

COMMENTARY

Immunity, inflammation and sepsis: new insights and persistent questions

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See related research by Giamarellos-Bourboulis *et al.*, <http://ccforum.com/content/15/1/R27>

Abstract

Sepsis is now understood to affect a variety of changes in the host, chief among them being alterations in immune system function. Proper immune function involves a competent proinflammatory response to stimuli as well as a regulated counteracting force to restore homeostasis and prevent systemic inflammation and organ dysfunction. Broad-spectrum suppression of the inflammatory response has not been shown to be beneficial for patients suffering from septic disease. In fact, sepsis-related immune suppression has become increasingly recognized as an important contributor to late morbidity and mortality in the critically ill. Giamarellos-Bourboulis and colleagues detail the impaired ability of septic patients to produce proinflammatory cytokines upon *ex vivo* stimulation, and introduce altered caspase-1 activity as potentially contributory to this process. Proper understanding of the cellular and molecular events resulting in immune suppression following sepsis is important in the identification of new strategies for treatment and the ideal timing of therapy.

In their most recent work, Giamarellos-Bourboulis and colleagues examine sepsis-related immune dysfunction by assessing the proinflammatory cytokine production capacity in septic patients and healthy volunteers following *ex vivo* stimulation [1]. A critical examination of their article not only reveals new insights into the possible mechanisms underlying sepsis-related immune system dysfunction, but also highlights the difficulties inherent in this line of inquiry. The authors report that septic

patients' isolated leukocytes produced lower amounts of the proinflammatory cytokines IL-1 β , IL-6 and, to a lesser extent, TNF α when stimulated within 24 hours of Gram-negative sepsis onset. Interestingly, greater severity of sepsis was correlated with a greater degree of impairment. Results were similar in healthy volunteers challenged with lipopolysaccharide, indicating an early shift to an immune-suppressed phenotype following systemic inflammation.

In our current understanding, an early anti-inflammatory phenotype following close on the heels of a severe inflammatory challenge (sepsis, trauma, burn injury, and so forth) acts as a counterweight to the systemic inflammatory response syndrome and restores immune homeostasis [2]. When short-lived and self-limited, this anti-inflammatory surge is best termed the compensatory anti-inflammatory response syndrome (CARS). In some patients, however, CARS is pathologically exaggerated and prolonged (beyond 48 hours). This persistent state – known as immunoparalysis – is associated with increased rates of nosocomial sepsis, multiorgan dysfunction syndrome and death in critically ill patients [3-5]. Although the features are similar, the distinction between CARS and immunoparalysis is important when contemplating therapy. The issue is one of timing: to reverse physiologic CARS too early in the course of illness risks further inflammatory insult. The literature, however, suggests that pathologic immunoparalysis is reversible, to the benefit of the patient, without iatrogenic hyperinflammation [6-8].

Although the identification of immunoparalysis, its impact on outcome, and its potential reversibility are becoming increasingly understood, relatively little is known about the cellular and molecular mechanisms driving the process. Previous authors have investigated the mechanisms of immunoparalysis at the transcriptome level [9-11]. This current report makes the case for post-translational forces as well. In addition to *ex vivo* cytokine production, Giamarellos-Bourboulis and colleagues examined levels of caspase-1, a protease that cleaves pro-IL-1 β into its active form. In their septic patients, reduced IL-1 β production capacity was associated with

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markedly diminished caspase-1 levels. In their healthy volunteers, injection with lipopolysaccharide resulted in lower levels of caspase-1, as well as impaired production of IL-1 β . Heretofore, immunoparalysis research has largely centered on the canonical proinflammatory cytokine TNF α . (Indeed, assessing *ex vivo* lipopolysaccharide-induced TNF α production capacity by isolated monocytes is a commonly used method for diagnosing immunoparalysis [2].) By introducing altered IL-1 β biology as a contributory process in the development of CARS/immunoparalysis, the authors lay the ground work for additional avenues of research into the cause(s) or diagnosis of these conditions. Further research is necessary to confirm a causal link between impaired caspase-1 function and IL-1 β production. It is also important to note that, like TNF α , IL-1 β is one of myriad proinflammatory cytokines whose production and regulation may be altered in immunoparalysis.

Despite these new and interesting contributions, placing the current work by Giamarellos-Bourboulis and colleagues into proper context is complicated by their study design. The early (within 24 hours) sampling window, without additional longitudinal samples, makes it impossible to distinguish patients with physiologic CARS from those with pathologic immunoparalysis. Previous evidence has shown that only patients unable to reverse an early anti-inflammatory phenotype by 3 to 4 days are at increased risk of poor outcome [3]. An early anti-inflammatory phenotype (possible CARS) is thus apparently not as concerning as prolonged immune suppression (probably immunoparalysis). Unfortunately, the mechanisms or predispositions mediating the transition from CARS to immunoparalysis are currently unknown.

The work by Giamarellos-Bourboulis and colleagues, and that of many other researchers, seeks to uncover the events surrounding sepsis-related immune system dysfunction. By understanding the mechanisms involved, such as altered caspase-1 action, novel therapeutic targets may be identified. Through careful targeting of therapy to those patients with true immunoparalysis, the best chance for improved outcomes will be realized.

Abbreviations

CARS, compensatory anti-inflammatory response syndrome; IL, interleukin; TNF, tumor necrosis factor.

Competing interests

The author declares that he has no competing interests.

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