Are histones real pathogenic agents in sepsis?

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We read with interest the recent Review article by van der Poll et al.1 (The immunopathology of sepsis and potential therapeutic targets. Nat. Rev. Immunol. http://dx.doi.org/10.1038/nri.2017.36 (2017)). This Review article describes various immunopathological aspects of sepsis and relevant targets as potential therapeutics. Unfortunately, we feel the authors failed to acknowledge highly relevant published data related to the possible pathogenic role of histones in sepsis.

In 2009, a paper by Xu et al.1, published in Nature Medicine, claimed that the main cause of death in sepsis is the release of highly toxic histones from neutrophils, possibly from those activated to make neutrophil extracellular traps1. Xu and co-workers also showed that the toxicity of histones could be abolished by either heparin, activated protein C or antithrombin to sepsis histones in many clinical disorders unrelated to sepsis.1–2. This has led to the suggestion that histones are not unique inflammation-inducing alarmins (also known as damage-associated molecular patterns (DAMPs)) but are actually markers of cell damage.3–4. Notably, in the context of sepsis, highly toxic cationic histones may function not alone but in synergy with oxidants and a range of pro-inflammatory agonists that are also released from activated neutrophils.5–8. Again, none of these publications was acknowledged in the Review by van der Poll and colleagues.

We believe this important information on the possible role of histones in sepsis should have been acknowledged in this Review to encourage unbiased reporting and scholarly debate.1–4.

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Subject categories
Biological sciences / Immunology
/ Inflammation / Sepsis [URI /631/250/256/1980]