BIOCHEMICAL PHARMACOLOGY 76 (2008) 1383–1388

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Review

Sepsis, apoptosis and complement

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ARTICLE INFO

Article history:
Received 23 May 2008
Accepted 10 September 2008

Keywords:
Apoptosis
Thymocytes
Adrenal medullary cells
C5a
C5aR
C5L2
Sepsis

ABSTRACT

Programmed cell death (apoptosis) is a prominent feature in human and experimental sepsis, especially as it involves the lymphoid system with resulting immunoparalysis. In addition, sepsis is associated with strong activation of the complement system, resulting in generation of the powerful anaphylatoxin, C5a, as well as the upregulation of the C5a receptor (C5aR) in a variety of different organs. The consequences of C5a interactions with C5aR can be directly linked to apoptosis of thymocytes and adrenal medullary cells after cecal ligation and puncture (CLP)-induced sepsis in rodents, as well as with other accompanying complications of CLP: cardiac dysfunction, consumptive coagulopathy, organ dysfunction, and lethality. This communication reviews the evidence for the adverse roles of C5a and C5aR in the setting of experimental sepsis and linkages to the various complications of sepsis, especially apoptosis as well as the roles of the two C5a receptors (C5aR and C5L2) in experimental sepsis.

Contents

Sepsis is a major cause of mortality in humans, resulting in >200,000 fatalities in the U.S., a number close to the number of deaths from acute myocardial infarction [1,2]. Septic shock is a major complication of sepsis, usually requiring vasopressor support in order to main vascular perfusion [3–5], although the reason for this complication is poorly understood. The inability of the heart during sepsis to maintain adequate cardiac output and blood pressure has been referred to as the "cardiomyopathy of sepsis" [6]. In addition to inadequate cardiac function during sepsis, it is well known in both human and experimental sepsis that a rapid caspase-dependent development of apoptosis of both T and B cells occurs at an early stage, leading to immunosuppression [7]. In rodent sepsis occurring after CLP, we have shown that robust

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0006-2952/$ – see front matter
doi:10.1016/j.bcp.2008.09.017

complement activation occurs, resulting in signaling paralysis of blood neutrophils (PMNs) and loss of their innate immune functions (phagocytosis, chemotaxis, respiratory burst), together with profound apoptosis of thymocytes [8–12]. Treatment of rodents with blocking antibodies either to the powerful complement-derived anaphylatoxin, C5a, or to its receptor, C5aR, is highly protective, resulting in greatly improved survival [9,11], reduced thymocyte apoptosis [11], retention of innate immune functions of PMNs [8], and attenuated consumptive coagulopathy after CLP [13]. In this report we will emphasize linkages between C5a, C5aR and development of apoptosis of thymocytes as well as onset of other complications (listed above) of experimental sepsis. As will be described below, during sepsis C5a is generated, upregulation of C5aR occurs, there is loss of innate immune functions of PMNs, contractility defects in cardiomyocytes develops [14], apoptosis of thymocytes [11] and adrenal medullary cells [15] are prominent, and lethality is high [9], all of which can be linked to C5a and its interactions with receptors during sepsis. As will be emphasized below, a link has now been established between catecholamine release, adrenal medullary cell apoptosis, and septic shock of sepsis [15]. The development of apoptosis after CLP appears to be linked to appearance of C5a and its interaction with the two C5a receptors (C5aR, C5L2). In the setting of endotoxemia, the use of the inhibitor of C1 esterase (C1 INH) was protective in the setting of lethal endotoxemia [16], although treatment with C1 INH did not reduce mortality in human sepsis [17]. This raises the question as to whether blockade of the early steps in the complement activation cascade is desirable, since most downstream products, especially those related to C3-derived opsonic (phagocytosis-promoting) products, would be curtailed in production.

1. Complement activation after CLP

As in many types of sepsis, both in humans and in animals, CLP triggers activation of all three complement pathways (Fig. 1), with evidence for engagement of all pathways (classical, alternative, lectin) of complement activation [18]. Precisely how sepsis triggers this complex and reinforcing pattern of activation is not understood. It seems clear that, if bacterial lipopolysaccharide plays a role in human sepsis, its participation is probably minor. CLP-induced sepsis is polymicrobial (involving both gram positive and gram negative bacteria) and, as such, features in plasma and in lymphoid tissues draining the peritoneal cavity both aerobic and anaerobic bacteria translocated from the gut. It should also be noted that approximately 50% of humans with sepsis have gram positive bacterial pneumonia [1–3]. While lipopolysaccharide (LPS) has been speculated to cause harmful outcomes, there is other evidence (in TLR4$^{-/-}$, CD14$^{-/-}$, and LPS-binding protein$^{-/-}$ mice) suggesting that, at least in the setting of CLP, LPS may not be a major determinant in the adverse outcomes [19–21].

All three pathways of complement activation converge to generate the ''C3 convertase'', which cleaves C3 into a small (C3a) and a large (C3b) fragmentation product (Fig. 1). C3b is known to be a vital opsonic product that coats bacteria and other microbes, resulting in uptake by phagocytic cells (neutrophils [PMNs] and macrophages), followed by oxygen-dependent intracellular killing of bacteria [22]. Mice deficient in C3 are incredibly sensitive to sepsis and die very quickly [9,23]. Downstream activation of complement results in C5 cleavage, productive of C5a and C5b. C5a is an extremely active proinflammatory peptide, reacting with high affinity receptors (C5aR and C5L2) on phagocytic cells at low nM concentrations, resulting in the case of C5aR in cell activation which causes generation of reactive oxygen species ($O_2^{\bullet}$, H_2O_2, $HO^{\bullet}$) that are toxic to other cells, connective tissue constituents and microbes. In addition, C5a causes enzyme secretion from phagocytic cells, which results in damage of nearby cells and matrix [24]. C5a is highly chemotactic for phagocytic cells, especially neutrophils. Collectively, the outcome of C5a generation in vivo is induction of the acute inflammatory response characterized by increased vascular permeability and accumulation (and activation) of neutrophils and tissue macrophages. In CLP mice, C5a can be detected in plasma in levels that are nearly 5-fold above those in sham sera, and by 24 h the levels have risen by at least 10-fold [15]. The reason for this lag in plasma C5a after CLP is probably related to the fact

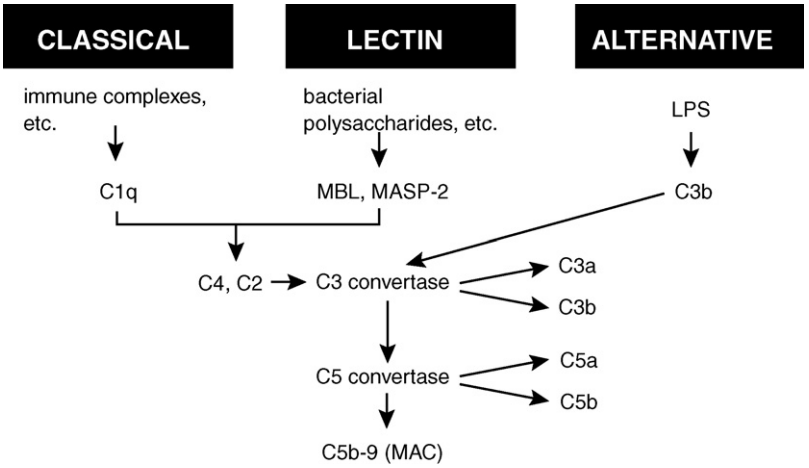

Fig. 1 – The three pathways of complement activation, collectively resulting in biologically active split products of C3 and C5.