Commentary

Lymphocytes, apoptosis and sepsis: making the jump from mice to humans

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Abstract

Sepsis is an important clinical problem with a mortality rate of 20% to 30%. Lymphocyte apoptosis has been recognized as an important step in the pathogenesis of experimental sepsis, by inducing a state of 'immune paralysis' that renders the host vulnerable to invading pathogens. The importance of lymphocyte apoptosis in human disease is now confirmed by Weber and colleagues, who demonstrate extensive apoptosis in circulating lymphocytes from patients with severe sepsis. Weber and colleagues' data set the basis for further studies aimed at modulating lymphocyte apoptosis in sepsis.

Lymphocyte apoptosis has been increasingly recognized as an important step in the pathogenesis of sepsis, by inducing a state of 'immune paralysis' that renders the host vulnerable to invading pathogens [1]. Sepsis is an important clinical problem, affecting more than 700,000 people each year in the United States alone, of whom 20% to 30% die [2]. The costs associated with sepsis amount to approximately $17 billion per year [3]. Clearly, sepsis is a major health problem and novel therapeutic strategies are required.

The traditional paradigm has been that sepsis results from an uncontrolled inflammatory response. This paradigm led to the development of agents aimed at blocking key mediators of inflammation, such as bacterial lipopolysaccharide, interleukin-1, and/or tumor necrosis factor-α among others. However, when many of these agents were tested in large phase III randomized controlled trials they failed to demonstrate a beneficial effect [4-6]. Thus, therapeutic strategies aimed at suppressing inflammation in sepsis have been disappointing.

Over the past decade, studies in experimental models and in patients suggested that the immune response of sepsis follows a biphasic pattern, with an initial 'hyperinflammatatory' phase characterized by high levels of pro-inflammatory cytokines, and a second phase characterized by decreased responsiveness of immune cells to inflammatory stimuli - the 'immunoparalysis' phase [7,8]. The immunoparalysis phase is an extremely vulnerable period when patients are at particular risk from invading bacteria. The mechanism for this immune paralysis appears to involve apoptosis of immune cells, in particular lymphocytes.

In a seminal study, Wang *et al*. [9] found that the intraperitoneal injection of Gram-negative bacteria to mice was followed by apoptosis of CD4+CD8+ lymphocytes in the thymus. Hotchkiss *et al*. [10,11] used a murine model of cecal ligation and puncture to show that lymphocyte apoptosis also involves lymphocytes from the spleen and most other vital organ systems, and later demonstrated that extensive lymphocyte apoptosis is also present in humans with sepsis. Studies using loss-of-function approaches suggested that the mechanisms of lymphocyte apoptosis in sepsis involve both the receptor-mediated and the mitochondrial pathways of apoptosis, with the later playing the predominant role (reviewed in [12]). Weber *et al*. [1] now extend these laboratory observations to the bedside, by demonstrating accelerated apoptosis in circulating lymphocytes (CD4, CD8 and CD19) from patients with severe sepsis, but not in non-septic, critically ill patients. This study is important because it confirms a pattern of activation of Bcl-2 family members predicted by animal studies, and sets the basis for further studies aimed at modulating lymphocyte apoptosis in sepsis.

One particularly interesting finding in Weber and colleagues' study is that the pro-apoptotic molecule Bim was markedly upregulated in the lymphocytes of patients with severe sepsis. This is important because, of the different components of the apoptosis cascade that have been tested in

animal models (FADD, Bid, Bcl2, caspases), only deletion of Bim is associated with complete protection from apoptosis [13]. However, it is important to note that blockade of lymphocyte apoptosis is not always protective in sepsis. For example, septic mice lacking MyD88 have decreased lymphocyte apoptosis but a significant increase in mortality [14]. MyD88 is an important proximal component of the main pathogen recognition pathways, suggesting that inhibition of lymphocyte apoptosis is protective only when the ability of the host to identify and respond to pathogens is preserved.

The study has some caveats. Patients were enrolled 4 hours after presentation, which may have been too early in the hospital course to catch the period of maximal apoptosis. Also, information on the effects of severe sepsis on the receptor-mediated pathway of apoptosis, particularly FADD and caspase 8, would have been interesting.

In summary, the study by Weber and colleagues reaffirms and advances our knowledge of specific pathways involved in lymphocyte apoptosis in patients suffering from severe sepsis, raising hopes for potential therapeutic targets that improve mortality in this patient population.

Competing interests

The authors declare that they have no competing interests.

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