Editorial

Prognostic and therapeutic role of damps in critical care illness

Júlia Faura[1], Alejandro Bustamante[1,2], Joan Montaner[1]

[1]Neurovascular Research Laboratory, Vall d'Hebron Institut de Recerca (VHIR) – Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Neurology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Correspondence to: Joan Montaner, MD, PhD. Neurovascular Research Laboratory, Vall d'Hebron Institut de Recerca (VHIR) – Universitat Autònoma de Barcelona, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain. Email: joan.montaner@vhir.org.

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In critical care illness, such as trauma, cardiac arrest or central nervous system (CNS) injury, tissue destruction exposes molecules that act as danger signals. These signals activate the innate immune system and initiate the immune response. However, this immune response can entail many complications for patients in intensive care units (ICUs). Hence, the danger signals, called damage-associated molecular patterns (DAMPs), could take part and be important in the prognosis of these patients either as biomarkers or as therapeutic targets (1).

DAMPs are molecules with physiological functions in normal conditions, but when they increase their concentration in the extracellular milieu, change to its soluble form or are released from inside the cell, are capable to activate innate and adaptive immunity (2). DAMPs can be extracellular or intracellular, both activating pattern recognition receptors (PRRs) such as toll-like receptors (TLRs).

In the review published by Schenck *et al.* (3), the relation between DAMPs, innate immune system and inflammation, and how this inflammation can be excessive and promote loss of homeostasis and multiple organ dysfunction it is presented. This could be the case of ICU patients. Also, the authors summarize the clinical evidences of different DAMPs in various critical care illnesses, in particular in trauma, CNS injury and infections.

The inflammation initiated by DAMP-PRR signaling begins with the formation of the inflammasome, causing in turn the activation of pro-inflammatory mediators' interleukin (IL)-1β and IL-18. The effects of these two cytokines are various: local pyrexia, hyperalgesia, vasodilatation and the production of other pro-inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF)-α. The inflammasome assembling also promotes proapoptotic and pyroptotic pathways. Furthermore, DAMPs shape the adaptive immune response through the maturation of immature dendritic cells (iDC) into immunomodulatory DCs (4).

However, this protective inflammatory response becomes dysregulated and pathogenic in some conditions. It happens in response to large stimuli, such as large amounts of tissue destruction, an especially virulent organism or a critical pathogen load. These highly pathogenic situations lead to an overproduction of DAMPs and an excessive and sustained inflammatory response. Many patients in ICUs go through these situations due to their critical illness, thus understanding and modulating DAMP response would suppose the palliation of the excessive innate immune activation and might help to reduce their stay in the units.

Various DAMPs are presented by Schenck and colleagues in relation with some critical illnesses. High-mobility group box (HMGB)-1, mitochondrial DNA (mtDNA) and heat shock proteins (HSPs) seem to be the more promising ones in the conditions presented in the publication. HMGB-1 has been particularly studied in various critical illnesses because of its cytokine, chemokine and growth factor activity in the inflammatory response. But its role as a prognostic biomarker or as a drug target is controversial. A recent study in critical ill patients has observed significant increased levels in plasma HMGB-1 but these levels were not related with disease severity, sepsis and mortality (5). Even so, HMGB-1 is well positioned to become a drug target in inflammatory-related diseases and other conditions, and at this point many active studies

are involved in the exploration of this molecule, either measuring plasma levels or related with interventions (6).

The prevention of the pathologic inflammation and its consequent complications could be a great advance for critical care illnesses. Examples such as sepsis or infections exacerbate the condition of the ICU patients and compromise their recovery, so controlling the dysregulation and hyperactivation of the immune system could reduce ICU stays and improve their outcome. Therefore, the efforts should direct towards the solid understanding of the mechanism of DAMPs release and activation of the immune system since many questions are still on the air.

Finding a biomarker able to predict critical care illness complications by diagnosing the excessive activation of the immune system and the inflammation could permit a faster intervention and reduce the severity of the ICU patients. For that, larger studies with more evidences are necessary to confirm the results of the studies presented in Schenck *et al.*'s review. The use of DAMPs as biomarkers could enable clinicians to monitor critical patients at bedside with only one measurement. However, biomarkers have some limitations in these acute situations. The determination must be fast, so it is necessary to develop point-of-care testing (POCT) for the bedside testing of a discovered biomarker, thus extending the application time of this biomarker to the clinics.

DAMPs can also be used as targets for the development of new treatments for critical care illnesses. In fact, DAMP-targeted therapies could enable the modulation of the immune response and stop the excessive inflammatory cascade. As an example, the above-mentioned HMGB1 has been studied as a therapeutic target in multiple diseases, using different approaches: antibody-based therapies; protein, oligonucleotides and small molecules inhibitors; blockage of the HMGB1-receptor signaling; and as a target of miRNAs (7). But one aspect that should be considered is that the targeting must be done discriminating the harmful role of the DAMP from the normal activity of the molecule. Hence, the targeting of DAMPs must be selective and time-resolved, to avoid compromising the other functions of the molecule in the human body (8). Best moment of initiation and duration of such treatments needs to be elucidated and blood biomarkers might be a good guide for that and also to monitor the efficacy of such trials (9).

In conclusion, DAMPs have multiple applications in the field of critical care illnesses, but it is important to elucidate their mechanisms of release and activation of the immune system to precisely manipulate the excessive inflammatory and innate immune responses, through the use of DAMPs as biomarkers and the development of new DAMP-targeted therapies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Timmermans K, Kox M, Scheffer GJ, et al. Danger in the intensive care unit: Damps in critically ill patients. Shock 2016;45:108-16.
2. Vourc'h M, Roquilly A, Asehnoune K. Trauma-Induced Damage-Associated Molecular Patterns-Mediated Remote Organ Injury and Immunosuppression in the Acutely Ill Patient. Front Immunol 2018;9:1330.
3. Schenck EJ, Ma KC, Murthy SB, et al. Danger Signals in the ICU. Crit Care Med 2018;46:791-8.
4. Land WG. The Role of Damage-Associated Molecular Patterns in Human Diseases: Part I - Promoting inflammation and immunity. Sultan Qaboos Univ Med J 2015;15:e9-21.
5. Yagmur E, Buendgens L, Herbers U, et al. High mobility group box 1 as a biomarker in critically ill patients. J Clin Lab Anal 2018;32:e22584.
6. VanPatten S, Al-Abed Y. High Mobility Group Box-1 (HMGb1): Current Wisdom and Advancement as a Potential Drug Target. J Med Chem 2018;61:5093-07.
7. Ugrinova I, Pasheva E. HMGB1 Protein: A Therapeutic Target Inside and Outside the Cell. Adv Protein Chem Struct Biol 2017;107:37-76.
8. Venereau E, De Leo F, Mezzapelle R, et al. HMGB1 as biomarker and drug target. Pharmacol Res 2016;111:534-44.
9. Bustamante A, Simats A, Vilar-Bergua A, et al. Blood/Brain Biomarkers of Inflammation After Stroke and Their Association With Outcome: From C-Reactive Protein to Damage-Associated Molecular Patterns. Neurotherapeutics 2016;13:671-84.

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