We are used to thinking of the kidney as a passive target for circulating complement components, the majority of which are produced by hepatic synthesis and deposited at local sites of tissue injury. Furthermore, the main, if not only, type of renal injury caused by complement was thought to be immune complex glomerulonephritis. An updated view has changed in 2 important respects. First, the kidney is now regarded an active participant in its own injury, insofar as several types of cell found in the kidney are capable of complement synthesis and thus have the potential for contributing to complement-mediated injury on their own doorstep. Second, complement affects a broader range of renal disease than was first thought. Namely, it contributes to several types of tubulointerstitial disease, including transplant rejection and progressive renal failure, as well as a significant role in vessel wall inflammation. Understanding which pool of complement contributes to what injury is an essential starting point for organizing better approaches to therapy, and also tells us something new about the potential for local regulation of the complement cascade and how this affects disease manifestation.

Most types of cell in the body are capable of producing complement, whether they are in a resting state or responding to noxious stimuli. The cellular sources of secreted complement proteins can be grouped into 3 types: hepatocytes, which generate at least 80% of circulating complement; resident tissue cells, which can be divided into specialized cells, such as astrocytes, and nonspecialized cells, such as fibroblasts; and migratory cells, including macrophages, polymorphs, and dendritic cells. Collectively, cells transferred within a transplanted human kidney can secrete 5% to 10% of the circulating pool of C3, which is the master component of the complement cascade vital to inflammatory responses. As an indication of the capacity for local expansion of the complement pool, tissue mRNA expression in inflamed kidney may increase several hundred times, and the spillover of secreted protein into the blood may double. Glomerular disease shows expansion of complement genes in glomerular mesangial and epithelial cells, whereas primary tubulointerstitial disease is linked with synthesis predominantly in the tubular epithelium. However, induction of glomerular disease in experimental models is soon followed by expression of complement genes in the proximal tubule, a pattern that also typifies chronic human glomerulonephritis.

This wave of expression of complement genes radiating from glomeruli to proximal tubules foretells a significant shift in the role of local complement in progressive renal disease (Table 1). A point to grasp is that peripheral organs, such as the kidney, have powers for self-regulation of the complement cascade. Most of the alternative and classic pathway components needed for complement activation are expressed in renal tissue. Their pro-
duction is regulated by a variety of homeostatic and pathologic factors, too numerous to comprehensively list here but including cytokines such as γ-IFN, TNF, and IL-1. These may have differential effects on hepatic and peripheral synthesis, and this could serve the function of complement at particular locations. In addition, complement control proteins that regulate the stability of enzyme complexes formed by the classic and alternative pathways are present on a variety of resident renal cells. Here, they bind activated C3 present on a variety of resident renal locations. In addition, complement functions of complement at particular sites may have differential effects on hepatic and peripheral synthesis.

One of the fundamental protective actions of complement is the clearance of invasive pathogens and removal of immune complexes and cell debris. This is evident in individuals with inherited C3 deficiency who develop recurrent bacterial infections and immune complex glomerulonephritis. But is this a function of local or systemic complement? Buildup of glomerular immune complexes is mirrored experimentally in C3 deficient mice injected with sheep Ig. However, only mice lacking in circulating complement are prone to renal immune complex deposition, whereas mice with selective intrarenal deficiency of C3 remain vulnerable to this condition. This suggests the major responsibility for preventing buildup of tissue complexes lies with circulating complement, whereas local tissue synthesis has no important clearing role that prevents immune complex accumulation at least in glomeruli.

In contrast to its physiologic function, complement activation leads to inflammation in several types of glomerulonephritis, such as systemic lupus erythematosus, IgA nephropathy, and membranous nephritis. In these examples, strong intraglomerular expression of complement occurs. Mesangiocapillary glomerulonephritis is reproduced spontaneously in mice lacking the soluble complement regulator, factor H, demonstrating that loss of complement regulation alone can be a powerful cause of glomerular inflammation. However, despite expectations for local production of complement to play an instrumental role, only the circulating components contribute to glomerular inflammation in these mice. This has left doubt over the pathophysiological role of intraglomerular complement gene expression.

In any event, the overwhelming site of complement gene expression in evolving glomerular diseases is the proximal tubular epithelium and in interstitial leukocytic infiltrate. Because current thinking favors a damaging effect of filtered protein on the renal tubule and noting that exposure to excessive protein induces tubular synthesis of complement, complementologists have proposed a role for complement in the pathogenesis of tubulointerstitial damage. Expanding evidence suggests that complement derived by local synthesis has a substantial effect on the progression to end-stage renal disease. This is illustrated by a study of glomerular proteinuria induced by Adriamycin in a susceptible strain of mouse. Despite the glomerular lesion of treated mice being independent of complement, renal survival is critically dependent on local C3 expressed mainly in the tubular epithelium. Although more work is needed specifically on progressive glomerular disease, the influence of local complement on renal outcome is confirmed in the wider perspective of tubulointerstitial disease.

GLOMERULAR DISEASE

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**TUBULOINTERSTITIAL DISEASE**

Traditionally, we relate complement to immune-mediated diseases. However, the range of conditions affected by complement encompasses nonimmunological inflammatory diseases. Postischemic acute renal failure is a good example. Models of renal reperfusion damage have identified important roles for the alternative and terminal pathways of complement activation.

### Table 1. Tissue site of complement gene expression with respect to glomerular and interstitial disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mesangial</th>
<th>GEC</th>
<th>Parietal</th>
<th>Tubule</th>
<th>Infiltrate</th>
<th>Vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>++</td>
<td>+</td>
<td>—</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Membranous</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SLE</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Tubulointerstitial</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Rejection</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reperfusion injury</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Infection</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
</tbody>
</table>

**GEC:** glomerularepithelial cells; **SLE:** systemic lupus erythematosus; +, ++, ++++, and −, subjective score of degree of expression.
leading to cell injury, making them valid targets for therapy. Reperfusion causes massive induction of complement gene expression, mostly affecting the proximal tubules in the hypoxia-sensitive corticomedullary region of the kidney. Kidney swap experiments between complement-producing and C3 deficient mice show the renal lesion dependent almost entirely on intrarenal synthesis, deficient mouse kidneys avoiding renal failure despite abundant circulating component. Interestingly, loss of cell-surface complement regulatory protein that normally curbs the activation of C3 also contributes to the pathogenesis of posts ischemic acute renal failure.

Kidneys transplanted across a major histocompatibility barrier exhibit a role for complement synthesis in transplant rejection that is far greater than can be explained by local tissue damage. In the absence of organ-autonomous C3, kidney allografts show prolonged survival associated with impaired immune responses of the recipient against histocompatibility antigens on donor tissue. Heeger et al. found corresponding results in heart transplant studies, where the absence of the complement regulator, DAF, leads to uncontrolled complement activation and shortened graft survival. It seems the properties of donor passenger leukocytes, which migrate and trigger the recipient immune response against the transplant, also depend on self-production of complement, offering new biochemical targets for modulating graft rejection.

The precise details for the effect of donor-cell complement on the recipient immune system are still being worked out, but this probably involves signaling receptors that are capable of sensing the soluble or membrane-bound fragments generated by complement activation, and which are expressed on antigen-presenting cells and T lymphocytes.

The results of human kidney transplantation also confirm that local synthesis of complement is important. Factor C3 comes in 2 main allelic variants (fast and slow), which associate with autoimmune disease and can be expected to have differences in function. The S and F variants expressed by the donor organ portend very different outcomes, which differ by 35% at 10 yr after transplantation. In contrast, recipient C3 alleles were found to have no detectable effect. Exactly how this happens is unknown, but unlike the absence of C3 in murine studies, the association of transplant outcome with C3 polymorphisms is independent of acute inflammatory events (reperfusion and rejection); indeed, the influence is only manifest after the first year. This suggests a late, complement-dependent inflammatory process with a long-term influence on outcome, a point worth bearing in mind with regard to progressive renal disease in general.

Two-Compartment Model and Clinical Strategy
A division of labor between systemic and local pools of complement would appear to explain many of the findings in renal disease (Table 2). While intraglomerular pathology remains in the domain of circulating complement components, tubulointerstitial diseases are vulnerable to the products of local synthesis, notably C3. Loss of cell-surface regulatory proteins at either glomerular or interstitial sites is also associated with excessive complement activation, with acute and progressive local injury. Hemolytic uremic syndrome (which is beyond the scope of the present article) is right on the dividing line because defects in circulating factor H lead to glomerular pathology that cannot be cured by transplantation, whereas defects of membrane-

Table 2. Provisional assignment of C3 function in different tissue compartments

<table>
<thead>
<tr>
<th>Pool</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating pool</td>
<td>clearance of systemic immune complexes</td>
</tr>
<tr>
<td></td>
<td>glomerular inflammation</td>
</tr>
<tr>
<td></td>
<td>antibody mediated rejection</td>
</tr>
<tr>
<td></td>
<td>hemolytic uremic syndrome?</td>
</tr>
<tr>
<td>Interstitial pool</td>
<td>defense against locally invasive infection</td>
</tr>
<tr>
<td></td>
<td>tubulointerstitial inflammation</td>
</tr>
<tr>
<td>Myeloid pool</td>
<td>regulation of B cell response</td>
</tr>
<tr>
<td></td>
<td>regulation of T cell response</td>
</tr>
</tbody>
</table>

Figure 1. (A) Cross section of mouse kidney after cold ischemic insult showing enhanced gene expression of C3 (blue) in the tubular epithelium. (B) Mouse dendritic cell expressing cytoplasmic C3 protein (red), which is then released from the cell and activated to generate the anaphylatoxin C3a (not shown). (C) Tubular epithelium treated with membrane-adherent complement regulator (green) delivered by infusion into donor kidney. Tubules are protected from the actions of cell-autonomous complement released into the interstitium.
bound regulators such as MCP, leading to indistinguishable disease, can be overcome by transplantation. The conundrum of why intraglomerular structures are vulnerable to circulating complement whereas interstitial structures are apparently not may be explained by the unusual fenestrated structure of the glomerular endothelium, meaning that the mesangium and basement membrane of the glomerulus are directly exposed to blood-borne components, whereas the interstitium is relatively impenetrable to the larger plasma components, such as C3 (180 kDa). A third or myeloid compartment may be necessary to explain the sufficiency of mononuclear cell synthesis of C3 in complement-stimulated immune regulation, which has only been touched upon here but represents an exciting advance in the field of complement biology and renal transplantation.

This proposed demarcation of complement territory into glomerular and interstitial disorders marks the beginning of new clinical strategies, notably in renal transplantation. Studies of graft-targeted complement regulator have already completed clinical safety evaluation. Having demonstrated the ability in preclinical models to expand the number of organs usable following prolonged cold ischemia (Figure 1). This approach looks to be suitable for targeting both the intravascular and extravascular pools. Furthermore, studies of polymorphisms in donor complement genes are already examining risk assessment and the value for individualized patient management.

REFERENCES


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DISCLOSURES

None.


