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Review

Janus face of complement-driven neutrophil activation during sepsis

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ABSTRACT

During local and systemic inflammation, the complement system and neutrophil granulocytes are activated not only by pathogens, but also by released endogenous danger signals. It is recognized increasingly that complement-mediated neutrophil activation plays an ambivalent role in sepsis pathophysiology. According to the current definition, the onset of organ dysfunction is a hallmark of sepsis. The preceding organ damage can be caused by excessive complement activation and neutrophil actions against the host, resulting in bystander injury of healthy tissue. However, in contrast, persistent and overwhelming inflammation also leads to a reduction in neutrophil responsiveness as well as complement components and thus may render patients at enhanced risk of spreading infection. This review provides an overview on the molecular and cellular processes that link complement with the two-faced functional alterations of neutrophils in sepsis. Finally, we describe novel tools to modulate this interplay beneficially in order to improve outcome.

1. Introduction

The first phase of the innate immune surveillance comprises neutrophil granulocytes as a cellular and the complement system as a fluid-phase defense strategy. Both are activated during local and systemic inflammation when exposed to pathogen- or damage-associated molecular patterns (PAMPs and DAMPs, respectively). However, the subsequent temporal-spatial response of the defense systems is frequently Janus-faced. In ancient Roman myths, the double-faced god Janus was responsible for beginnings, gates, transition, time and duality. As indicated in the present review, neutrophil granulocytes reveal many Janus-faced features during sepsis, particularly when interacting with the complement system.

Neutrophils account for the majority of leukocytes in whole blood, and during sepsis, their numbers can be either significantly increased or reduced. Previously, sepsis was defined as an infection-induced systemic inflammatory response syndrome including the clinical signs of tachypnea, tachycardia, fever and, of note, leukocytosis or leukopenia. According to the current definition, sepsis reflects a life-threatening organ dysfunction, which features an altered mental state, respiratory rate ≥22/min or a systolic blood pressure of ≤100 mmHg, hallmarks caused by a dysregulated host response to infection [1]. As addressed by this review, activation of neutrophils and the complement system can significantly contribute to the impaired host response and organ dysfunction on multiple organ levels. Septic shock additionally exhibits circulatory and cellular/metabolic dysfunction and is associated with an overall higher mortality. Patients with septic shock are identified by the requirement of vasopressors to maintain a mean arterial pressure of ≥65 mmHg and serum lactate levels ≥ 2 mmol/L (> 18 mg/dL) in the absence of hypovolemia [1]. As described below in detail, the current definition of septic shock includes, as new criteria, significant changes in the cellular and fluid-phase innate immune responses.

2. Complement activation during sepsis: insights from the current and former definitions of sepsis

Former criteria of sepsis defined this condition as a systemic inflammatory response to an infection [2] that is associated with local

Abbreviations: C3aR, C3a receptor; C5aR1/2, C5a receptor 1/2; CLP, cecal ligation and puncture; CXCR4, C-X-C chemokine receptor type 4; DAMPs/PAMPs, damage-/pathogen-associated molecular patterns; Efb, extracellular fibrinogen-binding protein; ERK, extracellular signal-regulated kinases; fH, factor H; IgG, immunoglobulin G; IL, interleukin; LPS, lipopolysaccharide; MAC, membrane-attack complex; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NETs, neutrophil extracellular traps; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PI-3K, phosphatidylinositide 3-kinase; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; SDF-1, stromal cell-derived factor 1; SOFA, sequential organ failure assessment; TCC, terminal complement complex; TLR, toll-like receptor; TNF, tumor necrosis factor

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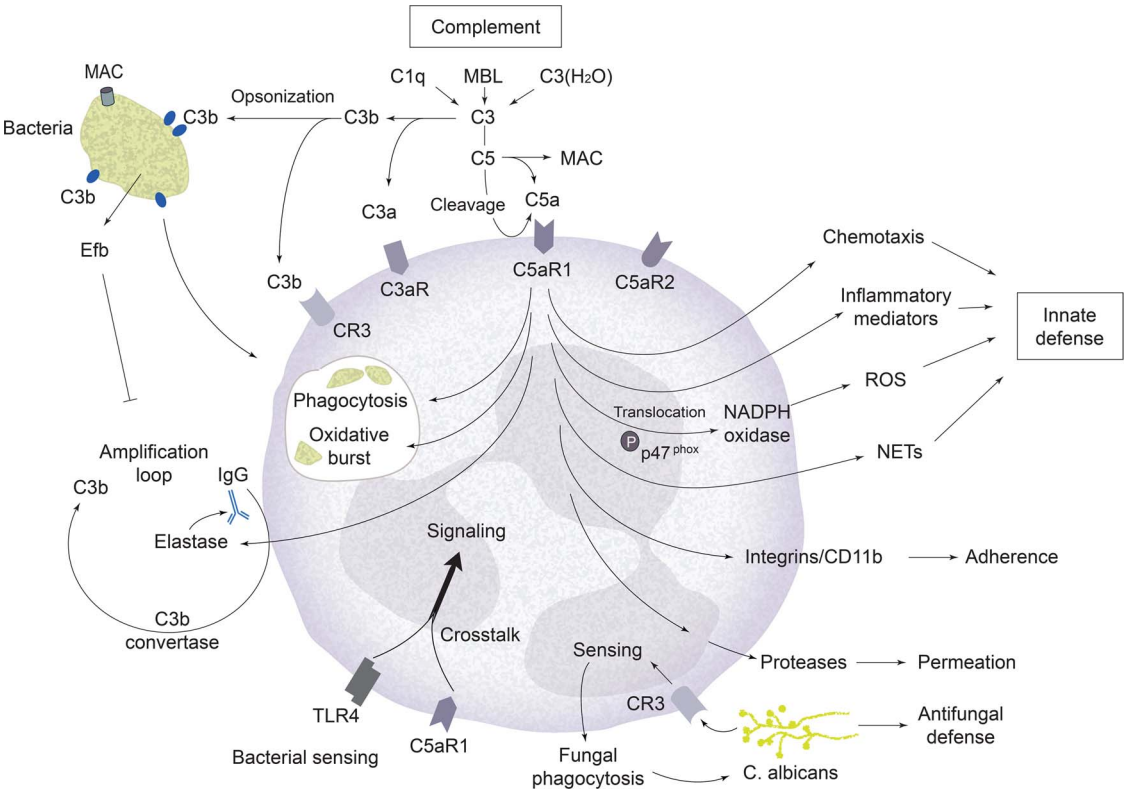

Fig. 1. Complement-dependent functions of neutrophils under non-septic conditions. Activation of the complement system results in opsonization and membrane-attack complex (MAC) formation on the microbial surface. Simultaneous stimulation of neutrophils via respective complement receptors leads to cellular activation and induction of the respiratory burst, phagocytosis of complement-opsonized particles and intracellular germ killing as well as the release of antimicrobial substances for extracellular defense. In addition to the secretion of several proteases that facilitate permeation into inflamed or infected tissue, complement stimulus and binding of toll-like receptor (TLR) ligands induce intracellular signaling pathways that further enhance the pro-inflammatory response. Secretion of neutrophil elastase can reinforce C3 activation by cleaving the F(ab') fragment off immunoglobulins which, together with dimeric C3b and naturally occurring antibodies, can form a C3 convertase precursor. Antifungal defense is also dependent on sensing via complement receptor 3 (CR3) and induction of phagocytosis of opsonized fungi. Abbreviations: C1q, complement component C1q; C3aR, C3a receptor; C5aR1/2, C5a receptor 1/2; CD11b, cluster of differentiation 11b; Efb, extracellular fibrinogen-binding protein; IgG, immunoglobulin G; NADPH, reduced nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; p47phox, 47 kDa subunit of NADPH oxidase.

and systemic complement activation, as is evident by the generation of the factors Bb, C3a, C3b/c, C5a and sC5b–9, the reduction of plasma levels of the zymogens C3 and C4 and the reduction in overall complement hemolytic activity [3,4]. Already 25 years earlier, both complement activation products and neutrophil degranulation markers (e.g. elastase) were found to be specifically increased in nonsurviving sepsis patients and thus correlate with disease severity [5]. Mechanistically, bacterial surfaces and PAMPs can robustly activate complement via the alternative pathway [6], leading to C3b deposition (i.e. opsonization) of microorganisms. The generated anaphylatoxins C3a and C5a form a potent chemotactic gradient, recruiting neutrophils and macrophages to the infection site to foster pathogen phagocytosis (Fig. 1). Of note, proteomic blood analyses from patients with bacteria-positive blood cultures [7] or from trauma patients who developed sepsis after severe injury [8] revealed altered expression levels of complement and coagulation proteins in addition to pathways addressing phagocytic activity and lipid metabolism. Other, pathogen-independent causes for complement activation during sepsis may result from a cross-talk with the serine proteases of the coagulation system [9,10]. In agreement with this, inhibition of both the coagulation and the complement cascade by C1-inhibitor (which inhibits both C1 and factor XII) exhibited protective effects in baboons with sepsis [11]. However, recent data from *Escherichia coli*-induced sepsis-like conditions in baboons suggested that there is no major contribution from the coagulation system to complement activation during sepsis [12]. Complement may also be activated via pentraxins, which function as soluble pattern recognition molecules that can activate the classical complement pathway. Upon exposure to bacteria and PAMPs, neutrophils can release pentraxin 3 from intracellular stores, for example, in association with the formation of neutrophil extracellular traps (NETs), to kill bacteria [13]. Additionally, natural antibodies that recognize microbial surfaces may contribute to sepsis-induced direct complement activation [14,15].

According to the current definition of sepsis, the initiation and particularly the further progression of complement activation has also to be considered for the diagnosis in addition to the key feature of organ dysfunction because of a dysregulated host response to infection [1]. It is important to note that after surgical control and antibiotic treatment there may still be ongoing complement activation, systemically or locally in a compartmentalized manner. Therefore, the differential temporal-spatial activation of complement in various organs may more accurately reflect the new sepsis definitions. Kidneys, for example, locally produce C3, which can be activated and deposited during sepsis [16]. Factor B is upregulated in renal tubule cells upon exposure to toll-like receptor 4 (TLR4) agonists and during experimental sepsis, and is involved in the regulation of sodium-transporter expression [16,17]. Absence of factor B (alternative pathway) was shown to reduce kidney organ injury during the course of sepsis and increase neutrophil migration towards the intraperitoneal infectious source [16]. In the lungs, enhanced myeloperoxidase concentrations are found during sepsis onset, indicating neutrophil infiltration and activation. However, in the absence of factor B or C1q (classical pathway), the local myeloperoxidase level is increased, which is associated with an aggravated structural injury [18]. In the liver, pro-carboxypeptidase B2, which is involved in fibrin degradation, but also cleaves and modulates the activity of C3a and C5a, is upregulated. There is increasing evidence that the anapyhylatoxin C5a is a major driver of sepsis-induced multiple