Abstract:
Sepsis is a clinical syndrome characterized by activation of the host inflammatory system in response to infection. The initial phase, manifested by shock, fever, and hypermetabolism, is largely secondary to a hyperinflammatory state and is responsible for the classic signs and symptoms of early sepsis. This review focuses on the early events after infection, offering an overview of the innate immune response in the sepsis syndrome, and concludes with a discussion of immune-targeted therapies.

Keywords:
sepsis; innate immune system; pattern recognition receptors; toll-like receptors; immunotherapy; cytokines; chemokines; complement; endothelium

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The Role of the Innate Immune System in Sepsis

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Central to the sepsis syndrome is the activation of host inflammatory cells and systemic release of inflammatory mediators in response to an infection. The innate immune system (IIS), an ancient and evolutionarily conserved process to combat pathogens, represents the first line of host defense against invading microorganisms. The IIS is composed of physical barriers, including the epithelial and endothelial layers, pattern recognition receptors (PRRs), complement, and a variety of effector cells, most importantly, neutrophils, monocytes, and natural killer (NK) cells. In response to an invading pathogen, the IIS initiates and propagates an inflammatory response that culminates in the clearance of microorganisms through phagocytosis and complement-mediated lysis. Simultaneously, it initiates an adaptive immune response through antigen presentation and lymphocyte recruitment.[1,2] To accomplish these goals, the IIS has a hardwired series of PRRs that identify both pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) released by the host.[3] Activation of PRRs results in altered gene transcription leading to an inflammatory burst. A balanced response by the IIS is essential for the restoration of homeostasis after pathogen clearance. When disproportionate, the innate immune response may drive excessive inflammation and organ injury, contributing to severe sepsis and septic shock.[4,5] This chapter will first discuss the clinical aspects of sepsis related specifically to the inflammatory burst, then provide an overview of critical elements of the innate immune response (the barriers, effectors, immune cells, and coagulation), briefly discuss cellular and mitochondrial dysfunction, and finally end with a discussion of attempted therapies directed against the innate immune response.

CLINICAL IMPACT OF THE INNATE IMMUNE RESPONSE

Many of the common clinical manifestations of infection relate to inflammation and the metabolic demands necessary to generate a fever. Raising the body's temperature is intended to impair pathogen replication and survival. This is achieved in the hypothalamus, where an altered inflammatory milieu increases the internal thermostat set point.[6] Heat must be generated as a by-product of metabolism, thus the rate of energy expenditure by the cells increases dramatically.[7] To meet the demand for oxygen, the cardiac output must increase, explaining why tachycardia is an almost universal sign of fever generation. With increased oxygen consumption, the production of carbon dioxide increases, resulting in compensatory tachypnea. Changes in vascular tone occur to redistribute blood flow, conserve heat, and promote immune cell migration to the site of infection. With ongoing inflammation, cellular and mitochondrial dysfunction may develop and contribute to deranged metabolism and organ dysfunction. Cumulatively, these changes drive the systemic demand for oxygen, and if demand outstrips cardiac output, shock develops. Beyond these global changes in the host response, innate immune effectors, unregulated coagulation, and endothelial failure contribute to organ dysfunction in severe sepsis.[8,9]

INNATE IMMUNE BARRIERS

Physical barriers are the cornerstones of innate immunity. Preventing pathogen invasion is far more efficient than clearance. The stratified squamous epithelium provides an effective barrier against pathogen entry at the skin and mucous membranes.[10] High cell turnover from the outmost layers also promotes shedding of adherent microorganisms. Mucous membranes have additional defenses, including secreted antimicrobial peptides (defensins) and resident macrophages that efficiently clear invading pathogens.[11-13] When a breach occurs, either through barrier disruption or successful penetrance, additional tiers of the IIS are engaged.

PATHOGEN RECOGNITION AND THE INITIATION OF INFLAMMATION

The initial recognition of potential threats is mediated by PRRs that identify both PAMPs and DAMPs.[3] PRRs are expressed on many cell types, including epithelial, endothelial, and professional antigen-presenting cells including macrophages and dendritic cells.[14,15] PRRs are a central component of the IIS that activate transcriptional pathways for the generation of cytokines.[16] PAMPs are conserved motifs expressed by a variety of pathogens, such as the bacterial cell wall components lipopolysaccharide (LPS) and peptidoglycan or microbial nucleic acids.[17] DAMPs are host-derived molecules released during inflammatory stress, often secondary to tissue damage and cell death. Examples include reactive oxygen species, extracellular adenosine triphosphate, heat shock proteins, fibrinogen, and hyaluronic acid.[18,19]

Toll-like receptors (TLRs) form the foundation for our understanding of the PRRs and their role in sepsis. When the TLRs are presented with their ligand(s), they initiate transmembrane signaling,[20] most often through the adaptor protein myeloid differentiation primary response 88, and drive transcription of cytokines through nuclear factor–κB (NF-κB).[21] Two TLRs, specifically TLR3 and TLR4, can use an additional pathway to activate NF-κB via different downstream mechanisms.[22] Additional PRRs include the retinoic acid–inducible gene I–like receptors, the nucleotide-binding oligomerization domain–like receptors, C-type lectin receptors, and absence in melanoma 2–like receptors. The identification of these PRRs has significantly advanced our understanding of infection and the pathophysiology of sepsis.[23]

The Inflammasome

Upon stimulation by their ligands, certain members of the nucleotide-binding oligomerization domain–like receptor family have the ability to form multimeric protein complexes known as inflammasomes. These inflammasomes serve to activate caspase 1, which allows maturation and secretion of the potent proinflammatory cytokines of the interleukin 1 (IL-1) family. Interleukin 1β (IL-1β), the prototypic inflammatory cytokine, has the ability to increase the expression of virtually all other cytokines, chemokines, and adhesion molecules. It is one of the main inducers of fever via cyclooxygenase 2–mediated production of prostaglandin E2 in the brain and likely contributes to peripheral vasodilation through the enhancement of inducible nitric oxide expression. In addition, IL-1β can stimulate bone marrow production and release of effector cells, especially neutrophils and platelets.[24] Because of the widespread effects of IL-1β, inflammasome activation is under tight control. However, when these regulatory mechanisms fail, unchecked inflammation may develop. Excessive