



Damage-associated molecular patterns in critical illness and multi-organ failure

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In the mid-90s, Polly Matzinger introduced the Danger model to explain how our immune system responds to harmful insults. According to this theory, the immune system may care less about identifying self versus non-self, but instead discriminate and respond based upon potential threat to host survival (1). Whether the nidus of critical illness is a sterile insult or septic process, alarm signals, such as damage-associated molecular patterns (DAMPs), from stressed and damaged cells have the potential to trigger the same downstream immune effectors as canonical pathogen-associated molecular patterns (PAMPs) expressed on bacteria and viruses (2). Thus, DAMPs remain an area of heightened clinical interest and deserve to be the focus of further targeted research.

Recently, Schenck *et al* outlined the role of DAMPs in critical illness and the subsequent pathogenesis of multiple organ failure (MOF) (3). This paper provides an interesting insight into why further understanding of DAMPs is key for emergency and critical care practitioners as well as the future prospect of targeting DAMPs as both diagnostic and therapeutic modalities in critical illness. The mechanisms underlying DAMP stimulation of innate immune receptors such as pattern recognition receptors (PRRs) and downstream innate immune and inflammatory responses have been extensively elucidated (4). However, the next step will entail an efficacious approach to manipulate this response to the host's benefit.

One key point which cannot be overemphasized is the principle of a balanced inflammatory response to

insult. There exists a fine line between a robust immune response to fight pathogens or heal damaged tissues and inflammatory derangement detrimental to host survival. Furthermore, the DAMP-mediated immune responses in the local microenvironment of injured or infected tissues may vary compared to the traditional immune markers that can be measured in the systemic circulation. It is also important to recognize that part of the dysregulated immune responses resulting in MOF is propagated by the vicious cycle of local DAMP release, micro tissue damage, and subsequent *de novo* DAMP generation (5).

Work to translate mechanistic knowledge of the DAMP-mediated immune response to clinically relevant patient-centered outcomes is ongoing. The levels of DAMPs such as cell-free DNA and high mobility group box 1 (HMGB1) in the bloodstream are correlated with morbidity and mortality of these patients with sepsis (6,7), and traumatic injury (8,9). However, the measurement of single or dual DAMP levels may not accurately reflect the true extent of inflammatory and innate immune responses in patients with sepsis and traumatic injuries because DAMPs are a broad spectrum of molecules of which immunological functions are highly redundant. Development of alternative approaches to determine total levels of pathological DAMPs is an unmet need for precise prediction of clinical outcomes of sepsis and trauma patients.

Rather than using downstream markers of organ injuries, taking a new perspective and looking at upstream harbingers of immune dysregulation may be

a key underpinning in the approach to critical illness. Furthermore, the chance to mitigate organ damage and prevent MOF by targeting DAMPs and PAMPs emphasizes an early, time-sensitive intervention that is fundamental to emergency care practitioners. As the field continues to evolve, thoughtful consideration of DAMPs as not only diagnostic tools, but also potential therapeutic targets in the emergency department and intensive care units will be of certain benefit. Future preclinical and clinical studies must also focus on the synergism of DAMPs and PAMPs in the pathogenesis of MOF as their complex physiologic interplay remains incompletely elucidated.

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Footnote

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References

1. Matzinger P. Tolerance, danger, and the extended family. *Annu Rev Immunol* 1994;12:991-1045.
2. Matzinger P. The danger model: a renewed sense of self. *Science* 2002;296:301-5.
3. Schenck EJ, Ma KC, Murthy SB, et al. Danger Signals in the ICU. *Crit Care Med* 2018;46:791-8.
4. Schaefer L. Complexity of danger: the diverse nature of damage-associated molecular patterns. *J Biol Chem* 2014;289:35237-45.
5. Eppensteiner J, Davis RP, Barbas AS, et al. Immunothrombotic Activity of Damage-Associated Molecular Patterns and Extracellular Vesicles in Secondary Organ Failure Induced by Trauma and Sterile Insults. *Front Immunol* 2018;9:190.
6. Kung CT, Hsiao SY, Tsai TC, et al. Plasma nuclear and mitochondrial DNA levels as predictors of outcome in severe sepsis patients in the emergency room. *J Transl Med* 2012;10:130.
7. Itagaki K, Kaczmarek E, Lee YT, et al. Mitochondrial DNA Released by Trauma Induces Neutrophil Extracellular Traps. *PLoS One* 2015;10:e0120549.
8. Lo YMD, Rainer TH, Chan LYS, et al. Plasma DNA as a Prognostic Marker in Trauma Patients. *Clin Chem* 2000;46:319.
9. Peltz ED, Moore EE, Eckels PC, et al. HMGB1 is markedly elevated within 6 hours of mechanical trauma in humans. *Shock* 2009;32:17-22.

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