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Tissue damage in post infectious sequelae is caused by a synergism between microbial and neutrophils-derived agonists: a concern for a disregard for already published data

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Abstract

Post infectious sequelae such as sepsis and septic shock are poorly understood and annually take the lives of millions over the world. Severe microbial infections caused by Gram Positive and Gram Negative bacteria and by fungi are the main causes, which are aggravated by the rapid development of antibiotic resistance. It is unfortunate that today all the clinical trials of sepsis which tested the efficacy of single antagonists failed. Sepsis was recently redefined as a synergistic multifactorial episode where no unique alarmin had been identified, which if inhibited could control the deleterious biochemical and immune immunological events characteristic of sepsis.

An apparent “breakthrough” in our understanding of sepsis pathogenicity was published in 2009 in Nature Medicine arguing that the main cause of mortality in sepsis is the release from neutrophils (PMNs) nets of highly toxic nuclear histone. This caused endothelial cell dysregulation leading to organ failure. However, this concept downplays the concept that concomitantly with the activation of PMNs, a plethora of additional pro-inflammatory agents is also released. These can act in synergy with histone to injure cells. Furthermore, since many additional clinical disorders not related to sepsis also reported high levels of circulating histones, this toxic agent may be considered just another marker of cell damage. The failure to treat sepsis by the administration of only single antagonists should be replaced by cocktails of appropriate anti inflammatory agents.

In 2009, two provocative articles were published in Nature Medicine suggesting that the main cause of death in sepsis is due to the release from neutrophils (PMNs) nets adhering to endothelial cells of highly bactericidal nuclear histones [1,2]. Dysregulation of endothelial cell functions then can lead to organ failure and demise of the patient. Cell damage and death could potentially be inhibited by heparin, activated protein C and by antibodies to histones [2]. However, these exciting and promising papers were soon followed by publications suggesting that high levels of circulating nuclear histones were also detected in other clinical disorders unrelated to sepsis, hinting that histones might not be the sole alarmin active agent in sepsis pathogenicity [3-9]. This assumption is based on a recent suggestion which re-defined sepsis as a multi-factorial synergistic phenomenon, where no single alarmin is generated which if neutralized successfully, might prevent the aftermath of severe microbial infections [9]. We also previously suggested that histone may not be a “unique evil alarmin” agent but only an additional “member of the gang” [8].

It is conceivable that concomitantly with PMN activation, consequent upon adherence to endothelial cell, the PMNs also release into the surrounding media a burst of NADPH-activated oxidants such as superoxide, nitric oxide (NO), peroxynitrite, HOCl and highly cationic peptides such as LL37, elastase, cathepsins C and G, many acid hydrolases and also TH1 cytokines probably have a role in the pathogenesis of cell damage in inflammation [10-27]. These toxic agents most probably do not act alone but in synergy (a crosstalk) with nuclear cationic histone and with additional cationic peptides to injure cells. Furthermore, the role played by the microbial cell-wall components LPS, lipoteichoic acid (LTA) and peptidoglycan (PPG) released following bacteriolysis induced either by antibiotics or by certain cationic peptides and their interactions with PMN products have not been clearly considered in the numerous publications on the role of histones in sepsis published in the literature [28-30].

It is therefore enigmatic and concerning that screening no less than 52 publications via Google Scholar and PUBMED, published since 2009, regarding the role of histones in the pathophysiology of sepsis revealed a disregard for a large number of publications on these subjects [10-30].

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Here, potentially, non-anticoagulant heparin may abolish not only histones' cationic charge toxic effect but also the synergism between histones and the various other pro-inflammatory agents generated by activated PMNs [31].

Disregarding this synergistic conceptual approach is a serious mishap/ flaw that may have halted advanced approaches to sepsis prevention and effective therapy of sepsis. This concept is also critical in view of the fact that actually all the clinical trials of sepsis conducted to date, which utilized only single antagonists have failed [32,33]. However, the suggestion made to replace single antagonists with cocktails of appropriate ant-inflammatory agents has not gained/ heeded any clinical interest to date [34]. After all, looking at similar models, today we successfully use cocktails of antagonists to treat the auto-immune deficiency syndrome (AIDS), tuberculosis and also malignancies. Why do we continue to pin our hopes on single antagonists when treating a multifactorial complex process like sepsis? [9].

Taken together, it is hoped that accepting the synergism concept of cell damage in post-infectious sequelae such as sepsis be reconsidered and that new approaches to sepsis treatment be established [35,36].

In conclusion, a cautionary comment

It is very obvious that today patients usually arrive at the Intensive Care Unit (ICU) too late when all the "horses have already left the stable" allowing the immune system to induce organ failure [37,38]. Novel means of detecting early markers of sepsis should be available to every family physicians office and indeed to first responders to recognize the severity of the illness. The inability to successfully control the deleterious aftermath of severe incurable microbial infections places sepsis and septic shock in the category of one of the least understood human disorders and may be categorized as an orphan disorder which necessitates a reassessment of our clinical approaches to dealing with post infectious sequelae.

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