Review Article

Purinergic Signaling and the Immune Response in Sepsis: A Review

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ABSTRACT

Purpose: Sepsis remains an unresolved clinical problem with high in-hospital mortality. Despite intensive research over decades, no treatments for sepsis have become available. Here we explore the role of ATP in the pathophysiology of sepsis. ATP is not only a universal energy carrier but it also acts as an extracellular signaling molecule that regulates immune function. ATP stimulates a large family of purinergic receptors found on the cell surface of virtually all mammalian cells. In severe sepsis and septic shock, ATP is released in large amounts into the extracellular space where it acts as a "danger" signal. In this review, we focus on the roles of ATP as a key regulator of immune cell function and as a disruptive signal that contributes to immune dysfunction in sepsis.

Methods: We summarized the current understanding of the pathophysiology of sepsis, with special emphasis on the emerging role of systemic ATP as a disruptive force that promotes morbidity and mortality in sepsis.

Findings: Over the past two decades, the discovery that regulated ATP release and purinergic signaling represent a novel regulatory mechanism in immune cell physiology has opened up new possibilities in the treatment of sepsis. Immune cells respond to stimulation with the release of cellular ATP, which regulates cell functions in autocrine and paracrine fashions. In sepsis, large amounts of systemic ATP produced by tissue damage and inflammation disrupt these regulatory purinergic signaling mechanisms, leading to immune dysfunction that promotes the pathophysiologic processes involved in sepsis.

Implications: The knowledge of these ATP-dependent signaling processes is likely to reveal exciting new avenues in the treatment of the unresolved clinical problem of sepsis. (*Clin Ther.* 2016;38:1054–1065)

Key words: adenosine, ATP, purinergic signaling, sepsis.

INTRODUCTION

Sepsis is a life-threatening condition that is characterized by severe systemic infection and systemic inflammation and causes tissue damage and organ dysfunction.[1,2] Despite substantial progress in the management of septic patients, sepsis remains a major public health problem that affects millions of patients worldwide each year.[3,4] Severe sepsis and septic shock are among the leading causes of death in intensive care units, with a mortality rate as high as 40%.[5,6] In addition, the prevalence of sepsis is further rising due to the increased use of immunosuppressive drugs, the widespread use of antibiotics, the emergence of drug-resistant pathogens, and the aging of the population.[7] Over the past few decades, growing knowledge about the pathophysiology of sepsis has yielded a considerable number of potential drug targets and the development of new therapies for sepsis.

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However, all of these therapies have failed in clinical trials.[6,8] As a result, there are still no specific pharmacologic agents available for the treatment of sepsis, and new directions for more effective treatment strategies are urgently needed.

Over the past few decades, a number of important discoveries have suggested that ATP plays an essential role as an extracellular signaling molecule.[9] The extracellular concentration of ATP increases in conditions that are associated with severe sepsis and septic shock, such as inflammation, ischemia, and hypoxia.[10] Increased extracellular ATP is frequently considered a "danger" signal that triggers proinflammatory responses, particularly of the innate immune system, and thereby contributes to systemic inflammation and secondary organ damage in sepsis.[11] In this brief review, we focus on how ATP and purinergic signaling regulate immune cell responses in sepsis.

METHODS

Using the PubMed database and the key terms "sepsis", "septic shock", "ATP", and "purinergic signaling" we searched for English-language clinical trials, animal experimental studies, and reviews published prior to March of 2016. Articles not referring to purinergic signaling, abstracts, and short reports in conference proceedings were excluded. The references from identified articles were searched manually for additional resources. Using data from all identified articles, we summarized the current understanding of the pathophysiology of sepsis, with emphasis on the emerging role of systemic ATP as a disruptive force that promotes morbidity and mortality in sepsis.

RESULTS

Approximately 550 articles were identified in the database search. Of these, about 150 publications focusing on the role of extracellular ATP or adenosine in sepsis, septic shock, or endotoxemia were thoroughly reviewed.

Pathophysiology

According to the current concept, sepsis arises from an overwhelming inflammatory host response to invading pathogens[1,2]. In 1991, a consensus conference further subclassified *sepsis* as *severe sepsis* (sepsis associated with organ dysfunction) and *septic shock* (severe sepsis associated with the need for vasopressors after adequate fluid resuscitation). In addition, the terms *systemic inflammatory response syndrome*, *multiple organ dysfunction syndrome*, and *multiple organ failure* were defined because symptoms of inflammatory diseases of noninfectious origin, including severe trauma, burns, pancreatitis, and ischemia-reperfusion injuries, overlap with those of sepsis.[12] The criteria defining *systemic inflammatory response syndrome* and *sepsis* have been questioned recently as being not sensitive or specific enough, and it was suggested to use the term *sepsis* only if there is evidence of organ dysfunction or organ failure.[2,6]

Systemic inflammation is initiated by pattern-recognition receptors such as Toll-like receptors and nucleotide-binding oligomerization domain–like receptors (NLRs) that are expressed by innate immune cells. These receptors are activated by pathogen-associated molecular patterns, such as endotoxin, but also damage-associated molecular patterns, or "alarmins," which are released from injured host tissue and include a diverse group of molecules such as high-mobility group B 1, uric acid, or chromosomal DNA.[13] The activation of these receptors induces the immediate recruitment and activation of neutrophils and macrophages to initiate bacterial clearance and tissue repair. In sepsis, excessive activation of these pathways leads to the massive release of proinflammatory cytokines, activation of the coagulation cascade, endothelial dysfunction, hemodynamic failure, and finally multiple organ dysfunction and death.[14] Numerous clinical trials in the past two decades have focused on blocking this hyperinflammatory response. Approaches including corticosteroid treatment and the targeting of various mediators of inflammation, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, complement factor C5a, and endotoxin, have failed in clinical trials.[6,8,14,15] These disappointing results were attributed to difficulties with the timing of intervention, the dosages of experimental drugs, and species differences between *in vivo* studies in animals versus in humans.[6] However, less attention has been given to the facts that the initial hyperinflammatory state in sepsis is offset by an antiinflammatory response and that sepsis is associated with immunosuppression, which reduces the ability of the host to clear infections. Antiinflammatory treatment strategies exacerbate this immunosuppressed state and likely further increase the susceptibility of septic patients to nosocomial infection.[14,16–18] Because pharmacologic agents indicated specifically for sepsis are not