REPLY

Are histones real pathogenic agents in sepsis?

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We thank Ginsburg and Koren for their brief overview of the potential role of extracellular histones in the pathogenesis of sepsis (Ginsburg, I. & Koren, E. Are histones real pathogenic agents in sepsis? *Nat. Rev. Immunol.* http://dx.doi.org/10.1038/nri.2017.156 (2017))[1]. Although our Review article (The immunopathology of sepsis and potential therapeutic targets. *Nat. Rev. Immunol.* **17**, 407–420 (2017))[2] covers a variety of immunological changes and mechanisms implicated in sepsis pathogenesis, the space allowed was not unlimited. We therefore chose to discuss damage-associated molecular patterns (DAMPs) in a general way, stating that "During sepsis, the host response is further disrupted owing to the release of ... DAMPs ... . DAMPs can activate many of the PRRs [pattern recognition receptors] that also recognize PAMPs [pathogen-associated molecular patterns], giving rise to a vicious cycle that also involves sustained immune activation and organ dysfunction" and "PRRs interact with diverse PAMPs and DAMPs, and this diversity can probably explain the similarity between the inflammatory reactions induced by different pathogens and ... different types of injury, either infectious or non-infectious" (REF. 2). We cited two Reviews from major journals to support these statements[3,4], and included the role of DAMPs in sepsis pathogenesis in figure 1. Since we fully agree that reporting should be unbiased, we would like to point out that besides histones, many other DAMPs have been implicated in sepsis pathogenesis. To name a few: high-mobility group box 1 (REF. 5), S100A8–S100A9 (REFS 6,7), cold-inducible RNA binding proteins[8], mitochondrial DNA[9], heat shock proteins, IL-1α and IL-33 (REFS 10,11). Other important topics unfortunately could also not be discussed in our Review, including mitochondrial dysfunction[12,13], oxidative stress[12,13], resolution of inflammation (with the role of bioactive lipids such as lipoxins and resolvins therein)[14] and the mechanisms that could contribute to late sequelae of sepsis[15]. The pathogenesis of sepsis is extremely complex and variable, depending on the pathogen (load and virulence), the host (genetics, epigenetics and comorbidity), the environment (including the microbiome) and the time elapsed after the start of the infection, with distinct host responses at local, regional and systemic levels. In this respect, as we tried to accentuate in our Review, it remains unclear which mechanisms are the main drivers of sepsis-associated pathology in time.

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Competing interests statement
The authors declare no competing interests.