Immune Activation in Sepsis

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KEYWORDS

• Sepsis • Inflammation • Immunosuppression

KEY POINTS

- Sepsis is a dysregulated multisystem response to infection.
- The immune responses begin as compartmentalized, progressive processes of microbial recognition, followed by triggering and amplification of inflammation and homeostatic regulation.
- How these immune responses become dysregulated and maladaptive remains a key conundrum.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] These dysregulated host responses underpin the clinical phenotypes that range from a mild, self-limiting illness to a severe progressive illness resulting in multiorgan failure and death. A complex, interlinked system of cells, receptors, secreted proteins, enzymes, and structural and chemical defense elements such as epithelium and associated antimicrobial proteins, together referred to as the immune system, protect the human body from infection. This protection involves four interlinked tasks: danger signal surveillance and recognition from nonself, effector functions in response to sensing danger signals, homeostatic regulation, and generation of immunologic memory in certain situations. Functionally distinct innate and adaptive immune systems work in synergy to perform these tasks. In this article, a simple conceptual overview is provided of the current understanding of these dysregulated immune responses in sepsis.

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Overview of Innate and Adaptive Immune System Response to Pathogens

Pathogens access a normally sterile area following breach of either epithelial or mucosal barriers (infection). The innate immune system is the first line of defense against infections (surveillance and recognition of nonself). The innate immune system consists of cells of myeloid lineage with the ability to clear and kill pathogens by phagocytosis (such as granulocytes, monocytes/macrophages, and dendritic cells) and the complement system of proteins, aside from epithelial- and mucosa-associated structural and chemical defense mechanisms.

Innate immunity to infection can be broadly categorized into two categories:

An immediate response (0–4 hours), where the infection is recognized by preformed, nonspecific, and broadly specific effectors such as the complement system

An early induced immune response (beyond 4 hours) with recruitment and activation of effector cells that rely on evolutionarily conserved pattern recognition receptors (PRRs) of danger signals for infection clearance

Innate immune cells with the ability to process and present antigens (antigen-presenting cells; APCs), in particular dendritic cells, form a link to the adaptive immune system. These inform the adaptive immune cells of danger, on the need to generate a specific immune response against the inciting pathogen, and also provide essential initiating signals for these responses. This occurs in secondary lymphoid organs such as spleen, lymph nodes, and mucosal-associated lymphoid tissues (MALT). The adaptive immune system consists of 2 major cell types: B and T lymphocytes. These cells express specific antigen-detecting receptors on the cell surface: B cell receptors (BCRs) and T cell receptors (TCRs). In contrast to the innate immune cell PRRs, the adaptive immune cell receptors have antigen specificity, (ie, the ability to individually identify different antigens as opposed to common patterns on antigens). This specificity is a product of creation of a diverse repertoire of receptors, plus selection and clonal expansion of the adaptive immune cells.

Complement and Coagulation Cascades in Sepsis

On breaching the epithelial surface barrier, the pathogen encounters complement system proteins (C), a group of soluble proteins produced by the liver that circulate normally in an inactive form. The complement system can be activated by antibody-coated pathogens (classical pathway), by the pathogen alone (alternative pathway), and by carbohydrate-binding proteins (eg, mannose-binding lectin, ficolins) that coat the pathogens (lectin pathway). All three pathways converge on generating a C3 convertase enzyme that cleaves the complement protein C3 into C3a and C3b. C3b remains on the pathogen surface as a potent opsonin that is recognized by phagocytes. C3a is released into the circulation, acting as a potent proinflammatory molecule that recruits more phagocytes to the site of infection. In sepsis, the complement system undergoes massive activation with deleterious effects. This is predominantly mediated by the activated complement molecules C3a and C5a, the anaphylatoxins.[2] The systemic activation of the coagulation and fibrinolytic systems results in deposition of fibrin and formation of microthrombi in the microcirculation; this may contribute to the impaired microcirculation seen in sepsis.[3] Activated complement products, C5a in particular, activate the coagulation system via tissue factor,[4] while thrombin from the activated coagulation cascade cleaves C5 into C5a and C5b independent of its upstream pathways.[5] This illustrates the positive feedback loop seen in sepsis between the dysregulated, systemic activation of the complement, coagulation, and fibrinolytic cascades, exacerbating tissue damage and organ dysfunction.[6,7]