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Is Histone a Solitary Vile Sepsis-Inducing Agent or Just "a Member of the Gang"?

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Abstract

In this communication we argue that it is improbable that the main cause of death in sepsis is that, upon release of extracellular traps from neutrophils adhering to endothelial cells, highly cationic toxic histones uniquely cause endothelial dysregulation, organ failure and death. Activation of neutrophils is always accompanied by a plethora of pro-inflammatory agents, which may act in synergy with histones to injure cells. Furthermore, many recent articles have shown a steep rise of circulating histones in many clinical disorders unrelated to sepsis. We argue therefore that histones do not act as unique alarmins with an outsized role, but are probably another marker of cell damage.

Keywords: Synergism; Neutrophil products; Cell damage; Histone

Synergistic Mechanisms of Cell Damage

Bacterial and fungal infections can cause sepsis and shock, which worldwide still results is high mortality. Septic shock may be broadly defined as a multifactorial, synergistic syndrome where no unique mediator has been identified which, if successfully inhibited, might prevent or ameliorate the septic syndrome. This syndrome consists of deleterious effects caused by the infection (direct injury through pathogen-associated molecular pattern molecules [PAMPs] such as endotoxins, lipoteichoic acid and peptidoglycan) and the host response (mainly through the immune system). As of today, all the numerous clinical trials of sepsis that used single antagonists, for example activated protein C (APC), have failed and currently there is no specific treatment for septic shock. The best treatment still consists of general measures: source control, supportive care and appropriate antibiotics. Unfortunately, the growing epidemic of resistance to antibiotics further worsens patients' prospects for survival. Nonetheless, there is encouraging evidence that mortality is falling with improved and early treatment [1-8].

In 2009, two teams of investigators reported that extracellular histones released from NETs (neutrophil extracellular traps) in response to inflammatory challenges contribute to endothelial dysfunction, organ failure and death during sepsis in a murine model [9,10]. They suggested that they can be targeted pharmacologically by antibodies against histones or by APC (which cleaves histones). In effect, anti-histone antibodies reduced the mortality in murine models of sepsis using lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF-α) or cecal ligation and puncture. *In vivo*, histone administration was lethal, causing neutrophil margination, vacuolization of endothelium, intra-alveolar hemorrhage and macro- and microvascular thrombosis. Yet, if the histone theory of sepsis pathogenicity is considered, we should also remember that in addition to the action of toxic histones, activated neutrophils also secrete a plethora of other toxic and inflammatory agonists [3,11-15]. These include superoxide (generated *via* NADPH oxidase), superoxide dismutase (dismutates superoxide to H_2O_2), myeloperoxidase -H_2O_2 generated HOCl, nitric oxide (NO) synthase (generates NO), the highly-toxic peroxynitrite, the polycation bactericidal LL-37, permeability inducing agents, cathelicidin, cationic elastase, gelatinase, several acid hydrolases, PLA2, as well as many cytokines and immune mediators (such as TNF-α, IL-1β, etc.). These agents are expected to be delivered at the inflammatory sites in addition to the PAMPs derived from the bacteria themselves following bacteriolysis (such as lipoteichoic acid [LTA] and peptidoglycan [PPG]) [16,17]. Thus, these mediators (immune derived and bacteria derived) always appear together in the context of sepsis, all of them capable of causing cell injury [18-20]. Therefore, the claim that histones are unique, toxic alarmins causing septic shock is questionable [2,3]. This assumption is further called into question since many publications published since 2009 have also reported the presence of high amounts of circulating histones in many clinical disorders unrelated to septic shock [21]. This raises serious questions whether histones are agents with a special role in pathogenicity; perhaps they are “regular” damage associated molecular pattern (DAMP) mediators, or perhaps just markers of tissue damage [2]. Of note, a synergistic toxicity to human umbilical cord endothelial cells in culture by histones combined with several pro-inflammatory agonists such as oxidants and proteinases has already been studied in detail many years ago by our group [11-15]. In fact, the proposition that the sepsis syndrome is derived from synergistic phenomena was already debated and presented in the year 2000 during a symposium at the Rockefeller Institute [22]; it is unclear to us why this proposition hasn't been studied more closely since.

Given that septic shock is a multifactorial, probably synergistic phenomenon, if we accept the proposition that histones play a role in septic shock pathogenicity (not necessarily a unique role), then sepsis patients may benefit from anti-histone agents such as non-

anticoagulant heparin [23] (which counteracts toxic cationic agents such as histones) as well as anti-histone antibodies [24]. This should be especially being the case if they were to be combined with cocktails of anti-inflammatory agents as suggested previously [11-14]. These may be anti-oxidants, proteinase, elastase and PLA2 inhibitors, and anti-cytokines and perhaps even IV-IgG. Also, since microbial agents undergoing bacteriolysis release a variety of PAMPs [16-20], it could also be considered that the antibiotics used for septic patients should perhaps be bacteriostatic but not bactericidal, thus avoiding a Jarisch–Herxheimer-like phenomenon [25].

The fact that the numerous clinical trials of sepsis which tried only single-agonist therapy failed, raises several questions [26]. Other possible reasons for the failure of single-arm clinical trials could also result from heterogeneous populations, non-effective drugs used, drugs not reaching their receptor sites or given in the wrong dose or in the wrong formulation. Also, changes in volume of distribution and protein binding due to sepsis physiology might change receptor-drug interaction and affect the treatment. In this respect, we would like to stress the fact that histones most probably are "deadly members of the gang". Therefore, antagonizing them on their own, much like antagonizing only TNF-α or IL-1β, most probably will fail. Another insight from the literature on histones and sepsis relates to the fact that the main obstacle to an efficient treatment of sepsis is still the late arrival and/or late identification of patients at risk. In too many cases, septic patients are beginning to be treated when in fact "all the horses have already irreversibly left the stable". Yet, as of today no single key marker of sepsis or impending sepsis has been found [26,27]; perhaps histones can be used as early markers of sepsis?

Conclusion

Histones represent a marker of cellular injury, a DAMP, and are mediators in the host response to infection and inflammation. We propose that they do not have a unique role in the pathogenesis of sepsis but rather are members of a complex blend of mediators and agents derived from bacteria, immune cells and tissue cells. Many of these agents probably act synergistically to bring about the sepsis syndrome and its systemic sequelae. In order to provide novel therapeutic approaches we should look for combinations of (antagonistic) compounds with the aim of breaking their synergism.

Disclosure

The authors declare that there is nothing to disclose and no conflict of interest.

References

1. Angus DC, T van der Poll (2013) Severe sepsis and septic shock. N Engl J Med 369: 840-851.
2. Ginsburg I, Koren E, Varani J, Kohen R (2016) Nuclear histones: major virulence factors or just additional early sepsis markers? A comment. Inflammopharmacology 24: 287-289.
3. Koren E, Ginsburg I (2016) Synergistic Aspects to Explain the Pathophysiology of Sepsis and Septic Shock-An Opinion. J Infect Dis Ther.
4. Opal SM (2014) The current understanding of sepsis and research priorities for the future. Virulence 5: 1-3.
5. Opal SM, Dellinger RP, Vincent JL, Masur H, Angus DC (2014) The next generation of sepsis trials: What's next after the demise of recombinant human activated Protein C? Crit Care Med 42: 1714-1721.
6. Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, Kurosawa S, Remick DG (2011) The pathogenesis of sepsis. Annu Rev Pathol 6: 19-48.
7. van der Poll T, Opal SM (2008) Host-pathogen interactions in sepsis. Lancet Infect Dis 8: 32-43.
8. Rhodes A, Evans LE, Alhazzani W, Levy NM, Antonelli M, et al. (2017) Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43: 304-377.
9. Chaput C, A Zychlinsky (2009) Sepsis: the dark side of histones. Nat Med 15: 1245-1246.
10. Xu J, Zhang X, Pelayo R, Monestier M, Ammollo CT, et al. (2009) Extracellular histones are major mediators of death in sepsis. Nat Med 15: 1318-1321.
11. Varani J, Ginsburg I, Schuger L, Gibbs DF, Bromberg J, et al. (1989) Endothelial cell killing by neutrophils. Synergistic interaction of oxygen products and proteases. Am J Pathol 135: 435-438.
12. Ginsburg I, Mitra RS, Gibbs DF, Varani J, Kohen R (1993) Killing of endothelial cells and release of arachidonic acid. Synergistic effects among hydrogen peroxide, membrane-damaging agents, cationic substances, and proteinases and their modulation by inhibitors. Inflammation 17: 295-319.
13. Ginsburg I, Misgav R, Pinson A, Varani J, Ward PA, et al. Synergism among oxidants, proteinases, phospholipases, microbial hemolysins, cationic proteins, and cytokines. Inflammation 16: 519-538.
14. Ginsburg I, Kohen R (1995) Synergistic effects among oxidants, membrane-damaging agents, fatty acids, proteinases, and xenobiotics: killing of epithelial cells and release of arachidonic acid. Inflammation 19: 101-118.
15. Kohen R, Nyska A (2002) Oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. Toxicol Pathol 30: 620-650.
16. Ginsburg I (2002) The role of bacteriolysis in the pathophysiology of inflammation, infection and post-infectious sequelae. APMIS 110: 753-770.
17. Ginsburg I, Koren E, Feuerstein O (2015) Is Bacteriolysis In vivo a Friend or a Foe? Relation to Sepsis, Chronic Granulomatous Inflammation and to Oral Disorders: an Overview Hypothesis.
18. Hurley JC (1992) Antibiotic-induced release of endotoxin: a reappraisal. Clin Infect Dis 15: 840-854.
19. Hurley JC (1995) Antibiotic-induced release of endotoxin. A therapeutic paradox. Drug Saf 12: 183-195.
20. JM Prins, SJ van Deventer, EJ Kuijper, P Speelman (1994) Clinical relevance of antibiotic-induced endotoxin release. Antimicrob Agents Chemother 38: 1211-1218.
21. Chen R, Kang R, Fan XG, Tang D (2014) Release and activity of histone in diseases. Cell Death Dis 5: e1370.
22. Horn DL, Morrison DC, Opal SM, Silverstein R, Visvanathan K, et al. (2000) What are the microbial components implicated in the pathogenesis of sepsis? Report on a symposium. Clin Infect Dis 31: 851-858.
23. Wildhagen KC, García de Frutos P, Reutelingsperger CP, Schrijver R, Aresté C, et al. (2014) Nonanticoagulant heparin prevents histone-mediated cytotoxicity in vitro and improves survival in sepsis. Blood 123: 1098-1101.
24. Cohen J (2002) The immunopathogenesis of sepsis. Nature 420: 885-891.
25. Belum GR, Belum VR, Chaitanya Arudra SK, Reddy BS (2013) The Jarisch-Herxheimer reaction: revisited. Travel Med Infect Dis 11: 231-237.
26. Marshall JC (2014) Why have clinical trials in sepsis failed? Trends Mol Med 20: 195-203.
27. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, et al. (2015) Sepsis: a roadmap for future research. Lancet Infect Dis 15: 581-614.