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Are histones real pathogenic agents in sepsis?

Isaac Ginsburg and Erez Koren

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.* **17**, 407–420 (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.*[2], 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 traps[3]. Xu and co-workers also showed that the toxicity of histones could be abolished by either heparin, activated protein C or antibodies to histones. However, despite being an important new insight, this study was not cited in the Review by van der Poll and colleagues. Since this study, several other papers have been published showing high levels of circulating histones in many clinical disorders unrelated to sepsis[3–7]. 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[8,9]. 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[10–13]. 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[14].

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Competing interests statement
The authors declare no competing interests.