

Roles of Complement and Extracellular Histones in Infectious Sepsis

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ABSTRACT

In North America, infectious sepsis is associated with bacteria, fungi, protozoa and viruses. It has been well established that age is an important factor. Septic patients of 60 years of age, or greater, are much more susceptible to lethality as compared to patients whose age is around 40 years of age. Recently, there is also evidence that sepsis associated with non-penetrating trauma, drug toxicity of liver, or hemorrhagic shock are associated with similar responses developing in infectious sepsis. Following onset of sepsis (infectious or non-infectious), during the first 2-3 days there is a “cytokine storm,” also involving proinflammatory chemokines. Typically, IL-1 β , IL-6, TNF and IL-17A and F rapidly rise in plasma. After day 3-4, this inflammatory cascade related to the innate immune system (involving neutrophils, macrophages and an array of proinflammatory mediators) results in reduced responsiveness of the innate immune system, followed by development of immune suppression. The precise molecular mechanisms for these outcomes are poorly understood. It is well known that sepsis activates the following complement activation pathways: classical, alternative and lectin pathways, resulting in release of two powerful anaphylatoxins: C3a and C5a. Each anaphylatoxin has powerful proinflammatory functions. In the setting of sepsis, C5a reacts with its high affinity receptors (C5aR1, C5aR2), especially on phagocytes (neutrophils, macrophages), resulting in release of proinflammatory factors (proteases, oxygen-derived free-radicals, extracellular histones, etc.). C5a has a molecular weight of approximately 12 kDa and is freely diffusible locally. Histones have only recently been shown to be released with a variety of inflammatory products from phagocytic cells activated by C5a. There is a great deal of work going on to define precisely how histones contribute to the adverse outcomes of sepsis.

Keywords: C5a anaphylatoxin; Multiorgan dysfunction; Innate immune system

ROLE OF C5a IN SEPSIS (INFECTIOUS, NON-INFECTIOUS)

Several years ago, we developed a rabbit antibody (IgG) that blocked mouse C5a when mouse neutrophils (PMNs) were incubated with C5a [1]. In the model of polymicrobial sepsis in young mice (3-4 months old), the antibody was highly protective, reducing the intensity of the cytokine and chemokine “storm” substantially, as determined by plasma levels of IL-1 β , IL-6, TNF and IL-17A and IL-17B, greatly improving survival after polymicrobial sepsis. We also demonstrated that this anti-C5a markedly reduced the intensity of acute lung injury (ALI) in mice following intratracheal administration of IgG immune complexes, rmC5a or LPS [2]. An engineered human mAb to human C5a has been developed and has been tested in Germany

and found to be safe when infused into healthy young adults. However, full-scale clinical trials have not yet been completed.

An alternative approach would be to use low molecular weight inhibitors to block the function of C5aR1 [3]. Several companies are developing low molecular weight inhibitors, but none have been assessed for safety and efficacy in septic humans. One of the concerns has been that C5aR2, which was also discovered by Gerard and colleagues, was originally described as a “scavenger receptor” which in the presence of C5a would not evoke responses in neutrophils [4]. It was postulated that C5aR2 was a natural regulatory protein for C5a. However, some reports, including our study dealing with ALI, indicated that both C5aR1 and C5aR2 contributed significantly to the development of ALI. Because of divergent reports related to the role of C5aR2

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in inflammatory injury, this has reduced the interest of pharmaceutical companies in developing an inhibitor of C5aR2, until this disparity is resolved.

ROLE OF EXTRACELLULAR HISTONES IN INFECTIOUS SEPSIS

In the past few years, there has been accumulating evidence that extracellular histones play an important role in various inflammatory disorders such as atherosclerosis [5] and infectious sepsis. Histones are important structural proteins in chromosomes, affecting a variety of functions in intact cells. In histones, DNA is wrapped around histones to create octamers, creating the nucleosome. Six nucleosomes are assembled to form a histone which also contains an important protein. The protein can be modified after cell contact to undergo changes including acetylation or deacetylation, methylation or demethylation, or ubiquitination. Such changes will alter responses of cells with histones in terms of signaling pathways. It is now known that some agonists, such as C5a or LPS, will also cause cells to release their histones which are referred to as “extracellular histones” [6,7].

Extracellular histones have strong proinflammatory activities and can be identified in plasma by ELISA technology. In mice undergoing polymicrobial sepsis, plasma histone content peaks in the first day or two, with levels of approximately 25 µg/ml. Similar levels have been found in plasma of septic humans, based on advanced mass spectrometry [8]. In mice with polymicrobial sepsis, neutralization of plasma histones has greatly improved survival which also appears to blockade of C5a by antibody [7]. It is going to be important to further refine the details of these studies.

Using mouse peritoneal exudate macrophages, release of IL-6 was most effective in the presence of H2A, followed by H2B, with much smaller responses with other histones. TNF release was greatest in presence of H2A=H2B. With CXCL1, data were similar to release of TNF. The same was true for CXCL2, as well as for CXCL3. The pattern of release of TNF and IL-6 from mouse peritoneal neutrophils also indicated that H2A and H2B were released in the greatest levels. All of these data have recently been published, indicating that in macrophages and

neutrophils, H2A and H2B seem to have the greatest ability to cause the release from phagocytes. Obviously, there is much more to be determined about the biological functions of histones in the setting of sepsis.

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DISCLOSURES

The authors confirm there are no competing financial interests to declare.

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