# Role of complement activation in acute kidney injury

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Rodríguez E, Barrios C, Soler MJ, et al.. Role of complement activation in acute kidney injury. Clin Nephrol Res. 2017;1(1):10-11.

Acute kidney injury has an estimated incidence of 14.9–49.6 per 1000 patient years and may affect 13–18% of hospitalized patients. The incidence is increasing, and it is expected to double over the next decade [1–3]. AKI has been considered a self-limiting disease, with good prognosis when recovery is noted during admission [4], but several studies demonstrated that survivors of AKI may experience considerable late decline in kidney function. Recent studies suggested that AKI episodes are associated with higher risk of developing chronic kidney disease (CKD) cardiovascular events and overall mortality [5–11].

It has long been known that complement activation is an important mechanism of renal injury in different diseases affecting each of the renal compartments (glomerulus, tubulointerstitium, and vascular departments) [12]. The complement system is an important innate humoral defense system comprised of more than 20 plasma proteins that may be activated in a cascade fashion by either the classic pathway (immune complex mediated) or the alternative pathway. A regulatory system of both plasma proteins and membrane bound proteins acts to prevent the inappropriate activation of complement by autologous cells. Complement activation has been shown to be an important event in the development of ischemic AKI in mice. Studies in complement-deficient mice have shown that mice are protected from renal failure after ischemia/reperfusion (I/R) [13], and that generation of the anaphylatoxin C5a [14] and the membrane attack complex (C5b-C9 or MAC) [15,16] may contribute to the pathogenesis of ischemic AKI. The proximal tubule is the primary damaged site after renal I/R; complement activation on the ischemic tubule is an important contributor to ischemic AKI. In addition, treatment with agents that inhibit the complement cascade at specific steps has proven effective at ameliorating ischemic AKI [14,17]; and therapeutic targeting of classical and lectin pathways protects from ischemia-reperfusion-induced renal damage in animal model of kidney transplantation [18]. There is growing evidence that, in animal model of transplant kidney, complement plays a critical role in the acute induction of endothelial-to -mesenchymal transition, suggesting that therapeutic inhibition may be essential to prevent vascular damage and tissue fibrosis [19]. Complement activation in kidney occurs via the alternative pathway [12] and is independent of natural antibody [20]. Uncontrolled alternative pathway activation within the microvasculature is the primary cause of atypical haemolytic uremic syndrome (aHUS) [21]. The complement is also an important mediator of injury in ANCA-associated vasculitis [22] and antiglomerular basement membrane disease [23]. The MAC forms pores in cells resulting in cell activation. At high concentration, it causes cell death by lysis. Sublytic doses of MAC can activate renal parenchymal cells, which then release proinflammatory cytokines, reactive oxygen species, vasoactive chemicals, and profibrotic factors [24-33].

**Complement Activation after Ischemia/Reperfusion (I/R)**

Intrarenal complement activation is detected and characterized primarily by inmunostaining renal tissue for C3 activation products, studies in murine and rat [12, 28,29] 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 [30]. Biopsies of human kidney with histologic evidence of acute tubular necrosis also showed C3 deposits along the tubular basement membrane [31]

Numerous studies have examined the three pathways of the complement system (Classic pathway, Mannose-Binding Lectin pathway and Alternative pathway) and the role of each of them in kidney injury, and the role is not clear at this point.

Factor H is the main regulatory protein of complement system, and genetic studies have shown that patients with mutations in Factor H or antibodies against Factor H are at increased risk for several types of renal disease, not only atypical HUS [32], recent data describes pathogenic role of Factor-H-related proteins [33].

It remains to be determined whether regulatory complement proteins play a role in the pathogenesis of AKI.

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***Received:*** *October 13, 2017,* ***Accepted:*** *October 23, 2017,* ***Published:*** *October 31, 2017*

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