Role of complement activation in acute kidney injury

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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 classical 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 uraemic 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].

REFERENCES

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