The potential role of complement in cardiac surgery-associated acute kidney injury

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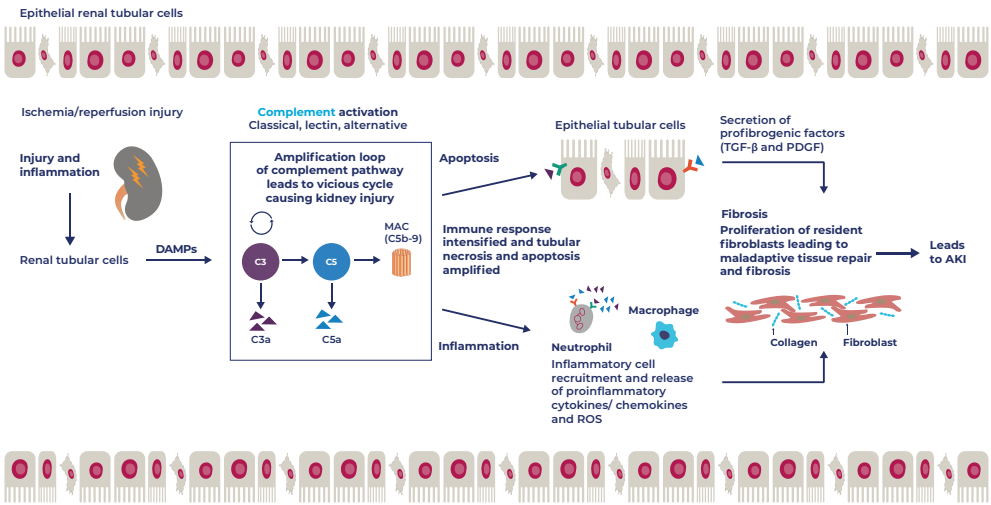
In recent years, the complement system has been implicated in the pathophysiology and progression of many disorders, notably modulating inflammation and causing endothelial and organ damage[1]. Acute kidney injury (AKI) is a major concern following cardiac surgery and has the potential to significantly impact patient outcomes. Cardiac surgery-associated acute kidney injury (CSA-AKI) occurs in ≥50% of patients with chronic kidney disease (CKD) undergoing cardiac surgery with cardiopulmonary bypass (CPB)[2].

Patients with pre-existing CKD undergoing cardiac surgery are at higher risk of perioperative AKI compared to those without CKD. Any AKI, even if resolved by hospital discharge, can affect the already diminished renal reserve in patients with preexisting CKD[3]. Due to the reduced renal reserve in these patients, the consequences are particularly poor and may include longer hospital stays with complications, increased need for acute dialysis, and further progression to end-stage kidney disease (ESKD)[3]. The long-term mortality rates for patients with prior CKD with or without AKI are 47% versus 39%, respectively[3].

THE POTENTIAL ROLE OF COMPLEMENT IN CSA-AKI

The causes of CSA-AKI are multifactorial and complex (**Fig. 1**). Ischemia due to early hypoperfusion followed by ischemia reperfusion injury (IRI) results in renal tissue damage[4]. Studies of renal transplant recipients and patients undergoing cardiac surgery suggest that damage and inflammation caused by IRI and CPB is amplified by complement activation[4]. The complement system can be activated through three pathways. Complement activation induces synthesis of pro-inflammatory cytokines and the membrane attack complex directly causes cell injury, apoptosis and necrosis, which in turn cause further complement activation and a vicious circle of inflammation and cell damage[4].

At Alexion, AstraZeneca Rare Disease, we are committed to continuing to investigate the potential role of the complement system in various diseases and accelerating the discovery and development of new therapies. We're building on our fundamental understanding of complement biology with our development efforts in haematology, nephrology and cardiology. We continue to evolve into new areas such as CSA-AKI where there is significant unmet need and the potential to improve the lives of patients.



AKI, acute kidney injury; **C**, complement component; **DAMP**, danger associated molecular pattern; **MAC**, membrane attack complex; **PDGF**, platelet-derived growth factor; **ROS**, reactive oxygen species; **TGF**, transforming growth factor.

Figure 1. Potential role of complement in acute kidney injury (AKI)[4]. Danger-associated molecular patterns (DAMPs) are endogenous ligands released from renal tubular cells following ischemia/reperfusion injury that activate the complement system through the classical, lectin and alternative pathways. Membrane attack complexes (MACs) formed following complement activation ultimately injure the kidney due to epithelial renal tubular cell apoptosis. Cleaved C3a and C5a fragments from complement activation promote inflammatory cell recruitment, which amplifies the immune response. Apoptotic epithelial tubular cells release pro-fibrinogenic factors, which, combined with complement-mediated inflammatory cell recruitment, promote fibrosis. This self-perpetuating amplification of cellular damage causes increased fibrosis and results in AKI.

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