clearing the infectious process [17].

Patients with SIRS have in common tissue injury with cells suffering or dying by necrosis. The systemic consequences of tissue injury such as shock and severe bacterial infections involve an integrated and complex response of various systems including neural, immune, hormonal, coagulation, and metabolic pathways [16]. It has long been thought that the immune system had evolved with the discrimination between noninfectious self from infectious nonself [18]. This concept can easily be challenged in human pathophysiology. Clearly tissue injury induces a systemic inflammatory response and an immune dysfunction, in the absence of infection. Conversely, an immune tolerance to infections is also common, such as in bacteremia following tooth brushing. Another concept of immunity was proposed in 1994 by Matzinger [19, 20], the "danger model". She hypothesized that the immune system has evolved with the discrimination of what is *dangerous* and what is not. In addition, she has put forward the notion that in order for the immune system to be significantly activated by micro-organisms two simultaneous or sequential signals are needed: one microbial signal, such as Gram-negative lipopolysaccharide, and an endogenous "danger signal", a mediator signaling tissue injury [21]. This concept now makes substantial sense to the ICU physician, and adds meat to the bone of the "two-hit concept" frequently observed in the pathogenesis of sepsis [7]. This notion is also found in the stimulation of an adaptive immune

response to a vaccine. A vaccine usually works better when adjuvants create a certain amount of local tissue injury, helping the recognition of the microbial antigen(s) to enhance the immune response [22].

When significant, tissue injury alone is capable of inducing the clinical syndrome known as SIRS [7]. In the past 5 years candidate endogenous mediators potentially sustaining these effects have been discovered. The most prominent is certainly the high-mobility group box 1 (HMGB1) protein, but other endogenous molecules such as antibacterial peptides, S100, and heat-shock proteins may also play a role [23, 24]. These molecules, now known as "alarmins" [25, 26] have in common an intracellular compartmentalization in physiological conditions. In situations of cell suffering or cell death, alarmins are released in the extracellular milieu and activate immune cells [27]. This is due to both an active secretion of alarmins by injured (or activated) tissue cells, and a passive release by cells undergoing necrosis. They also enhance immune functions to microbial antigens [28]. Interestingly, some of these "danger signals" share with pathogen-associated molecular patterns the same innate immune receptors, such as the Toll-like receptors (TLRs) [29].

HMGB1 functions as a DNA-binding molecule in normal cell physiology but can surprisingly act as a proinflammatory cytokine when released by cells [30]. It activates cells via TLR2, TLR4, and the receptor for advanced glycosylation end-products [31, 32]. HMGB1 was initially recognized as a critical endogenous mediator of lethality in a model of murine endotoxemia [33]. HMGB1 release was subsequently documented in a variety of inflammatory and infectious animal models, as well as in critically ill patients with sepsis and other conditions [34, 35]. In animal models of "aseptic SIRS," such as pancreatitis, hemorrhagic shock, and trauma, HMGB1 blockade decreases the inflammatory response and improves outcomes [36–38].

Coagulation has recently been demonstrated to be a key innate element in the septic response [39]. A certain degree of disseminated intravascular coagulation is almost invariably associated with sepsis. This is due to the abnormal intravascular expression of tissue factor and the subsequent generation of thrombin. Decreased circulating levels of endogenous proteins with antithrombin activity (activated protein C, antithrombin, and tissue factor pathway inhibitor) have also been reported by several groups. In their contribution to *Intensive Care Medicine* Hagiwara and collaborators [40] now report that treatment of endotoxemic rats with antithrombin (AT) decreased both lung injury and lethality. Importantly, they observed lower lung and systemic HMGB1 concentrations and lower circulating proinflammatory cytokines in AT-treated rats. Antithrombin, similarly to the activated protein C, exerts anti-inflammatory activity in addition to its antithrombotic effects [41]. Interestingly, Hagiwara et al. also show that murine macrophages cultured with AT secrete less HMGB1 and proinflammatory mediators in response to LPS, as a consequence of decreased NF-κB activation. The anti-inflammatory effect of AT on cells must therefore be at least partially direct and not only mediated through a decreased thrombin activity. Although it is known that AT binds to cells through an interaction with glycosaminoglycans, the downstream events remain poorly understood [41]. A large AT trial failed to demonstrate a benefit in patients with severe sepsis. However, a subgroup of patients who did not concomitantly receive heparin seemed to benefit from AT treatment [42, 43]. In vivo AT could exert both direct and indirect protective effects. AT inhibits the generation of thrombin with, as a consequence, decreased deleterious disseminated intravascular coagulation and possibly thrombin-associated inflammation. It may also directly prevent tissue injury associated with sepsis by interacting with endothelial and mononuclear cells and the release of "danger signals" such as HMGB1. This is in accordance with a recent report showing that HMGB1 promotes intravascular coagulation in a similar model, suggesting a participation of this alarmin in the pathogenesis of disseminated intravascular coagulation [44]. Although Hagiwara et al. found that AT treatment improved outcome in their lipopolysaccharide model and concomitantly decreased the inflammatory response and HMGB1 release, they did not make a direct association between these three aspects. These crucial points require further studies.

We are progressing rapidly with our understanding of the systemic consequences of tissue injury and the pathogenesis of multiple organ dysfunction. Undoubtedly the identification of alarmins—signaling tissue injury—and their pathways of cell activation ("danger signals") opens a new and exciting field and will lead to the recognition of new therapeutic targets. It appears conceptually sound to block signals originating from tissue necrosis while leaving intact those originating from pathogens. Targeting HMGB1 in sepsis is tempting since it has been clearly linked with lethality and is a late mediator, offering the possibility of delayed treatment [45]. The history of sepsis therapies, however, urges us to be cautious. Nature has selected alarmins during evolution for good reasons, and it is likely that some of the signals sent by these molecules benefit our patients [46].

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