The Role of the Complement System in Acute Kidney Injury

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Summary: Acute kidney injury is a common and severe clinical problem. Patients who develop acute kidney injury are at increased risk of death despite supportive measures such as hemodialysis. Research in recent years has shown that tissue inflammation is central to the pathogenesis of renal injury, even after nonimmune insults such as ischemia/reperfusion and toxins. Examination of clinical samples and preclinical models has shown that activation of the complement system is a critical cause of acute kidney injury. Furthermore, complement activation within the injured kidney is a proximal trigger of many downstream inflammatory events within the renal parenchyma that exacerbate injury to the kidney. Complement activation also may account for the systemic inflammatory events that contribute to remote organ injury and patient mortality. Complement inhibitory drugs have now entered clinical use and may provide an important new therapeutic approach for patients suffering from, or at high risk of developing, acute kidney injury.
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Acute kidney injury (AKI) is a common clinical syndrome caused by a wide range of hemodynamic, ischemic, metabolic, inflammatory, and toxic insults to the kidney. AKI is associated with prolonged hospital stays, and patients who develop AKI have an increased risk of death despite supportive care. Currently, there is no specific treatment for AKI. A growing body of experimental evidence, however, now indicates that complement activation contributes to the pathogenesis of AKI. Complement inhibitory therapies may represent an effective strategy for attenuating or preventing AKI and its complications.

It has long been known that the complement system is activated in immune complex glomerulonephritis. It also has become clear in recent years that the complement system is involved in a diverse array of other renal diseases. The involvement of this immune system in the pathogenesis of so many diseases of the kidney suggests that the kidney may be intrinsically susceptible to complement-mediated injury. As discussed later, complement activation in the kidney often is caused by impaired or inadequate control of the complement system by the body's endogenous complement regulatory proteins. An important clinical question is whether complement activation is a common final pathway of renal damage in AKI of different etiologies.

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ACUTE KIDNEY INJURY

AKI is a severe and common clinical condition. AKI is defined as a loss of renal function over a matter of days. Clinically, AKI is diagnosed by an increase in serum creatinine level, reflecting an acute decline in the glomerular filtration rate. This can be caused by the rapid progression of an underlying renal disease (such as rapidly progressive glomerulonephritis or hemolytic uremic syndrome), or it can be the result of renal injury caused by drugs, ischemia, infections, or nephrotoxic metabolites. Ischemia/reperfusion (I/R) is a common cause of AKI in hospitalized patients, and is a major factor in the development of AKI after transplantation, cardiac surgery, and sepsis.[1,2]

A full discussion of the causes and adverse consequences of AKI is beyond the scope of this review, and interested readers are referred to several excellent publications on the subject.[2–4]

The conditions that cause AKI can target specific anatomic structures within the kidney, including the glomerulus, tubulointerstitium, and/or vasculature. Complement activation is an important mechanism of renal injury in diseases affecting each of these compartments. Uncontrolled alternative pathway activation within the microvasculature, for example, is the primary cause of atypical hemolytic uremic syndrome (aHUS).[5] The complement system is also an important mediator of injury in ANCA-associated vasculitis[6] and anti–glomerular basement membrane disease.[7] The proximal tubule is the primary site of injury after renal I/R, and complement activation on the ischemic tubule is an important cause of ischemic AKI.[8] The mechanisms that cause a decrease in glomerular filtration rate during AKI are complex and likely vary among patients

with AKI caused by different etiologies. It remains to be determined whether engagement of the complement system in all of these different diverse forms of AKI represents independent phenomena, or whether complement activation is a generalizable response of the kidney to injury.

Many different components of both the innate and adaptive immune systems have been implicated in the pathogenesis of AKI. Ischemic renal injury, for example, leads to a robust inflammatory response within the kidney. In response to hypoxic injury, tubular epithelial cells produce numerous inflammatory cytokines,[9–12] and neutrophils, macrophages, and T cells infiltrate the kidney.[9,13,14] The complement system and the Toll-like receptors are early sensors of tissue injury. Blockade of complement activation, Toll-like receptor 2, or Toll-like receptor 4 prevents many of the downstream inflammatory manifestations of AKI.[8,15–18] Although AKI is defined predominantly by kidney dysfunction, extrarenal complications also are important.[11,19] The role of complement activation in these extrarenal manifestations has not been examined in AKI, but studies have linked complement activation to remote organ injury after ischemia of other organs such as the intestine and skeletal muscle.[20,21] Regarded together, these studies indicate that complement activation within the kidney after I/R is an important trigger of the subsequent inflammatory response both within the kidney and possibly in remote organs.

COMPLEMENT ACTIVATION AFTER RENAL I/R

Intrarenal complement activation is detected and characterized primarily by immunostaining renal tissue for C3 activation products. Studies in murine[8,22] and rat[23] models have shown increased deposition of C3 along the tubular basement membrane after I/R. Deposition of C3 is not seen in peritubular capillaries or within the glomeruli.[24] Biopsies of human kidneys with histologic evidence of acute tubular necrosis also showed C3 deposits along the tubular basement membrane.[22] Similar to what is seen in rodents, patchy tubulointerstitial C3 was seen in histologically normal kidneys, but the extent of deposition was increased in kidneys with acute tubular necrosis.

MECHANISMS OF COMPLEMENT ACTIVATION IN THE ISCHEMIC KIDNEY

AKI is episodic and frequently is caused by clinically apparent factors (eg, hypotension or nephrotoxins). Thus, complement activation within the kidney is likely a secondary event in the development of injury. On the other hand, not all individuals develop AKI after exposure to the same renal insults, and patient factors (such as variation in the genes for complement regulatory proteins) likely contribute to an individual's risk of developing kidney injury after exposure to a particular renal insult. Most of the preclinical studies examining the role of complement in AKI have used models of I/R. The histologic changes in the kidney vary in location between different types of insults, so it is possible that activation of the complement system will differ among causes of AKI that target different locations within the kidney.

What causes complement activation in the injured tubulointerstitium? Conditions in the kidney may favor alternative pathway activation at baseline (Fig. 1). Complement proteins in plasma, for example, are concentrated by filtration of protein-free plasma at the glomerulus. Alternative pathway activation on tubular epithelial cells also is promoted by synthesis of ammonia, which can nonenzymatically form an amide linkage with the thioester bond in C3.[25] This nucleophilic modification of C3 forms a molecule with C3b-like properties that can form an alternative pathway convertase.[25,26] An acidic environment also promotes alternative pathway activation on tubular epithelial cells.[27] There is compelling evidence that extrahepatic production of complement proteins, particularly by renal tubular epithelial cells, can promote local complement activation and injury. Pathogens or cellular microparticles can increase alternative pathway activation in the bloodstream, and when these entities enter the renal microvasculature they may increase activation of the alternative pathway in plasma further.

There are several mechanisms by which the complement system can be directly activated on injured host cells. Circulating molecules may bind, or recognize, molecular signatures that are generated or displayed on damaged tissues. Natural antibodies, for example, bind to neo-epitopes displayed on injured tissue.[28] Immune molecules such as natural antibodies, lectins, and C-reactive protein can recognize injury markers and then activate the complement system. All cells of the body express complement regulatory proteins, and the expression of these proteins also can be disrupted by tissue injury.[29] Along these lines, the apical-basolateral organization of the tubular epithelial cell is disrupted by ischemia, and proteins that ordinarily are restricted to the apical side of the cell may gain access to the basolateral surface. All of these events may occur simultaneously, creating a microenvironment that favors complement activation in an acutely injured kidney.

The Classic Pathway

The classic pathway of complement is activated by immune complexes that deposit or form within the glomeruli in diseases such as lupus nephritis and membranoproliferative glomerulonephritis type I. The