Abstract:

The systemic inflammatory response syndrome is a manifestation of the host's immune response to infection. With an aim to eradicate the pathogen, the immune system is activated to encourage a state of inflammation, which is followed by a number of interactions to restore homeostasis. This balance is mediated by a complex interplay among many immune components, which at times can lead to an excessive anti-inflammatory environment, the compensatory anti-inflammatory response syndrome. Numerous cellular and chemokine mediators such as monocytes and granulocyte-macrophage colony-stimulating factor are involved in the manifestation of this syndrome and, if further dysregulated, can lead to immunoparalysis, a prolonged anti-inflammatory environment placing the host at risk for potentially life-threatening infections. Understanding these complex immune reactions may help better identify immune dysregulation during sepsis, holding important implications for the clinician when managing septic patients.

Keywords:

sepsis; immune system; systemic inflammatory response syndrome (SIRS); compensatory anti-inflammatory response syndrome (CARS); immunoparalysis

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Immune Dysregulation in Sepsis

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The host response to overwhelming infection can lead to the harmful constellation of symptoms manifested clinically as the systemic inflammatory response syndrome (SIRS).[1] This condition is a result of an intricate interplay between the innate and adaptive immune systems. The ultimate aim of this interaction is to eradicate the infection from the host; however, as the immune system strives to return to a state of equilibrium, this same interaction can lead to profound immune dysregulation. Anti-inflammatory pathways counter the initial inflammatory response in an attempt to restore the host to homeostasis. Excessive activation of these pathways may lead to a maladaptive anti-inflammatory environment, the compensatory anti-inflammatory response syndrome (CARS). During this period, the host immune system response is blunted, which can lead to prolonged immunosuppression, or immunoparalysis.[1,2] This unbalanced immune state can place affected children at risk for poor outcomes such as secondary infections and mortality.[1–4]

INNATE AND ADAPTIVE IMMUNITY

A review of the expected host response to pathogens is crucial to understanding the progression to both CARS and immunoparalysis. The innate immune response to an infection is rapid, broad, and not pathogen specific. The precursor to activating the innate immune response is activation of first-line host cells such as monocytes, neutrophils, mast cells, natural killer cells, and dendritic cells, by the pathogen.[2] These, together, recognize a threat via pathogen-associated molecular patterns, a general group of pathogen molecules that activate receptors, primarily toll-like receptors, which are present on cells within the innate immune system.[5] The process is designed to eradicate the offender as rapidly as possible, using mechanisms such as phagocytosis and other modes of intercellular death. This leads to a rapid release of proinflammatory cytokines and

chemokines, such as interferon-α, tissue necrosis factor α (TNF-α), interleukin (IL) 1, and IL-12.[5] Recruitment and activation of macrophages by cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, and interferon-α promote phagocytosis, opsonization, debris clearance, and further microbicidal and tumoricidal activity.[2,5] This broad immune response leads to an inflammatory state that, when kept in check, can help to eradicate the pathogen and clear infection; organ dysfunction is encountered when this rapid response is unchecked by counter-regulatory mechanisms.[6,7]

This innate response creates the foundation for the subsequent antigen-specific stage, known as *adaptive immunity*, which perpetuates the inflammatory process in a much more targeted fashion.[6,8] Adaptive immunity involves long-term mobilization of the host immune system and takes days to achieve. Monocytes are activated to macrophages, which play a major defensive role against pathogens via antigen presentation. The antigen is presented onto major histocompatibility complex class II molecules on the surface of the macrophage. One such molecule, human leukocyte antigen (HLA-DR), presents the antigen on the macrophage surface to T cells. Although this activates the adaptive immune system, T cells also play a key role in the development of CARS/immunoparalysis.[9] They do this by producing both proinflammatory and anti-inflammatory signals, which help to regulate the immune response to avoid progressing toward SIRS or CARS.[10]

The differentiation of T cells into $CD4^+$ lymphocytes (helper T cells) and the smaller subtype T-helper 1 (T_H1) and T-helper 2 (T_H2) cells plays a critical role in regulating the inflammatory state.[9,10] T_H1 cells may be thought of as the proinflammatory lymphocyte, whereas T_H2 cells are the anti-inflammatory counterpart. The former release GM-CSF and interferon-γ, which activate macrophages and promote phagocytosis. T_H1 cells also secrete TNF-α, which activates endothelia and induces fever. Conversely, T_H2 cells induce B lymphocytes to release neutralizing antibodies and produce anti-inflammatory cytokines such as transforming growth factor B (TGF-B), IL-4, IL-6, IL-10, and IL-13, all of which inhibit macrophage activation and further stimulate T_H2 production.[10]

COMPENSATORY ANTI-INFLAMMATORY RESPONSE AND IMMUNOPARALYSIS

During proinflammatory states, the adaptive immune system modulates the degree of inflammation by producing counter-regulatory cytokines and cell mediators. SIRS represents the extreme of a proinflammatory state, whereas its anti-inflammatory counterpart is CARS, a state characterized by promotion of immune suppression and down-regulation of systemic inflammation.[11] Historically, the first description of CARS evolved from a more complete understanding of SIRS and septic shock. Early research on sepsis suggested that death was caused by an extreme proinflammatory state.[12] The theory that massive, uncontrolled inflammatory cytokines led to death prompted a number of trials that attempted to directly or indirectly block these proinflammatory cascades. These studies used high-dose glucocorticoids and antibodies directed against inflammatory mediators such as endotoxin, TNF-α, and IL-1. Unfortunately, there was no improvement in overall survival after sepsis.[10] Subsequent studies that examined the trajectory of immune response during septic shock suggested that the development of a persistent compensatory anti-inflammatory state was detrimental, leading to increased susceptibility to infections and death.[13] Furthermore, it was recognized that death occurred later in sepsis and was associated with the development of secondary infections despite broad-spectrum antibiotics.[13] Similar findings were reported in patients with other etiologies of profound SIRS, such as burns, who demonstrated impaired lymphocyte function, and an overall state of anergy, leading to increased susceptibility to infections.[14] This prolongation of an anti-inflammatory environment, despite resolution of the inflammatory state, was termed *immunoparalysis*.

The balance of this immune environment is dictated by activation of adaptive immunity via innate immunity, which involves an interplay among several cellular/molecular components such as lymphocytes, monocytes, and neutrophils. As discussed earlier, when an antigen is presented to a naïve $CD4^+$ lymphocyte via HLA-DR cell surface receptors of the phagocyte, it differentiates into 4 subtypes (T_H1, T_H2, regulatory T cells [T_{reg}], T-17).[10] One factor that leads to the development of CARS is overactivity of the anti-inflammatory subtype T_H2. In addition, T_{reg} promote immunosuppression through secretion of IL-10, TGF-B, and inhibiting proinflammatory cells. Interleukin 10 is thought to be one of the most relevant cytokines in CARS because it regulates T-cell populations and participates in a number of immunosuppressive roles, including down-regulation of TNF.[10,15] Finally, T-17 lymphocytes have been shown to mediate chemotaxis.[10] Pathologically, CARS is characterized by a predominance of T_H2 cells over T_H1 cells, decreased circulating monocytes and neutrophils, and a predominance of T_{reg} cells.[12] In the