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DAMPS, PAMPS and the Origins of SIRS in Bacterial Sepsis

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Despite decades of research and advances in clinical management, morbidity and mortality from sepsis and injury remain substantial and have shown only modest improvements (1). The concept of the systemic inflammatory response or SIRS was promulgated in 1992 by the Consensus Committee of the American College of Chest physicians in hopes to provide a more precise definition for the well described syndrome of inflammation that arose following sepsis and injury that led to multiple organ failure (MOF) and death (2). Initially, it was presumed that MOF and death following an infectious insult were the body's response to microbial products, such as 'pathogen-associated molecular patterns' (PAMPs), and it wasn't until the late 1980s that researchers fully realized that SIRS and MOF could occur in the absence of an obvious source of infection (1). Early theories implicated intestinal bacterial translocation following shock as the cause of 'sepsis syndrome' without an obvious source of infection (3).

It wasn't until the late-1990's that Polly Matzinger published the 'danger hypothesis' where she proposed that host innate immune surveillance was focused not on differentiating 'self' from 'nonself', but on identifying the presence of endogenous danger signals (4). Subsequent studies identified a variety of "'damage-associated molecular pattern (DAMP)" molecules as potent activators of the innate immune system initiating SIRS, and when exaggerated, MOF and death (4). Since then there have been discoveries of multiple endogenous danger signals released during tissue injury that include several heat shock proteins, HMGB-1, oxidized lipoproteins, and other cytosolic constituents such as ATP, all of which can contribute to a potent SIRS response (5). More recently, the Hauser group observed that tissue injury caused by trauma results in the release of mitochondrial products, including mitochondrial DNA (mtDNA) and formyl peptides, leading to the activation of innate immunity and a sepsis-like state (6). In their sentinel study, the authors showed that mtDNA was significantly elevated in severely injured trauma patients compared to healthy controls, and that these mitochondrial products played a role in the activation, migration, and function of human neutrophils (6).

In this issue of *Shock*, Sursal and colleagues sought to answer the question as to whether it is the endogenous DAMPs or residual bacterial PAMPs that cause a sustained SIRS response and death following lethal cases of bacteremia in nonhuman primates (7). They utilized a common method that simultaneously detected mtDNA and bacterial DNA using polymerase chain reactions (PCRs) to distinguish between an exogenous microbial or an endogenous host source of SIRS. In this report they performed a retrospective analysis of serum collected from nonhuman primates and tested for mtDNA and bDNA following lethal *Bacillus anthracis* (anthrax)-induced sepsis; non-lethal, self-limited gram negative sepsis using *E. coli*, and sterile tissue injury caused by infusion of Shiga-like toxin-1 (Stx1). Interestingly, they examined a fourth group of samples which consisted of baboons that were pretreated with drotrecogin alfa (aPC) prior to infusion of the lethal anthrax dose. Importantly, they utilized this group in this study not to examine the effects of aPC as a therapy, but rather as an analytic tool to distinguish between the direct effects of the bacteremia versus the effects induced by tissue damage as evidenced by circulating mtDNA levels (7).

Their results showed that following lethal anthrax challenge, bDNA only transiently increased while mtDNA levels remained elevated until death, suggesting ongoing tissue damage long after the bacteria were cleared. Remarkably, in subjects pre-treated with aPC, mtDNA levels declined following bacterial clearance, spared organ function, and allowed the animals to survive. Although this is an early report shedding some light on the simultaneous uses of bDNA and mtDNA as biomarkers, the Hauser group speculates that plasma bDNA and mtDNA levels may be promising biomarkers to help distinguish sepsis from sterile SIRS and help guide clinical management in the future.

With the over 100 unsuccessful clinical trials utilizing various biological response modifiers, most consisting of agents to suppress or block the SIRS response (8,9), many researchers have become interested in the development of biomarkers to help prospectively identify an immunological profile that can identify which patients with sepsis have increased risk from mortality, and to guide clinical management and/or drug therapy (10). Cytokine measurements, notably IL-6, procalcitonin, and CRP have been the mainstay of biomarker research to date, with varying degrees of success (11). Therefore, the search continues for non-cytokine biomarkers; alarmins and other endogenous danger signals hold promise but current clinical and experimental data are lacking. Another endogenous danger signal of nuclear origins, HMGB-1 has recently garnered interest as a late biomarker in sepsis when Gibot et al. showed that HMGB-1 plasma concentrations correlated to the degree of organ dysfunction and can distinguish between survivors and nonsurvivors (12). Additionally, Cohen et al showed that plasma levels of HMGB1 were increased early after severe trauma, correlated with the severity of injury, tissue hypoperfusion, and SIRS, and that survivors had significantly lower plasma levels of HMGB-1 than non-survivors (13). When taking into consideration the early findings of the Hauser group reported in this issue of *Shock*, one could envision that measuring plasma levels of endogenous danger signals is worth further exploration as a tool to add into one's clinical arsenal.

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