Complement in renal transplantation

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Introduction

Over the past two decades, renal transplantation has become a highly successful treatment for end-stage kidney disease, with 85% of kidney grafts still functioning at the end of the first year. Nonetheless, a significant number of grafts undergo damage in the early period, and the incidence of late graft loss due to chronic rejection has not substantially changed [1]. It is thought that both alloantigen-dependent and -independent mechanisms contribute to this late graft loss. It is, therefore, vital that all potential mechanisms of graft injury are considered, especially where the mechanism of injury may not be controlled by current immunosuppressive drug regimens, such as injuries caused by intrinsic stimuli including complement activation in the kidney, ischemia/reperfusion (I/R) and surgical procedure. In this chapter, we discuss the complement system in renal transplantation and potential contributions of locally produced complement in the kidney to renal graft injury or rejection.

Complement and renal transplantation

The complement system is pivotal in the regulation of inflammation and host defense (reviewed in [2]). The complement system consists of a set of distinct plasma proteins that react in a cascade manner to opsonize pathogens, and induce a series of inflammatory responses. It can be activated through three pathways, the classical pathway, the mannose-binding lectin (MBL) pathway and the alternative pathway, which are triggered by a number of stimuli including bound antibodies, pathogen surfaces and spontaneously hydrolyzed C3. The function of the complement system in the regulation of inflammation and host defense is achieved by complement split products (e.g., C3b, C4b, C3a and C5a) in cooperation with antibody and phagocytes, as well as the formation complement membrane attack complex (MAC). Complement activation is well controlled by numerous complement inhibitors and regulators under normal circumstances. However, in the event of
inappropriate or excessive activation, complement can cause tissue injury. In addition to their role in host defense and stimulation of a nonspecific inflammatory response, complement also participates in the regulation of the antigen-specific immune response including T cells and B cells (reviewed in [2, 3]).

Renal transplantation is an intricate procedure; the organ graft could suffer I/R injury, hyperacute rejection, acute rejection and chronic rejection as well as infection. All of these events are associated with the development of nonspecific inflammatory injury and antigen-specific immune response in the organ graft and recipient. Given the functions in both the innate and adaptive immune responses, complement may play an important role in renal transplantation.

**Role of complement in renal I/R injury**

I/R injury is an important form of injury that occurs upon reperfusion of vascularized tissue after an extended period of ischemia. It is an unavoidable event in organ transplantation. Numerous clinical and experimental studies have shown that renal I/R injury has a major impact on short- and long-term graft survival after organ transplantation [4–6]. During I/R insult, the depletion of ATP causes intracellular accumulation of ions and water, resulting in cell swelling. Subsequently, multiple enzyme systems associated with the metabolism of oxygen, lipid, phospholipid, nucleotide are activated, leading to cytoskeleton disruption, membrane damage, DNA degradation and eventually cell death. This injury becomes manifest through the participation of a number of components such as complement activation, molecular oxygen, neutrophils and adhesion molecules such as P-selectin [7–9]. More recently, T cells and B cells have also been considered as components contributing to the process of reperfusion injury [10–12].

Complement activation is an early event in the course of reperfusion injury, which is evident by detecting activated complement product on renal tubules as early as 30 min after reperfusion [13]. The generation of complement effector molecules may influence the function of other factors, such as free radicals, neutrophils and the products of activated endothelium [14]. Thus, activation of complement is an important event in the setting of I/R injury. Complement activation after hypoxia and reperfusion causes vascular and parenchymal cell injury, which may be mediated through a variety of effector products. Complement activation releases a number of biologically active products, several of which possess pro-inflammatory activity in vitro. The early products C4a, C3a and C5a, the anaphylatoxins, can induce smooth muscle contraction, cause the release of histamine, and lead to increased vascular permeability [15]. In addition, C5a can act directly on neutrophils, promoting chemotaxis and activation, and can act on both neutrophils and endothelium to up-regulate cell adhesion molecules such as CD11b/CD18 and intercellular adhesion molecule (ICAM-1) [15, 16]. The MAC, C5b-9, inserts into the membrane