A Crry for polar shedding


Masaomi Nangaku

Division of Nephrology and Endocrinology, University of Tokyo School of Medicine

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Renal ischaemia plays a crucial role in the pathogenesis of acute renal failure. This ischaemia is also the primary factor in radio-contrast nephropathy, kidney transplantation and the progression of various kinds of chronic kidney diseases.

Ischaemic renal failure is associated with the loss of tubular epithelial cell polarity [1,2]. This change in cell polarity has multiple functional sequelae which result from the subsequent incorrect targeting of membrane proteins. Sodium/potassium-ATPase, for example, which is usually confined to the basolateral domain, is misdirected to the apical membrane, resulting in impaired transcellular sodium transport. Misdirected targeting of integrins, which anchor epithelial cells to extracellular matrix, causes viable tubular epithelial cells to be shed into the tubule lumen. In a recent article in J. Clin Invest, Thurman et al. [3] demonstrated the critical role of the loss of polarized localization of a complement regulatory protein, Crry, in the pathogenesis of ischaemic acute renal failure in mice. Complement activation leads to tissue injury through various mechanisms, including the generation of chemotactic factors and C5b-9 formation on the resident renal cells, with subsequent activation and injury. Complement activation is regulated by a number of complement regulatory proteins. Mice and rats are endowed with a potent transmembrane complement regulatory protein present on the basolateral membrane of tubular cells which works at the C3/C5 convertase step, called Crry [4]. While other complement regulatory proteins such as DAF and CD59 are expressed exclusively within the glomeruli and vasculature in the mouse kidney, Crry is present on the basolateral membrane of tubular cells. During renal ischaemia, however, Crry localization is altered, with a decrease in concentration on the basolateral membrane prior to complement deposition (Figure 1). Crry shifts from a triton-insoluble to a triton-soluble form after ischaemia/reperfusion, suggesting detachment of the molecule from the actin cytoskeleton. Complement activation precedes morphological injury after ischaemia/reperfusion injury of the kidney, and tubules that retain Crry are protected from complement deposition. The authors also observed an increase in C3 synthesis in the kidney after ischaemia/reperfusion. The important role of local complement synthesis in ischaemic renal injury was recently confirmed in animal transplantation experiments [5].

Correspondence and offprint requests to: Dr Masaomi Nangaku, Division of Nephrology and Endocrinology, University of Tokyo School of Medicine, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. Email: mnangaku-tky@umin.ac.jp

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The primary effect of complement in the ischaemic area is on the kidney’s parenchymal cells rather than vascular endothelial cells [6]. Spontaneous activation of the alternative pathway, so-called ‘tickover’, occurs in any type of cell, and complement regulatory proteins protect host cells from deleterious local complement activation. Thurman’s study [3] demonstrated that the loss of polarity not only induces functional disturbances of tubular cells, but also causes tubular cell injury itself via unlimited complement activation arising from the alteration of Crry localization under ischaemia. A previous report demonstrated activation of the complement pathway by damaged tubular cells per se, although the authors did not examine the expression of complement regulatory proteins [7]. On these bases, even a minor injury to tubular cells may induce activation of complement components without appropriate regulation by complement regulatory proteins, no matter what the cause of the original tubular injury.

While details of the interaction between Crry and actin remain to be elucidated, cytoskeletal alterations in tubular cells may be the central event in a vicious cycle of ischaemic renal injury. Human proximal tubular epithelial cells incubated with serum show the predominant activation of the alternative pathway of complement [8]. This event is followed by marked cytoskeleton alterations with C5b-9-dependent disruption of the actin cortical network. Thus, not only ischaemia but also complement attack per se cause derangement of the cytoskeleton. Disassembly of the actin cytoskeleton might then exacerbate the complement cytotoxicity, with the potential involvement of a signal transduction pathway [9].

Insights from Thurman and colleagues [3] study may also be extended from ischaemic acute renal failure to embrace a broad spectrum of renal diseases. Given recent studies implicating chronic hypoxia of the kidney as a final common pathway in end-stage renal disease [10–12], it may be interesting to investigate whether cytoskeletal derangement and local complement activation might also result from chronic ischaemia. Many previous studies have emphasized a pathogenic role for urinary complement components in the progression of renal disease. For example, urine samples from patients induced the deposition of C3 and C9 on the surface of a cultured human proximal tubular cell line via the alternative pathway, the mechanism of which may include the provision of a ‘protected site’ on their surface [13]. In support of a deleterious effect of complement components in urine, anti-proteinuric therapies have been shown to ameliorate complement deposition in tubules, in association with improvements in renal function [14]. Further, experiments in complement-deficient animals have shown that C5b-9 formation is essential in tubulointerstitial injury and the progression of renal dysfunction in proteinuric states [15,16]. After renal ischaemia/reperfusion, Crry is seen diffusely throughout the proximal tubular cells and within the tubular lumen, potentially with the shedding of vesicles containing Crry. While such redistribution and shedding of vesicles enhances complement activation on the basolateral side of tubules, it may serve to protect against activation on the luminal side of tubular cells. One study showed that down-regulation of Crry in tubules utilizing in vivo anti-sense oligonucleotides increases susceptibility of the kidney to proteinuric damage [17], and further studies are needed to clarify the effects of the redistribution of complement regulatory proteins in proteinuric diseases.

A second important message of Thurman’s article is that the non-genetically determined loss of complement regulatory proteins may significantly contribute to organ injury. The exact localization of cell surface complement regulatory proteins is clearly very important. Shutdown of the alternative pathway by inhibitory monoclonal antibody against essential complement components such as factor B is effective in the amelioration of ischaemic renal injury [18]. Recent progress in molecular biological techniques has also made feasible a variety of new approaches which utilize recombinant soluble complement inhibitors [19]. The potentially disastrous side effects of systemic inhibition of the innate immune system cannot be ignored, however, and future therapies involving exogenous complement inhibitors will be thoroughly dependent on the strategic targeting of recombinant complement regulatory proteins to specific sites [20].

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References


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