Editorial

Danger associated molecular patterns in injury: a double-edged sword?

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We read with great interest the study by Timmermans *et al.* entitled "Plasma levels of danger associated molecular patterns are associated with immune suppression in trauma patients" which was recently published in *Intensive Care Medicine* (1). This very interesting work shed light on immune functions after trauma as the authors investigated various aspects of host response in these severely injured patients. In particular, the concentrations of several plasma danger associated molecular patterns (DAMPs, i.e., mitochondrial DNA, nuclear DNA, heat shock protein-70) and plasma cytokines (IL-6, IL-8, IL-10) were evaluated in parallel with mRNA expression of HLA-DR and innate immune functionality through whole blood cytokine release upon LPS challenge. One major result is the first time report of the swiftness of immunosuppression development in those patients. Indeed, by collecting blood at the trauma scene and emergency room, the authors were able to show that, in parallel with expected increased DAMPs levels, usual markers indicative of immunosuppression were already measurable: reduced HLA-DR mRNA expression, increased IL-10 and IL-6 plasma levels (while those of TNF were unchanged). Most importantly, innate immune cells response to LPS stimulation was readily altered as a decreased release of IL-6 and TNF was observed whereas IL-10 production was significantly enhanced even at early sampling times. This shows that, at the systemic level, immunosuppression is occurring immediately at the onset of injury. Another interesting finding of the present study is to observe that the magnitude of HLA-DR fall inversely correlated with elevated DAMPs concentrations. In addition, both HLA-DR mRNA ratio <1 (between measurements at day 3 and at emergency room samples) and circulating nuclear DNA values were associated with increased rate of secondary infections. This confirms results obtained by flow cytometry (2).

Overall, the present results look very similar to recent data obtained in patients with cardiac arrest. Indeed, the same group reported a negative correlation between *ex vivo* cytokine release and DAMPs levels, including heat shock protein 70 (HSP-70) and extracellular newly identified receptor for advanced glycation and products-binding protein (EN-RAGE) (3). In parallel, we observed a decreased expression of monocyte HLA-DR in the post-cardiac arrest syndrome after non shockable out-of-hospital cardiac arrest while surviving patients tended to present with higher mHLA-DR values (4). Although mortality after cardio-pulmonary resuscitation is mainly due to brain injury and cardiovascular failure, this impaired immune response might significantly contribute to the poor prognosis of cardiac arrest (4,5). Experimentally, pharmacological agents, readily available in clinical practice, by limiting ischemia/reperfusion-induced mitochondrial damage, prevent the post-cardiac arrest syndrome (6,7). Nevertheless, whether these protective effects are linked with a decrease in circulating mitochondrial DAMPs remains to be investigated.

Interestingly, whereas the concept of induced immunosuppression was initially described after severe sepsis and septic shock, it has progressively been extended to trauma and cardiac arrest, both non-septic triggers. This

underlines the role of alarmins and DAMPs in the initiation of such tremendous systemic inflammation and raises the question of the link between the magnitude of initial severity and the depth of injury-induced immunosuppression. Beyond the plausible hypothesis that the observed immune defects may play a role in the increased susceptibility to secondary infections, one may also hypothesize that such immune alterations may represent a protective mechanism to limit extension of tissue damage and additional organ failures. An explanation, evoked in all these recent papers, although not mechanistically explored yet, would rely on a possible direct role of DAMPs in the development of injury-induced immunosuppression. Further investigations are now warranted to properly delineate the role of DAMPs during this process. In addition, as previously performed with IL-6 (8), it would be likely informative to design large studies to explore the potential as biomarkers of mixing early DAMPs and delayed HLA-DR measurements in predicting harmful clinical outcomes, both organ failure and secondary infections, opposite putative consequences of DAMPs double-edged sword.

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Footnote

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