CRITICAL CARE

COMMENTARY

Early alterations of B cells in patients with septic shock: another piece in the complex puzzle of the immune response in sepsis

Massimo Girardis*[1] and Andrea Cossarizza[2]

See related research by Monserrat *et al.*, http://ccforum.com/content/17/3/R105

Abstract

Impairment of the inflammatory-immune response is currently accepted as a hallmark of severe sepsis even in the early stages of the disease. In this context, the alterations of the circulating B-lymphocytes have never been described in detail. The study by Monserrat and colleagues in the previous issue of *Critical Care* indicated that, in patients with septic shock, the B-cell compartment is early and deeply altered with different patterns in subset distribution and activation between survivors and non-survivors.

The immune system has evolved for several million years to ameliorate the defenses of our organism from any kind of pathogens, including those causing sepsis, a life-threatening condition in which almost all components of the innate and adaptive immune system have to work together in a coordinated manner. However, in septic hosts, a deregulated response to infection may lead to a sustained systemic inflammation that causes the failure to clear primary pathogens and alters immune responses. The study by Monserrat and colleagues [1] in the previous issue of *Critical Care* adds one more piece in this complex puzzle by evaluating the early subset distribution and activation of circulating B-lymphocytes in patients with septic shock. But what is the relevance of the B-cell compartment in this puzzle? To better understand this issue, a brief and schematic description of the immune response is desirable.

Inflammatory response to pathogens can be triggered by several mechanisms. The first is the activation of several Toll-like receptors present on cells of the innate immunity (for example, monocytes, granulocytes, dendritic cells, and natural killer cells) that recognize pathogen-associated molecular patterns (PAMPs) present in or released by the invading microorganisms. The activation of these cells results in the production of pro-inflammatory cytokines – that is, interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α) – and vasoactive peptides, complement, and reactive oxygen species that together start a generalized inflammation [2]. A second response mechanism involves the activation of $CD4^+$ T lymphocytes that bear particular amino-acid sequences in the variable region of the β-chain (V) of their T-cell receptor (TCR). Each T cell bearing a given Vβ TCR can bind bacterial (or even viral) products in a non-major histocompatibility complex-restricted manner (that is, outside from the region where the clonal-specific recognition of a unique antigen occurs); for this reason, such molecules, which activate a large percentage of T cells that are in fact specific for other molecules, are defined as superantigens (SAgs) [3]. An SAg like the staphylococcal enterotoxin B is massively released during sepsis and can activate up to 30% of T cells, which produce several cytokines, including IL-17A, IL-2, interferon-gamma, and TNF-α. However, activated cells have a high tendency to develop mitochondrial damage and undergo apoptosis, and this clearly results in a further impaired immune response [4]. Pro-inflammatory cytokines can also activate a high amount of B cells. A family of B-lymphocytes (known as B-1 cells, which are unable to further differentiate into mature B cells) located mainly in the peritoneal and pleural cavities can produce immunoglobulin M (IgM) and IL-10 and modulate the systemic inflammatory response. Studies in mice have identified the presence of an effector B-cell population that protects against microbial sepsis [5]. These cells, defined as innate response activators, depend on PAMP receptors and produce granulocyte-macrophage colony-stimulating factor. Their deletion impairs bacterial

*Correspondence: girardis.massimo@unimo.it
[1]Intensive Care Unit, University of Modena and Reggio Emilia, L.go del Pozzo 71, 41125 Modena, Italy
Full list of author information is available at the end of the article

clearance, elicits a cytokine storm, and can precipitate septic shock.

The above brief description highlighted the role and the importance of the B-cell compartment in the initial immune response to infection; hence, the data provided by Monserrat and colleagues [1] are really helpful in providing more insight in this issue. In 52 septic shock patients who were admitted to the intensive care unit (ICU), the authors observed an early (that is, within 24 hours) and sustained circulating B-cell reduction that was associated with a significant redistribution of B-cell subsets compared with healthy subjects. The $CD19^+CD23^+$ B cells (activated regulatory B cells) were lower in non-survivors than in survivors for the 7 days of the follow-up, whereas $CD19^+CD69^+$ (early activated B cells) and the expression of critical antigens on B cells (CD80, a T-cell co-stimulation molecule, and CD95, an apoptosis susceptibility marker) were higher in non-survivors. Moreover, lymphopenia and an increased expression of CD80 persisted in survivors for all 28 days of the study period. The authors concluded that, in patients with septic shock, the circulating B-cell compartment is early and deeply altered in both quantitative and qualitative terms and that there is a close relationship between these alterations and patient outcome.

The final message from the article is sound and in accordance with previous studies on the other components of the immune response (that is, dendritic cells, natural killer cells, and T-lymphocytes) that in patients with septic shock revealed a significant decrease in the number and function of the immune cells with early signs of apoptosis and cell exhaustion in non-survivors [6-10]. However, the reasons for this different pattern between survivors and non-survivors remained to be clarified. A recent article by Gogos and colleagues [9] indicated that the alterations in natural killer cells and T-lymphocytes depend on the severity of sepsis and the site and type of infection. The time length from infection to the onset of septic shock (and to its treatment) may also have an important role: the longer the time, the larger the expected activation and exhaustion of the inflammatory and immune response [10,11]. Lastly, genetic factors could also be connected to the expression of different immune patterns among patients with similar types of infection and sepsis severity [12]. Unfortunately, owing to the low number of patients studied and the difficulties to define the time length from infection to ICU admission, the article by Monserrat and colleagues [1] cannot offer a proper analysis of these issues and leaves the question open.

Whatever the reasons for the differences observed in the immune system, the study by Monserrat and colleagues emphasizes once again that immunosuppression is common even in the early stages of sepsis and that patients with sepsis constitute a complex and heterogeneous population requiring specific monitoring and individualized therapeutic approaches. Immune-modulatory therapies tailored to the immune state of the patients will be the object of future clinical trials [13]. In the meantime, as in other pathologies with variable disorders of the immune system (for example, cancer and rheumatologic diseases), monitoring the immune-inflammatory state in septic shock patients admitted to the ICU could be useful for identifying the high-risk patients and the fluctuating inflammatory-immune response.

Abbreviations

ICU, intensive care unit; IL, interleukin; PAMP, pathogen-associated molecular pattern; SAg, superantigen; TCR, T-cell receptor; TNF-α, tumor necrosis factor-alpha; V, variable region of the beta-chain.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Intensive Care Unit, University of Modena and Reggio Emilia, L.go del Pozzo 71, 41125 Modena, Italy. [2]Immunology, Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, via Campi 287, 41125 Modena, Italy.

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