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Review

Anaphylatoxins in organ transplantation

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ABSTRACT

C3a and C5a (also called anaphylatoxins) are inflammatory peptides generated during complement activation. They do not only play important roles in innate immunity through the initiation and regulation of inflammatory responses, but also significantly influence adaptive immune responses. Organ transplantation triggers an initial inflammatory response and subsequent to the specific immune response (also called the alloimmune response), both of which contribute to graft rejection. Emerging evidence suggests that anaphylatoxins, particularly C5a, are significantly involved in both inflammatory and alloimmune responses following organ transplantation, thus influencing graft outcome. This review will provide the information on our current understanding of the roles for anaphylatoxins in ischemia–reperfusion injury, graft rejection, and transplant tolerance, and the therapeutic potential of targeting anaphylatoxin receptors in organ transplantation.

1. Background

The complement system consists of a set of soluble and membrane-bound proteins, including pathway components, enzymes, receptors and regulators. Complement activation occurs rapidly in response to infection and other conditions including physical and chemical stresses. In response, complement activation generates a set of effector molecules which have diverse biological functions. The terminal product C5b-9 (also called membrane attack complex) mediates direct killing of certain pathogens and can also cause host tissue damage; the large fragments C3b/iC3b/C3d mediate oposonophagocytosis of pathogens/pathogenic particles; while the small fragments C3a and C5a induce local inflammation. C3a and C5a are inflammatory peptides which chemoattract inflammatory cells such as eosinophils, basophils, neutrophils and monocytes to the sites of infection and injury. Through binding to their specific receptors C3aR and C5aR, C3a and C5a activate/trigger these cells to release inflammatory cytokines and toxic substances (e.g. histamine, reactive oxygen species) which contribute to local inflammation. All of these biological functions mediated by complement effector molecules are critical for fighting infection [1].

Although traditionally the complement system is thought to be one of the most important innate defence mechanisms, a large body of research has demonstrated that complement does more than just the elimination of invasive microbes and removal of the waste. Complement, as an integral part of the immune system, plays important roles in regulating/coordinating many inflammatory and immunological processes. Among complement effectors, the small fragments C3a and C5a have been identified to play diverse roles in both homeostasis and disease [2]. In particular, C5a is becoming increasingly implicated in the pathogenesis of inflammatory and immune-mediated diseases such as sepsis, bacterial infection, autoimmune disease, tumor growth, ischemia/reperfusion injury and graft rejection; while both C3a and C5a have been shown to be involved in allergic asthma, tissue repair and regeneration, metabolism and transplant tolerance. As the discussion on the roles of anaphylatoxins in non-transplant settings is beyond the scope of this article, the reader is referred to other recent reviews on those topics [2–8].

Organ and tissue transplantation triggers two major events: (i) initial inflammatory responses mediated by reperfusion of ischemic tissue and trauma within the first few days of the surgical procedure and (ii) subsequent alloimmune responses mediated by recognition of donor antigen by the recipient immune system. Much research has demonstrated that both events contribute to allograft rejection [9–13]. Thus, organ and tissue transplantation represents a good example for how the interaction between the innate and adaptive arms of the immune response influences transplant outcomes. The aim of this review is to provide an overview of the current understanding of the roles for anaphylatoxins in ischemia/reperfusion injury, alloimmune regulation, graft rejection

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and transplant tolerance with emphasis on the kidney, and discuss the possible mechanisms for the participation of anaphylatoxins to those events.

2. Anaphylatoxins and anaphylatoxin receptors

The small fragments (C3a and C5a) are released during the course of complement activation. These fragments are also called anaphylatoxins, as they can cause systemically anaphylactic shock when produced in large amounts. Although C3a and C5a are bioactive fragments, the relative potencies of the anaphylatoxins are C5a > C3a [14]. C3a and C5a are small (~10 kDa) cleavage fragments of C3 and C5, respectively. They are powerful mediators of inflammation and exert their biological functions through interacting with their specific receptors C3aR and C5aR with nanomolar affinities [5]. Both receptors are members of the G protein-coupled receptor superfamily containing seven transmembrane domains. C3aR and C5aR are mainly expressed on myeloid cells (e.g. granulocytes, monocytes/macrophages, dendritic cells), they are also expressed on non-myeloid cells (e.g. epithelial cells, endothelial cells) [5]. C5L2 is an additional receptor for C5a and structurally homologous with C5aR but lacks G-protein coupling and is mainly intracellular [15]. The functional significance of C5L2 is uncertain, but it has been suggested that C5L2 may serve as a high affinity decoy receptor for C5a or as a negative regulator of C5aR-mediated signaling in neutrophils [16,17]. However, emerging evidence suggests that C5L2 signaling can also drive or regulate inflammatory diseases such as sepsis, allergic asthma and the development of T cell responses [18–20].

The effects of C3a and C5a are commonly thought to be pro-inflammatory, though with different potency [14]. Increasing evidence, however, indicates that C3a and C5a may also exert some distinct functions in inflammation and adaptive immune responses [2,5]. For example, divergent effects of C3a and C5a have been reported in humoral and cell-mediated immune responses (in PBMC culture systems) [21] and several disease models (e.g. asthma, Gram-negative bacteraemia and liver regeneration) [22–26]. The divergent effects may be explained by that C3a and C5a are predominantly involved in certain types of inflammatory cells and thus generating different cytokine milieus. Although both C3a and C5a can activate eosinophils, basophils and mast cells [27–30], C3a seems has no direct effect on neutrophils [31]. C5a is a potent chemoattactant and activator of neutrophils, and neutrophil activation has been linked with Th1 immunity [31,32], while C3a is a potent activator of eosinophils, basophils, and upon activation these cells can rapidly produce IL-4 and IL-13 which are signature cytokines of Th2 immunity [28,33].

3. Anaphylatoxins in IR injury

3.1. Complement is an important mediator of IR injury

IR injury occurs upon reperfusion of vascularized tissue and organ after an extended period of ischemia. It is a common source of morbidity and mortality in a wide variety of conditions including myocardial infarction, stroke, gut ischemia and acute renal tubular necrosis. IR injury is also an unavoidable event in organ transplantation and has a major impact on short- and long-term graft survival [9–11]. Renal IR injury is characterized histologically by cellular infiltration and renal tubular epithelial cell damage at cortical medullar junction. Although multiple factors such as inflammatory cells, cytokines, chemokines, adhesion molecules and the coagulation system are thought to contribute to the pathogenesis, the complement system has been recognized as an important mediator of IR injury. Studies using mice deficient in complement components (e.g. C3, C5, C6, factor B) or complement inhibitors (e.g. CD55, CD59) have demonstrated that lack of complement activation protected mice from renal IR injury, indicating that complement activation significantly contribute to the pathogenesis of renal IR injury [34–38]. With regard to the contributory effectors of complement activation, studies using mice deficient in C6 and terminal pathway complement inhibitor CD59 have suggested that the formation of MAC (C5b-9) in renal tubular epithelial cells is a critical effector mechanism through which complement mediates renal IR injury [34,37,38].

3.2. Roles of C5a in IR injury

During the past 10 years, anaphylatoxins particularly C5a has received much attention as an important mediator to IR injury. The role of C5a/C5aR signaling in IR injury has been investigated in various organs (e.g. kidney, intestine, heart, brain and limb) by using different approaches including C5aR deficient mice, C5aR antagonist (C5aRa), anti-C5 or -C5a antibodies and C5aR siRNA (Tables 1 and 2). The studies on kidneys will be discussed in more detail below, the studies on other organs are summarized in Table 2.

Studies in the native kidney IR injury model have clearly demonstrated that mice, in the absence of C5aR signaling, were protected from renal IR injury. C5aR−/− mice or the rodents received therapeutic agents (i.e. C5aRa, C5aR siRNA or anti-C5 antibody which inhibits the generation of the ligand for C5aR and the formation of C5b-9) exhibited significantly reduced acute kidney injury, as evidenced by improved renal function, reduced renal tissue damage and intrarenal synthesis of pro-inflammatory cytokines (e.g. TNF-α, IL-β) and chemokines (e.g. KC, MCP-1, MIP-1, 2) as well as neutrophils infiltration and tissue MPO activity, compared with WT mice or the mice treated with control agents [39–43] (Table 1). Studies in mouse kidney transplantation (isograft model) have also shown that treatment recipients with C5aRa significantly increased early graft survival (from 29% to 57%), and reduced renal tissue damage and intrarenal synthesis of pro-inflammatory mediators (i.e. TNF-α, MIP-2, KC) [44] (Table 1). Together, these findings strongly suggest that C5a/C5aR signaling is an important pathogenic factor in the development of renal IR injury.

An important question arising from these findings is how C5a participates in the development of renal IR injury. The pathologic hallmark of renal IR injury, during the acute phase, is renal tubule destruction and cellular infiltration of neutrophils and mono/macrophages. It is well-known that C5aR is most abundantly expressed on neutrophils and mono/macrophages. Recent studies have shown that the significant expression of C5aR was also detected on renal tubular epithelial cells in human and mouse kidneys [41,44–46]. This suggests that C5a, generated during complement activation, in response to metabolic and surgical stress, can act on both inflammatory cells and renal tubular epithelial cells. In support this, studies using mouse chimeras between wild type [WT] and C3aR/C5aR double knockout (DKO) have found that lack of C3aR and C5aR expression in renal cells or circulating leukocytes protected mice from renal IR injury. As C3aR−/− mice only had a very small reduction of renal IR injury suggesting a minimum role for C3a/C3aR signaling in this model, thus results from chimera studies would mainly reflect the role of C5a/C5aR signaling in renal IR injury, which is through acting on both renal and inflammatory cells [39]. In addition, most animal studies listed in Table 1 have observed that C5aR deficiency or C5a or C5aR blockade resulted in a clearly reduction of infiltrating leukocytes, particularly neutrophils and mono/macrophages in the kidney following IR insult, indicating that C5a–C5aR signaling plays an essential role in the recruitment of neutrophils and mono/macrophages in this type of injury. Another change consistently observed in those studies is that intrarenal synthesis of inflammatory cytokine (e.g. TNF-α)