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Emerging perspectives: harnessing the power of the complement system in managing pediatric acute kidney injury

Bradley Dixon*

Department of Urology, University of Colorado, Aurora, USA

✉ ***Bradley Dixon***
Department of Urology,
University of Colorado,
Aurora, USA
E-mail: Dixon82@gmail.com

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Description

Pediatric Acute Kidney Injury (AKI) is a significant clinical problem with substantial morbidity and mortality rates. It is characterized by the sudden decline in renal function and can arise from various etiologies such as sepsis, nephrotoxic medications, and ischemia-reperfusion injury. Although the pathogenesis of pediatric AKI is multifactorial, emerging evidence suggests that the complement system plays a crucial role in its development and progression. The complement system is a complex network of proteins that functions as part of the innate immune system, contributing to inflammation, opsonization, and immune surveillance. Dysregulation of the complement system has been implicated in the pathogenesis of several renal diseases, including AKI. This study aims to explore the role of the complement system in pediatric AKI, highlighting its contribution to the pathogenesis and its potential as a therapeutic target. The complement system is activated through three main pathways: classical, lectin, and alternative. Each pathway converges at the formation of the Membrane Attack Complex (MAC), which leads to cell lysis and tissue damage. In pediatric AKI, the complement system can be activated through multiple mechanisms, including immune complex deposition, ischemia-reperfusion injury, and direct activation by pathogens. One of the primary pathways through which the complement system is activated in pediatric AKI is through the lectin pathway. The lectin pathway is triggered by the binding of pattern recognition molecules, such as Mannose-Binding Lectin (MBL), to Pathogen-Associated Molecular Patterns (PAMPs) on the surface of microorganisms. In pediatric AKI, the release of endogenous ligands, such as Damage-Associated Molecular Patterns (DAMPs), can activate the lectin pathway, leading to complement-mediated injury. Experimental studies have shown that MBL deficiency or inhibition of the lectin pathway can ameliorate renal injury in animal models of pediatric AKI, suggesting a crucial role for this pathway in the pathogenesis. The alternative pathway of complement activation is also implicated in pediatric AKI. It can be triggered spontaneously by the hydrolysis of C3 or facilitated by properdin binding to pathogens or injured cells. Excessive activation of the alternative pathway in pediatric AKI leads to the generation of C5a and the formation of the MAC, resulting in endothelial injury, inflammation, and renal dysfunction. Animal studies have demonstrated that blockade of the alternative pathway components, such as C5a or C5a receptors, attenuates renal injury and improves renal function in models of pediatric AKI. Moreover, the complement system can contribute to pediatric AKI through the activation of inflammatory cells, such as neutrophils and macrophages. Complement activation generates chemotactic peptides, including C3a and C5a, which attract and activate these cells. The recruitment of

inflammatory cells promotes tissue inflammation and injury, exacerbating renal dysfunction in pediatric AKI. Additionally, the release of reactive oxygen species by activated neutrophils further amplifies the damage to renal cells. Given the critical role of the complement system in the pathogenesis of pediatric AKI, targeting this system represents a promising therapeutic strategy. Several approaches have been investigated to modulate complement activation and mitigate renal injury. Pharmacological inhibition of complement components or downstream effectors has shown promise in preclinical models of pediatric AKI. For instance, blocking the MAC formation using C5 inhibitors or membrane-bound complement regulators has been shown to ameliorate renal injury and preserve renal function. Furthermore, targeting complement activation products, such as C3a and C5a, through receptor antagonists or neutralizing antibodies, has shown beneficial effects in reducing renal inflammation and injury in experimental models.

Another therapeutic avenue involves modulating the lectin pathway. MBL deficiency has been associated with a reduced risk of AKI in pediatric populations, suggesting that inhibiting MBL or other lectin pathway components could be a potential therapeutic approach. Small molecules or antibodies targeting MBL or lectin pathway proteins have shown promise in preclinical studies and hold potential for clinical translation. Additionally, strategies targeting the alternative pathway have been explored. Inhibiting properdin, a key regulator of the alternative pathway, has been shown to attenuate renal injury in animal models of pediatric AKI. Other approaches, such as blocking C5a or C5a receptors, have also demonstrated efficacy in reducing inflammation and improving renal outcomes in preclinical studies.

Conclusion

Pediatric AKI is a significant clinical challenge, and understanding the underlying pathogenic mechanisms is essential for developing effective therapeutic strategies. The complement system has emerged as a vital player in the pathogenesis of pediatric AKI, contributing to renal inflammation, tissue damage, and dysfunction. Targeting the complement system holds promise as a therapeutic approach to mitigate renal injury and improve outcomes in pediatric AKI. Pharmacological interventions aimed at inhibiting complement activation, blocking complement components, or modulating downstream effectors have shown encouraging results in preclinical models. However, further research is needed to optimize these strategies, determine the appropriate timing and duration of intervention, and assess their safety and efficacy in pediatric populations. The complement system represents a promising therapeutic target in pediatric AKI. Expanding the knowledge of complement-mediated mechanisms in pediatric AKI and translating this knowledge into effective therapies could pave the way for improved outcomes and reduced morbidity in this vulnerable patient population.