Targeting the complement cascade: novel treatments coming down the pike

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The complement cascade is a vital component of both the innate and adaptive immune systems. Complement activation also contributes to the pathogenesis of many diseases, however, and the kidney is particularly susceptible to complement-mediated injury. Drugs that block complement activation can rapidly reduce tissue inflammation and also attenuate the adaptive immune response to foreign and tissue antigens. Eculizumab is a monoclonal antibody that prevents the cleavage of C5. It has been approved for the treatment of atypical hemolytic uremic syndrome, and it has been used in selected patients with other kidney diseases. Many additional drugs are also in development for blocking the complement cascade, including new monoclonal antibodies, recombinant proteins, small molecules, and small interfering RNA agents. Validation of these new drugs as effective treatments for kidney diseases faces several challenges. Many complement-mediated kidney diseases are rare, so it is not feasible to test all of the new drugs in numerous different rare diseases. The onset and course of the diseases are heterogeneous; many of these diseases also carry a lifelong risk of recurrence, and it is not clear how long complement inhibition must be maintained. In spite of these challenges, new therapeutic options for targeting the complement system will likely become available in the near future and may prove useful for treating patients with kidney disease.

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The kidney is a common target of immune-mediated injury. Several kidney diseases are caused by autoimmunity against antigens expressed within the glomeruli, and the innate immune system also frequently causes renal injury. Furthermore, kidney failure causes dysregulation of the immune system. Chronic kidney disease is associated with a reduced ability to fight infection, for example, yet patients with CKD also have evidence of chronic systemic inflammation.[1] Thus, there is a delicate interrelationship between the kidney and the immune system (Figure 1), and immunomodulatory drugs may be beneficial for treating many different kidney diseases and their complications.

The complement cascade is a vital component of both the innate and adaptive immune systems, making it an important therapeutic target. Drugs that block complement activation can rapidly reduce tissue inflammation and also attenuate the adaptive immune response to foreign and tissue antigens. Although the specific mechanisms vary, complement activation contributes to the pathogenesis of almost every kidney disease.[2] This protein cascade is amenable to many different pharmacologic approaches, and anti-complement drugs could play a larger role in the treatment of kidney disease in the years to come.

THE COMPLEMENT SYSTEM

The complement system is composed of more than 30 plasma and membrane-bound proteins. Activation of the system proceeds in a cascade fashion via the following 3 initiation pathways: the classical (CP), lectin (LP), and alternative (AP). During activation the proteins C2, C4, C3, and C5 are cleaved. The resultant protein fragments bind to nearby tissues or enter the systemic circulation, eliciting both local and systemic responses. The complement system mediates detection and removal of pathogens, local inflammatory reactions, the recruitment and activation of phagocytes, direct cell lysis, and the removal of apoptotic cells and immune complexes.

These downstream effects are primarily mediated by C3a, C5a, C3b, and C5b-9 (Figure 2). C3a and C5a (the "anaphylatoxins") are small peptides released during complement activation that bind to transmembrane-spanning G protein–coupled receptors (C3aR and C5aR). C5a also binds to a non–G protein–coupled receptor (C5L2). The anaphylatoxin receptors are expressed on myeloid and non-myeloid cells. They induce vasodilation, cytokine and chemokine release,

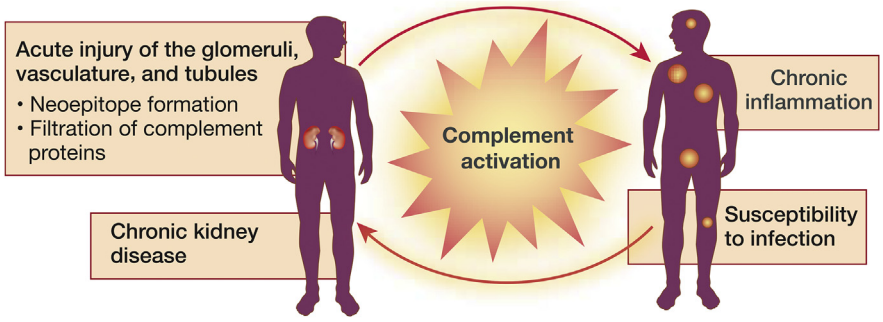

Figure 1 | The complement system and kidney disease. Complement activation contributes to the pathogenesis of acute and chronic kidney injury. Damage to the kidney, in turn, increases local and systemic complement activation. The complement cascade may link kidney disease with an increased susceptibility to infection and systemic inflammation. Complement inhibitory drugs hold the promise of blocking many forms of immune-mediated kidney injury and reducing the systemic effects of kidney disease.

and the recruitment of immune cells, and they induce an oxidative burst by macrophages, eosinophils, and neutrophils. C5a also contributes to T-cell and antigen-presenting-cell activation, expansion, and survival.

During complement activation, C3b is fixed to nearby cells where it amplifies AP activation and contributes to formation of the C5 convertase (activating enzyme). C3 fragments bound to the surface of cells are also ligands for 4 different complement receptors (CR1–4). C5b-9 (also referred to as the terminal complement complex [TCC] and the membrane attack complex [MAC]) is a multimer that forms pores in the outer membranes of target cells. The flux of fluid and ions through C5b-9 pores can cause cell activation, proliferation, apoptosis, or lysis.

COMPLEMENT AND THE KIDNEY

Given its promiscuous involvement in both the innate and adaptive immune responses, the complement system may provide a convenient "node" for treating a variety of distinct renal diseases. IgM- and IgG-containing immune complexes are strong activators of the CP, which is implicated in many forms of glomerulonephritis, including lupus nephritis and cryoglobulinemia. The CP is also activated in antibody-mediated transplant rejection (AMR). The LP is activated when mannose-binding lectin (MBL) proteins or ficolin bind to carbohydrates present on bacteria surfaces. The MBLs and ficolin also bind to molecules displayed on damaged cells, and detection of MBL proteins in the glomeruli of patients with IgA nephropathy suggests involvement of the LP.[3]

AP activation is involved in the pathogenesis of many different types of kidney disease. The AP is continually activated in plasma by the conversion of C3 to its hydrolyzed form, C3(H_2O), which forms part of an initiation C3 convertase. This convertase generates more C3b, self-amplifying AP activation. Spontaneous AP activation provides a rapid response to pathogens, but it must be tightly regulated on host tissues. This balance is maintained by a group of complement regulatory proteins.[4] Congenital and acquired defects in complement regulation are associated with inflammation, and the kidney is particularly susceptible in

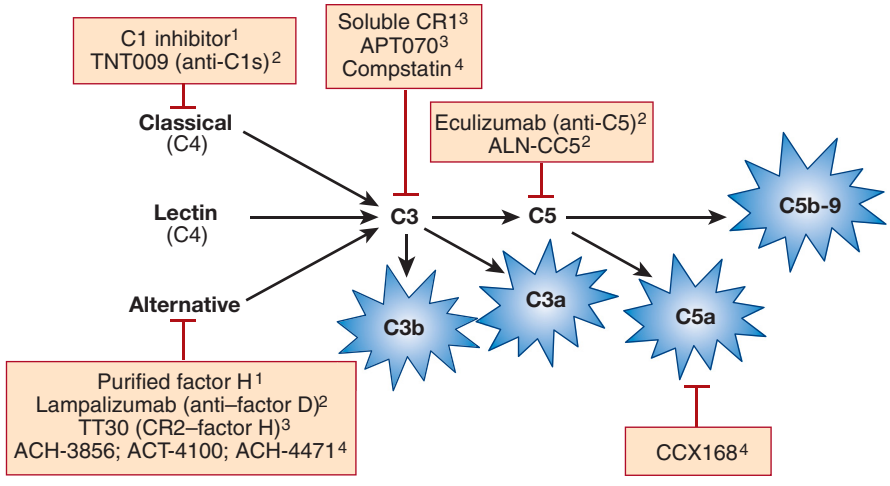

Figure 2 | Overview of drugs that target the complement cascade. Complement activation is initiated through the following 3 pathways: the classical pathway, alternative pathway, and lectin pathway. Full activation leads to the generation of several biologically active fragments, namely C3a, C5a, C3b, and C5b-9. Drugs are currently being developed to selectively block the classical pathway, the alternative pathway, activation at the level of C3, activation at the level of C5, and C5a. [1]Purified proteins, [2]monoclonal antibodies, [3]engineered proteins, [4]small molecules, [5]small interfering RNA.

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