Kidney International, Vol. 59 (2001), pp. 1227–1235

PERSPECTIVES IN BASIC SCIENCE

Intrarenal synthesis of complement

WUDING ZHOU, JAMES E. MARSH, and STEVEN H. SACKS

Department of Nephrology and Transplantation, Guy's Hospital, London, England, United Kingdom

Intrarenal synthesis of complement. During the past decade, research has shown that the kidney has the capacity to synthesize most of the activation pathway components of the complement cascade. As well as implying physiological roles in local clearance of immune complexes and defense against invasive organisms, an increasing amount of evidence indicates that the intrarenal synthesis of complement makes an important contribution in the pathogenesis of renal injury. Here we review this evidence and present a case for more definitive investigation of these functions.

An article by Feucht et al in 1989 attracted attention to the possibility that the local synthesis of complement components might be an inherent feature of the human kidney [1]. It described the isolation of gene transcripts for C4 from the cortex of normal human kidney. In the previous year, published work by Passwell et al in Washington (USA) found that the kidney of mice with lupus nephritis expressed increased amounts of RNA message for C4, C2, C3, and factor B [2]. Moreover, they showed that tissue slices prepared from the inflamed kidneys of these mice could incorporate amino acids present in the culture medium into complement proteins, indicating that local complement gene expression could result in significant protein synthesis. A strong possibility was that infiltrating cells, which were abundant in the nephritic tissue, had produced these components. This was because previous work in the principal author's laboratory and subsequently in several other laboratories had already shown that cells of bone marrow origin (for example, macrophages and monocytes) were capable of producing a wide range of complement components [3, 4]. However, a number of other research groups, namely in Leiden, Toronto, London, and Bari, subsequently set out to investigate which, if any, indigenous cell types in the kidney had the capacity to synthesize complement proteins. In 1991, Brooimans et al reported the synthesis of complement by proximal tubular epithelial cells grown from normal human kidney [5]. In the same year, in situ hybridization studies reported by Witte, Welch, and Beischel confirmed that the renal tubule was a prominent site for local complement gene expression in normal and diseased kidneys [6]. In 1993, our group at Guy's published a series of experiments in which cultured human glomerular mesangial and epithelial cells were shown to be able to secrete a variety of classic and alternative pathway components [7–9]. Montinaro et al reported similar findings with mesangial cells [10]. Several years later, Sheerin et al demonstrated the potential for glomerular endothelial synthesis of complement using a rat glomerular endothelial cell line [11]. Thus, the stage was set for a comprehensive description of the range and cellular origin of complement proteins generated locally within normal and diseased kidneys, from mouse to humans. Today, although we have a detailed picture of the renal complement system, including recent quantitation of the contribution made by the transplanted kidney to the pool of circulating C3 [12], we have only a limited knowledge about the functional importance of local complement synthesis, with particular regard to disease. In this review, against a background of incontrovertible evidence showing that complement plays a role in the pathogenesis of renal disease [13, 14], we consider the current evidence that suggests local production of complement may be contributing to renal injury in a variety of conditions.

Key words: complement cascade, protein synthesis, gene expression of complement, renal complement system, pathogenesis of renal disease, immune complexes.

Received for publication August 3, 2000
and in revised form October 27, 2000
Accepted for publication November 1, 2000

COMPLEMENT SYSTEM AND MECHANISMS OF TISSUE INJURY

There are several ways in which complement activation can lead to tissue injury (Fig. 1). These have been reviewed extensively elsewhere [15]. First, the cleavage of C3 and then C5 generates small biologically active peptides, C3a and C5a. These stimulate the vascular and cellular components of inflammation, leading to vasodilation, increased vascular permeability, and leukocyte infiltration. Second, the large cleavage fragments C3b and subsequently C5b lead to the formation of the mem-

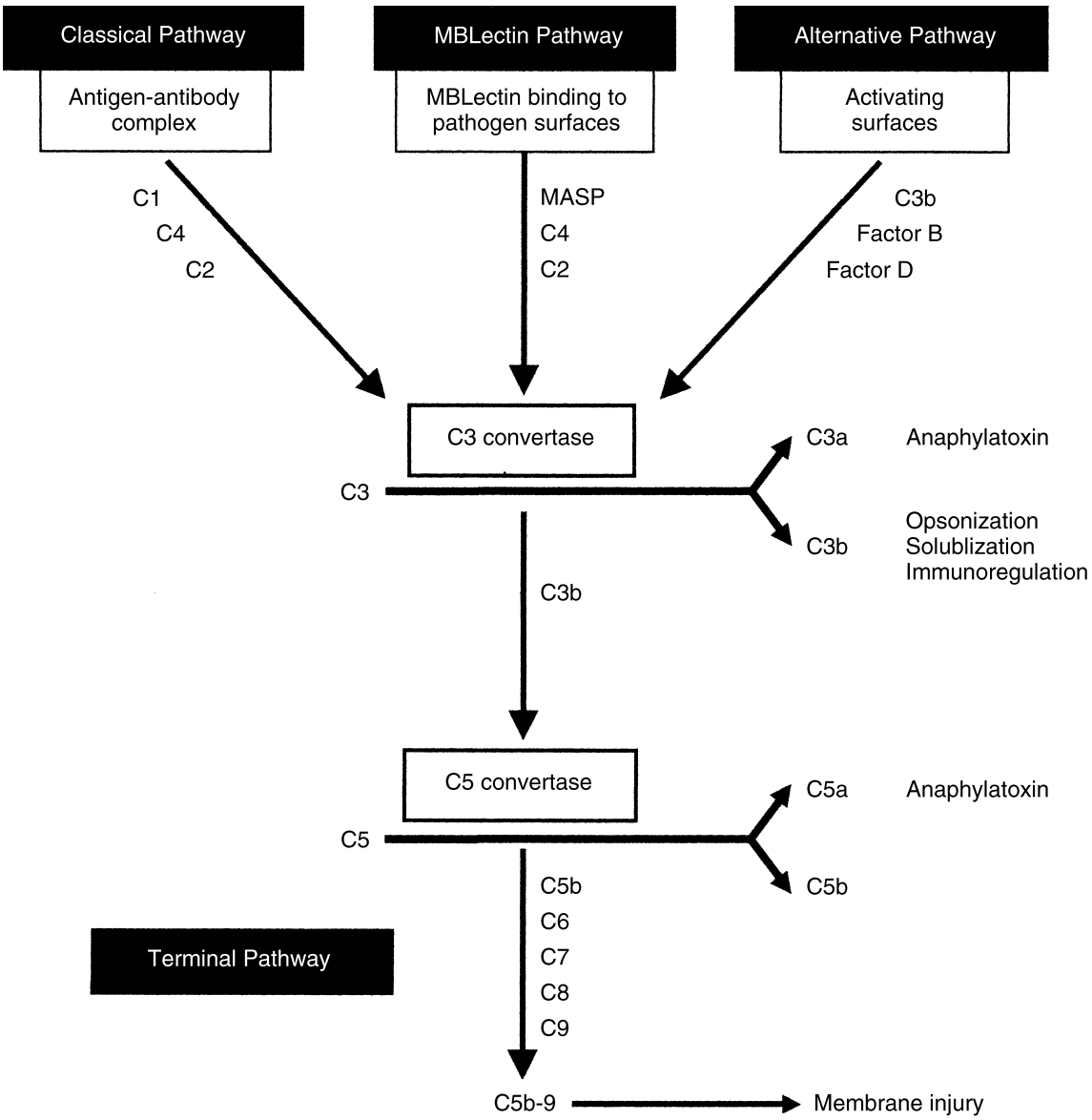

Fig. 1. The complement cascade. The central step of the complement cascade involves the cleavage of C3. This is achievable by activation of the classic, alternative, or lectin pathways. Activation of these pathways generates converting enzyme complexes that cleave C3. Cleavage of C3 and subsequently C5 results in the generation of anaphylatoxins (C3a and C5a) and MAC (C5b-9). The large cleavage product C3b and its degradation products (iC3b or C3 dg) mediate a number of biologically important effects including enhancement of T-cell and B-cell function and disposal of immune complexes and apoptotic cells. Abbreviations are: MBL, mannan-binding lectin; MASP, MBL-associated serine protease.

brane attack complex (MAC; C5b-9). The MAC forms pores in cells resulting in cell activation or, at higher concentration, to cell death by lysis. Sublytic doses of MAC can activate renal parenchymal cells, which then release proinflammatory cytokines, reactive oxygen species, vasoactive chemicals, and profibrotic factors [16–18]. In addition to initiating the terminal pathway of complement activation, C3b and C4b deposition on target cells increases the potential for interaction with inflammatory cells bearing receptors for these ligands [15]. A fourth, more recently elucidated mechanism of potential injury is the enhancement of the immune response caused by breakdown fragments of C3 (for example, C3b and C3d) binding to antigen, greatly lowering the threshold for stimulation of antigen-specific lymphocytes [19–21]. These mechanisms are initiated by cleavage of C3 by converting enzymes. These enzyme complexes are generated by antibody and non–antibody-mediated mechanisms acting through the classic, alternative, and lectin complement pathways (Fig. 1). Complement-regulatory proteins, which can be soluble (for example, C4 binding protein, factor H) or cell bound (for example, decay accelerating factor,

Table 1. Differential detection of complement gene expression in normal human kidney [24]

	Cortex	Glomeruli	Tubules	Medulla
C1q	++	++	++	++
C2	+	+/−	++	+
C3	+	+/−	++	+/−
C4	+	+	++	+
Factor B	+	+/−	+/−	+
Factor D	+	++	++	+
Factor H	+	+	++	+
Properdin	+	++	+/−	+/−

Relative expression of RT-PCR product obtained with RNA from fractionated renal tissue based on 10 subjects. Symbols are: (+) detected, (++) strongly detected, (+/−) weakly detected.

CD59), block the early cleavage steps of C3 and C5 or inhibit the assembly of MAC, preventing self-injury by background or heightened complement activity.

RANGE AND CELLULAR ORIGIN OF COMPLEMENT COMPONENTS PRODUCED BY THE KIDNEY

The main source of circulating complement is the liver, as shown after liver transplantation when the plasma C3 allotype becomes that of the donor. However, smaller but significant amounts of complement components are produced in other organs, such as the brain, blood vessels, lungs, intestine, joints, and skin as well as the kidney [22]. Naughton et al estimated that approximately 10% of circulating C3 arises from sources other than the liver [23]. More recently, a study of the conversion of one C3 allotype to another following kidney transplantation has suggested that about 5% of circulating C3 is derived from the single donor kidney [12].

A comprehensive range of complement genes are expressed in the kidney, including most components of the activation pathways. Our current state of knowledge is summarized in Table 1 [24]. It can be seen that there are regional differences in complement mRNA expression within the kidney. The main components of complement synthesized in the liver (C2, C4, C3, and factor B) are more strongly detected in the renal cortex consisting mainly of tubules, whereas some components that are primarily produced at extrahepatic sites (for example, C1q and factor D) are detected strongly in glomeruli. The reason for this differential distribution is unknown, but it suggests that certain factors have a specialized function in the glomerulus. For example, C1q, which is synthesized mainly in mononuclear phagocytes and epithelial cells, has been suggested to play an important role in the clearance of immune complexes and apoptotic bodies in the kidney [25–27]. Local expression of C1q could have a kinetic advantage over deposition of a circulating component. Factor D, on the other hand, which is synthesized primarily by adipocytes, participates in the cleavage of factor B and thus contributes to alternative pathway function. Clustering of the components of the activation pathways in the tubule may act as a front line defense against pathogens. Several types of nonrenal cell such as macrophages, neural cells, and fibroblasts express the terminal (C5-C9) as well as activation pathway components [3, 28, 29]. The expression of terminal pathway components in renal cells has not been described.

As indicated earlier, four types of resident kidney cell are capable of synthesizing complement proteins when grown in tissue culture. Their complement products are shown in Table 2. In general, the secretion of C3 by such cells occurs spontaneously and may approach levels comparable with those produced by cultured hepatoma cells. In contrast, the expression of C4 is often weakly detected in cultured cells, even though the signal derived from tissue mRNA may be strong. This discrepancy between in vivo and in vitro expression may be due to rapid loss of ability to synthesize C4 in vitro, as noticed in monocyte studies [38]. Factor B is also weakly detected in vitro. However, many stimulators, including cytokines, growth factors, immune complexes, serum proteins, and human cytomegalovirus, can increase the expression of C3, C4, and factor B by cultured cells (Table 2). Glomerular endothelial cells, in contrast with renal epithelial and mesangial cells, are less well studied because it has been very difficult to isolate and grow the cells in culture. However, Sheerin et al demonstrated the production of C3 by transformed rat glomerular endothelial cells [11].

Complement is an acute phase protein in which synthesis rapidly increases during infection or inflammation. The responsive nature of renal complement synthesis is illustrated by the finding in allograft recipients that the level of circulating donor-derived C3 is increased during episodes of rejection [12]. Numerous factors have been shown to regulate the production of complement by renal cells (Table 2). The effects of some of these signals are tissue specific, and the response may even vary with different cell types in the same tissue. For example, interleukin-1 (IL-1) may induce a twofold to threefold increase in the renal expression of C2 in mice, but has no effect on hepatic synthesis of C2 [39]. Another example is tumor necrosis factor-α, which regulates the transcription of C3 in glomerular endothelial cells [11], but has no such effect in glomerular mesangial cells [7]. The cytokines IL-2 and interferon-γ (IFN-γ) appear to play a major role in regulating the production of C3 and C4 by proximal tubular cells [5, 37]. Furthermore, IFN-γ induces changes in renal gene transcription while in hepatocytes may act at the level of RNA translation to increase local complement synthesis [8, 23]. This local variation in the regulation of complement may allow fine tuning of tissue levels expressed without alteration of circulating levels.

In addition to the complement activation pathway

Table 2. Complement synthesis in cells of renal origin

Cell type	Factors	Stimulators	References
Glomerular epithelial	C3	IFN-γ	[8]
	C4	IFN-γ	[9]
Glomerular mesangial	C2	HCMV	[30]
	C3	IFN-γ, Immune complex, IL-1	[7, 31, 32]
	C4	IFN-γ	[7, 33]
	FB	HCMV, IL-1, TNF-α, IFN-γ	[30, 33]
	FH	IFN-γ	[32]
Glomerular endothelial	C3	TNF-α	[11]
Proximal tubular epithelial	C2	IFN-γ	[34]
	C3	IL-2, Serum proteins, IL-1	[5, 35, 36]
	C4	IFN-γ	[37]
	Factor H	IFN-γ	[34]
	Factor B	IL-1	[36]

Abbreviations are: IFN-γ, interferon-gamma; HCMV, human cytomegalovirus; IL-1, interleukin-1; IL-2, interleukin-2; TNF-α, tumor necrosis factor-α.

components, a number of complement regulatory proteins, particularly membrane-bound proteins, are synthesized within the kidney [40–44]. These include decay-accelerating factor (DAF/CD55), membrane cofactor protein (MCP/CD46), complement receptor type 1 (CR1/CD35), and MAC inhibition factor (MACIF/CD59). DAF, MCP, and CR1 inhibit complement activation at the level of the C3 and C5 converting enzyme complexes, while CD59 prevents the formation of the MAC. The distribution of these inhibitory proteins in normal and diseased kidneys has been comprehensively studied and is the subject of excellent recent reviews by Nangaku, Johnson, and Couser [45, 46]. These and other groups have found that complement regulatory proteins are widely expressed in the glomeruli and renal tubules, the level of expression of these molecules varying with the anatomical segment or cell type of the kidney [40, 44]. The renal tubule is relatively deficient in DAF and CD59, helping to explain the vulnerability of the renal tubule to complement attack [44, 47]. Expression of these molecules is up-regulated during the activation of complement [48], as occurs in a number of forms of renal disease [40, 43, 49–51]. Not surprisingly, overexpression of complement regulatory protein in mice markedly ameliorates nephrotoxic serum nephritis [52]. This indicates that complement regulatory proteins play a protective role against complement-mediated renal injury. The kidney therefore has a set of positive and negative internal controls with the ability to influence complement activation on the renal structures.

EXPRESSION OF NATIVE COMPLEMENT COMPONENTS IN INJURED KIDNEY

A number of studies have examined complement gene expression in injured kidney, defining the extent and site of local complement gene expression in renal disease. These studies can be divided into (*1*) experimental studies, which have investigated local complement gene expression over time, and (*2*) clinical biopsy studies, which provide a cross-sectional view at different stages of disease. In general, these have focused on C3 and C4 because of the pivotal role of these components in complement activation. The main findings are summarized in Tables 3 and 4. Several general conclusions can be made: (*1*) In experimentally induced nephritis, there is an early increase in the glomerular expression of C3 and C4. (*2*) This change occurs in glomerular epithelial cells, parietal epithelial cells, or mesangial cells, according to the primary site of the immune attack. (*3*) Following the glomerular insult, there is a progressive increase in the tubular epithelial expression of C3 and C4. (*4*) With patient biopsy material, taken unavoidably at various stages of evolution of renal disease, there is predominant tubular expression of C3 and C4. The level of C3 gene expression broadly correlates with the severity of tissue injury, where studies have paid attention to this factor.

NEPHRITIS

In a rat model of membranous glomerulonephritis (passive Heymann nephritis), glomerular injury was accompanied by enhanced glomerular expression of the transcripts for C3 and C4 [54, 55]. This predominantly occurred in the podocytes but also involved the mesangial areas, as shown by in situ hybridization techniques. Tubular expression of complement was also induced following the glomerular injury. Moreover, the overall level of C3 mRNA expression by semiquantitative polymerase chain reaction (PCR) correlated with the severity of injury (proteinuria) [54]. Similarly, with a mouse model of crescentic glomerulonephritis (generated by a single dose of antiglomerular basement membrane antibody), competitive PCR showed a 15-fold rise in the level of C3 transcript (abstract; Sheerin et al, *J Am Soc Nephrol* 10:537A, 1999). This was located mainly in the tubular epithelium by 14 days after the disease induction (unpub-

Table 3. Animal studies of local complement synthesis in the kidney

Disease model	Factors	Findings	Location of complement synthesis	References
SLE				
MRL *lpr*/*lpr* mice with spontaneous lupus nephritis	C3, C2, C4 and factor B	Increased expression correlating with progressive disease	Glomerulus; infiltrating macrophages	[2]
(NZB × NZW) F1 mice with spontaneous lupus nephritis	C3, C2, C4 and factor B	Increased expression correlating with progressive disease		[53]
Membranous nephropathy				
Passive Heymann nephritis (rats)	C3	Increased expression correlating with progressive proteinuria over 14 days	Mesangial and glomerular epithelial cells; weak expression in tubular epithelial cells	[54]
Passive Heymann nephritis (rats)	C4	Increased expression correlating with progressive proteinuria	Glomerular epithelial and proximal tubular cells	[55]
Anti-GBM disease				
Murine model	C3	Increased expression over 10–14 days	Predominantly by tubular cells, but also by glomerular epithelial and mesangial cells	[a]
Transplantation				
Rat kidney transplantation (allografts and isografts)	C3	Initial increase in expression both isografts and allografts, and subsequent increase only in allografts	Vessel wall and mesangial cells following reperfusion; allografts subsequently demonstrated increased expression in tubular epithelial cells, parietal epithelial cells, vessel walls and some infiltrating cells	[56]

Abbreviations are: SLE, systemic lupus erythematosus; Anti-GBM disease, anti-glomerular basement membrane disease.
[a] Sheerin et al (unpublished data)

lished data). Two spontaneous mouse models of lupus nephritis showed up-regulation of C3, C4, and factor B at protein and mRNA levels, coincident with the development of renal disease [2, 53]. Altered expression did not occur in the liver, suggesting the local expression was functionally relevant to the observed organ pathology. Complement mRNA was mainly located in tubular epithelial cells and the cellular infiltrate [53]. Thus, experimental models of kidney disease, both spontaneous and induced, demonstrate a shift in complement gene expression away from the primary site of injury to the tubule.

Analysis of human glomerular disease tells much the same story, although the biopsies reported are from a heterogeneous mix of cases in each disease group. Welch, Beischel, and Witte examined biopsies from 23 patients with a variety of glomerular and interstitial disorders [6, 57]. They concluded that the renal tubule was an important site for complement synthesis in many of these conditions. A prospective series of 41 biopsies analyzed by semiquantitative polymerase chain reaction (PCR) showed that 55% of the patients with immune complex glomerulonephritis demonstrated increased expression of C3. Biopsies from patients with interstitial nephritis exhibited the greatest increases in C3 expression [58]. This suggests that the response to an immunologic insult plays a decisive part in up-regulating local complement synthesis. Miyazaki et al performed a series of elegant in situ hybridization studies in patients with IgA nephropathy and lupus nephritis [49, 59]. Their findings substantiate the importance of glomerular C3 synthesis during the evolution of these conditions, and again show that enhancement of tubular complement gene expression is a consequence of glomerular disease.

Two recent studies from Schena's group have evaluated the clinical utility of measuring complement mRNA as an index of progressive glomerular disease [61, 62]. The first study, in patients with IgA nephropathy, examined the hypothesis that the level of C3 PCR product derived by renal biopsy correlated with the severity of the disease. An elevated C3 level distinguished those patients with increased proteinuria, interstitial damage, and glomerular changes. However, there was no clear relationship between renal C3 expression and serum creatinine. A study of 22 patients with membranous nephropathy by the same authors also suggested a positive relationship between C3 gene expression and progressive disease [62]. Similarly, the intensity of C3 expression at both the glomerular and tubulointerstitial level correlated with the severity of glomerular injury [62].

The putative link between complement and chronic renal disease is an interesting one. Several years ago Nath, Hostetter, and Hostetter suggested that complement activation on the renal tubule might contribute to tubular damage [65]. This notion has been reinforced by work showing that renal tubular cells can spontaneously activate complement and then undergo proinflammatory changes [16]. Complement inhibitory studies using administered [66, 67] or genetically overexpressed complement receptors [68] also support this view. A logical extension of this hypothesis is that local overproduction of C3 by the renal tubules themselves may contribute to tubulointerstitial injury. Furthermore, Tang et al have

Table 4. Clinical studies of local renal complement synthesis

Diseases	Factors	Analysis	Findings	References
MCGN ($N = 1$) and lupus nephritis ($N = 1$)	C4	Northern analysis and in situ hybridization	C4 only expressed in tubular epithelial cells; no difference between healthy and diseased kidneys	[6]
Glomerulonephritis ($N = 9$) and interstitial nephritis ($N = 6$)	C3, C4	Northern analysis and in situ hybridization	Up-regulation of C3 expression in the tubules correlating with the pattern of glomerular disease; no upregulation in C4 expression in disease	[57]
Glomerulonephritis ($N = 20$) and interstitial nephritis ($N = 4$)	C3	RT-PCR	Increased C3 expression in immune-mediated GN, and in interstitial nephritis, but not in nonimmune glomerular injury	[58]
IgA nephropathy ($N = 15$) and lupus nephritis ($N = 5$)	C3	In situ hybridization	Increased C3 expression in immune-mediated GN in mesangial cells, glomerular epithelial and parietal epithelial cells, and tubular epithelial cells; some staining also noted in infiltrating mononuclear cells	[59]
IgA nephropathy ($N = 10$) and other immune-mediated nephropathy ($N = 7$)	C3, C4, factor B	In situ hybridization	Predominant expression of C3 and factor B in the tubular epithelial cells and to a lesser extent in parietal epithelial cells; no correlation of C4 with disease	[60]
IgA nephropathy ($N = 25$)	C3	RT-PCR and in situ hybridization	C3 expressed in 56% of patients, particularly in severe disease; predominant expression by tubular cells, also in glomerular crescents	[61]
Membranous nephropathy ($N = 22$)	C3	In situ hybridization	C3 expressed in 77% of biopsies by tubular and glomerular parietal epithelial cells; expression correlated with disease severity and urinary C5b-9 levels	[62]
Transplantation ($N = 30$)	C3	RT-PCR and immunofluorescence	Up-regulation of C3 expression in association with rejection	[63]
Transplantation ($N = 9$)	C3	Allotype specific RT-PCR and immunofluorescence	Donor derived complement detected in 66% predominantly in the tubules, but also in glomeruli	[64]

Abbreviation is: MCGN, mesangiocapillary glomerulonephritis.

shown that serum protein applied to the luminal surface of proximal tubular epithelial cells increases the basolateral secretion of C3 several-fold [35]. Thus, lateral secretion of C3 stimulated by supraphysiological levels of protein in the tubular lumen might amplify the detrimental effects of complement on the tubules and interstitium.

TRANSPLANTATION

Important qualitative and quantitative information regarding the significance of local complement expression has come from transplantation studies in rodents and humans. Syngeneic rat kidney transplants demonstrate a burst of C3 mRNA expression located in the glomeruli and blood vessels [56]. This may be an effect of ischemia/reperfusion injury [69] on the blood vessel wall. Allografts show a secondary wave of complement gene expression in the kidney tubules, which coincides with infiltration by leukocytes and is associated with the local expression of cytokines such as interleukin-2 (IL-2) and interferon-γ (IFN-γ) [56]. With clinical transplantation, a valuable approach has been to investigate the different allelic forms of C3 (C3f and C3s). Analysis of C3f negative recipients of a C3F positive kidney has enabled (*1*) allele-specific detection of donor C3 mRNA and protein in graft biopsies and (*2*) allele-specific measurement of donor C3 in the recipient serum and urine. Using these approaches, Andrews et al showed that the donor kidney exhibits substantial potential for the local synthesis of C3, sufficient to spill over into the recipient circulation and urine [63, 64, 70]. During transplant rejection, the local synthesis of C3 is increased mainly in the tubular epithelial cells at their basolateral surface [70]. Moreover, the expression of C3f by the donor kidney is associated with an increased risk of late renal dysfunction, providing a clue as to the detrimental effect that local C3 synthesis could have on the transplanted kidney [64]. Although infiltrating cells may also contribute to the local production of complement, in general, the expression of C3 by infiltrating cells is overshadowed by intrinsic expression.

FUNCTIONAL INTERPRETATION

Protection

The coordinate expression of multiple components of complement at the same site, under the control of common regulatory stimuli, argues in favor of a physiological role for intrarenal complement synthesis. One such role may be to facilitate the clearance of glomerular immune complexes. Indeed, patients with inherited complement deficiencies, particularly of the early components, display reduced clearance of immune complexes and a tendency to accumulate these in the glomerulus [71]. Although most immune complexes are cleared in the liver or spleen, the kidney is also an important organ for immune complex handling. With its large blood flow and filtration barrier function, the glomerular basement

membrane forms a charge and size selective trap. Furthermore, some immune complexes are formed in situ at the glomerular basement membrane and need to be effectively removed. Complement-deficient mice appear to have impaired glomerular handling of complexes that form in situ between antibody and planted antigen [72]. Although systemic complement is undoubtedly important for efficient immune complex handling, it is likely that local complement synthesis at the site of formation or deposition of immune complexes might facilitate their removal, maintaining the integrity of the glomerular barrier. The observation that immune complex binding to mesangial cells stimulates the production of C3 lends support to this idea [31]. Besides increasing the solubility of immune complexes, the split product C3b enhances their uptake by phagocytic cells (for example, mesangial cells) [73]. Moreover, recent studies suggest that iC3b and C1q mark the surface of apoptotic cells, enhancing their physiological clearance [26, 74]. Potentially, the secretion of early complement components by the tubular epithelium may also serve to enhance the barrier function of the tubule as a defense against invasive microorganisms. Indeed, complement products that serve in this role are normally too large to cross the glomerular filtration barrier. However, as shown in a recent study, complement components are detected in the urine [62, 75].

Injury

The disease expression studies referred to previously in this article provide strong circumstantial support for a link between local complement gene expression and tissue injury, but do not establish a causal relationship. A common feature of many of these disease studies is that significant glomerular injury is invariably accompanied by elevated expression of tubular complement, apparently in a time-dependent manner. The renal tubule may therefore serve as a dominant source of locally produced C3 in protracted glomerular disease, persistent oversynthesis having a more important influence on the evolution of chronic tubule injury than on acute glomerular injury. How will experimental approaches help to work this out? A strategy presently being investigated in our laboratory involves mice that have been transplanted with a kidney from congenic C3 deficient donors. This creates an animal whose kidney is unable to synthesize C3, but which is bathed in circulating complement components. Using this approach, it is possible to make some preliminary conclusions. Glomerulonephritis induced in such kidneys is associated with substantial sparing of tubulointerstitial damage compared with that in wild-type kidneys (abstract; Sheerin et al, *ibid*). Using a similar approach to transplant organs across a major histocompatibility barrier, it has also become possible to evaluate models of chronic rejection in the absence of locally synthesized C3. Early data from such studies indicate a significant role for local complement synthesis. Much work is needed to confirm these initial results and to extend these studies to a broader range of physiological and pathological functions.

CONCLUSION

The ability to synthesize complement components appears to go back to simple creatures such as sea urchins and jawless fish, as represented in modern day descendants of these organisms [76]. Organs such as the kidney seem to have taken on specialized functions of complement that may provide the organ with protection against pathogenic stimuli. One consequence is that excessive expression of these components may result in or add to inflammatory injury. Organ transplantation between complement-sufficient and -deficient animals offers a means to dissect the importance of these possible functions, and the early indications are consistent with a pathogenic role for local synthesis of complement in renal disease. The analysis of these questions will be further enhanced once it becomes possible to routinely engineer animals with tissue or cell-specific deficiencies of these components.

Reprint requests to Dr. Steven H. Sacks, Department of Nephrology and Transplantation, 5th Floor, Thomas Guy House, Guy's Hospital, King's College London, St. Thomas Street, London, England SE1 9RT, United Kingdom.
E-mail: steven.sacks@kcl.ac.uk

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