The complement system in renal diseases

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Introduction

The association between the complement system and renal disease has been appreciated for a long time. The complement system may be involved in the initiation, pathogenesis and resolution of glomerulonephritis (GN) in many ways. The activation of complement and its deleterious consequences have been observed in many renal diseases: some primary forms of GN, GN associated with systemic diseases, acute and chronic humoral rejection of renal transplant, cholesterol renal emboli, hemodialysis and others.

Understanding of relations of complement and GN evolved from the initial observation of depletion of serum complement in some forms of GN and identification of complement deposits in kidney biopsy specimens. Varying glomerulonephritides are associated with alterations in the serum concentration of specific complement components, the presence of complement breakdown products in the circulation, glomerular complement deposits and circulating complement-activating factors.

The evidence for the role of complement in enhancing renal injury comes also from experimental data obtained by depletion of complement with cobra venom. Studies utilizing cobra venom factor to produce generalized complement depletion in animals have shown that most of the morphological and functional changes which occur in some forms of GN are complement dependent [1]. More recently, molecular biology techniques of genetically manipulated mice, administration of recombinant complement regulatory proteins [2, 3], monoclonal anti-C5 antibodies that block or reduce kidney damage [4–6], have provided additional evidence for multiple and important roles of complement in glomerular diseases and implications for complement-targeted therapy to control ongoing inflammation in the kidney.

Hypocomplementemia in GN

Evidence of complement activation in GN comes from characteristic patterns of a decrease in the serum concentrations of specific components, some of which are vir-

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tually diagnostic of certain nephritides. Hypocomplementemia is used as a marker for diagnosis and monitoring efficacy of treatment. The components most frequently measured in clinical practice are C3, C4, C2 and total hemolytic complement (CH50). Several commercial antisera are available for each, and rapid nephelometric assays are in widespread use. The CH50 is a functional measurement, based on the ability of serum to support complement-mediated lysis of sensitized erythrocytes.

In chronic bacteremic states or in lupus nephritis, circulating or deposited immune complexes may act as classical pathway activators [7]. These disorders are frequently accompanied by reduction of the classical pathway activation proteins C1q, C2, C4 along with C3 [8, 9]. Typical patients with acute post-streptococcal GN have reductions of C3, C5 and properdin. Normalization of C3 usually occurs within 6–8 weeks [10].

The other major group of hypocomplementic GN, membranoproliferative GN (MPGN), is somewhat more variable. Type II MPGN usually is associated with a reduction in C3 only. Evidence of either classical pathway activation or terminal component depression is seen in type I MPGN.

In all these situations, depression of serum complement component concentrations is assumed to represent activation, although synthetic defects are occasionally suggested.

Complement activation fragments in circulation

Complement activation, whether in the fluid phase or on surface, often results in the generation of soluble fragments, which can be detected in circulation. The detection of these complement fragments during the course of glomerular injury provides additional evidence of ongoing complement activation. The fragments most often assayed are C3a and C5a. Commercial assays are available for both, and elevated levels appear to be compatible with ongoing complement activation. Neither, however, is currently in wide clinical usage. These tests are frequently used in testing biocompatibility of dialysis membranes.

Complement activation in hemodialysis patients occurs due to the bioincompatibility of some types of dialysis membranes [11]. Complement activation proceeds via the alternate pathway during hemodialysis [12–14]. New cuprophane membranes activate complement to the greatest degree [15]. The hydroxyl group on the surface of the cuprophane membrane is thought to promote the deposition of C3b and the association of C3b with factor B; this is followed by the activation of factor B by factor D, eventually resulting in formation of the C3 convertase C3bBb and the C5 convertase. There are several sequelae of complement activation on hemodialysis membranes: release of anaphylatoxins (C3a and C5a), formation of the membrane attack complex (C5b-9) and activation of neutrophils and mono-

cytes. C3a and C5a are potent, biologically active agents capable of producing intense vascular smooth muscle contraction, increased vascular permeability, and the release of histamines from mast cells [16].

Several types of membranes result in specific patterns of complement activation. Complement activation is greatest with cuprophane, intermediate with cellulose acetate and minimal with polyacrylonitrile [17].

Complement deposits in glomeruli

Deposition of complement, visualized by immunofluorescence, immunochemistry or electron microscopy is a frequent feature of GN, usually in parallel with antibody deposition [2, 8, 18]. Complement deposits may be dominant, for example in MPGN, or characteristic such as in post-streptococcal GN, IgA nephropathy, and membranous nephropathy (MN). In class IV lupus nephritis and some forms of rapidly progressive GN, immune deposits including complement are generally found in mesangial and subendothelial distribution. Complement deposits generally contain either both C4 and C3, corresponding to the plasma patterns of classical complement activation, or C3 without the early components, corresponding to alternative pathway of complement activation [19].

Immune complex diseases and complement

Multiple relationships exist between complement system and immune-mediated nephropathies. Most forms of glomerulonephritides are associated with immune complex deposition. Under physiological conditions, complement promotes the clearance of immune complexes, both modifying the immune complex size and favoring the physiological clearance by the erythrocyte transport system [20–22]. Deposition of complement proteins (C3bi) on the surface of immune complexes facilitates clearance through interaction with erythrocyte-bound CR1 and the reticuloendothelial system.

However, depending on circumstances, complement may be not a friend, it can be a foe. If immune complexes cannot be eliminated, then complement becomes chronically activated and can incite inflammation. Chronic infections can perpetuate the formation of immune complexes, which in hepatitis C infection and bacterial endocarditis cause relentless activation and consumption of complement.

Immune complexes in glomeruli, either deposited from the circulation or generated *in situ*, can activate the complement system. Active products of this system include the anaphylatoxins C3a and C5a, C3b, and the C5b-9 membrane attack complex. The outcomes of this are glomerular changes: either increased permeability of glomerular basement membrane (GBM) or inflammation. The pattern of

glomerular injury seen in immune complex-mediated glomerular diseases is related to the site of formation of immune deposits. If complement is activated at a site accessible to blood constituents, such as subendothelial and mesangial regions, the generated C3a, C5a and C3b can interact with circulating or intrinsic glomerular cells bearing relevant receptors, and striking changes seen by light microscopy occur, particularly hypercellularity, which may reflect infiltration by circulating inflammatory cells such as neutrophils and monocytes, or proliferation of glomerular cells, particularly mesangial cells. The histological result is proliferative GN (focal proliferative, diffuse proliferative, proliferative and exudative, membranoproliferative, rapidly progressive) and clinically active urine sediment (red cells, white cells, and cellular and granular casts), proteinuria, and often an acute decline in renal functions. The examples are post-infectious GN, IgA nephropathy, rapidly progressive GN, lupus nephritis, and MPGN.

In a privileged site such as subepithelial space, immune deposits can also activate complement, but there is no influx of inflammatory cells, since the chemoattractants are separated from the circulation by the GBM. Thus, injury is limited to the GBM and glomerular epithelial cells and the primary clinical manifestation is proteinuria, which is often in the nephrotic range. Histologically, these patients most commonly have MN [3, 21, 22].

A plethora of recent studies establishes that both circulating inflammatory cells and resident glomerular cells can mediate glomerular injury acutely by release of oxidants, proteases and probably other chemoattractants and GBM-degrading molecules. Chronic injury is also augmented by release of various cytokines and growth factors, which results in increased deposition of extracellular matrix leading to scarring and sclerosis.

Deficiencies of complement components and GN

Deficiencies or polymorphism of certain complement components are also associated with disease, especially with infections but also with autoimmune and renal diseases. The detailed description of this topic is presented in separate chapters of this book (see chapters by Goodship et al., Skerka and Józsi, and Zipfel et al.).

Our understanding of some of the roles of complement derived from the studies of individuals or experimental animals deficient in some of complement components. Several of these deficiencies are associated with renal disease, either in primary renal diseases or in systemic disease with renal involvement, such as systemic lupus erythematosus (SLE). Complement deficiencies can cause renal disease by uncontrolled complement activation, or aberrant handling of immune complexes or secondary to the development of SLE.

Primary C3 deficiencies result in increased susceptibility to infections and in MPGN [21–24]. The renal disease in these patients may be explained by an aber-

rant handling of immune complexes in the absence of C3. A rare relation between C9 deficiency and renal disease has been described [3]. One report relates C9 deficiency to immune complex GN [25], and another report to IgA nephropathy [26]. How C9 deficiency contributes to renal disease is unknown. Mice deficient in clusterin, a fluid-phase complement regulator, which inhibits the incorporation of C5b-9, also develop renal disease [27].

A direct interaction between complement and renal injury was concluded from families with a Factor H deficiency [3, 28, 29]. Factor H deficiency results in low plasma levels of Factor B, unhindered activation of fluid-phase C3, severe depletion of plasma C3 and in consumption of the terminal complement components C5–C9 (see chapter by Zipfel et al.). Continuous activation and turnover of C3 in the vicinity of the GBM may cause C3b to bind to glomeruli and incite inflammation.

Both MPGN and idiopathic hemolytic uremic syndrome are associated with Factor H deficiency (see chapters by Skerka and Józsi, and Zipfel et al.). A high index of suspicion for Factor H deficiency is needed in patients with reduced levels of C3 and recurrent hemolytic–uremic syndrome or MPGN. Factor H-deficient pigs [30, 31] and Factor H knockout mice [32] develop spontaneous renal disease and display MPGN-like symptoms, confirming the importance of Factor H in complement regulation. In pigs, Factor H deficiency leads to the development of MPGN with dense deposits, similar to human type II MPGN observed in patients with nephritic factor (NeF) and in some very rare patients with Factor H deficiency [29]. The administration of purified Factor H to pigs prevents the formation of immune deposits and subsequent glomerular damage, and, even when administered later, allows regression of nephritis. Factor H deficit/mutation carries a great risk (21–65%) of recurrence in the living donor renal transplant (see chapter by Goodship et al.).

Factor I deficiency results in uncontrolled C3 activation and recurrent infections. Some of these patients exhibit focal segmental GN [33], indicating that uncontrolled activation of C3 results in the generation of active C3 fragments and renal disease.

Antibodies against complement components

In autoimmune individuals an antibody response against complement components can occur. Some of these antibodies show such a high degree of correlation with renal disease that the term NeF was introduced to indicate this activity. Anti-complement autoantibodies can contribute to renal disease by deregulating complement activation or influencing immune complex deposition in glomeruli. Several autoantibodies directed against complement components have been identified in patients [3], some of which are related to renal disease directly: C3 nephritic factor (C3NeF), C4NeF, C3NeF:P, anti-Factor H, and anti-C1q.

One of the first demonstrations of complement activation by circulating factor was the recognition that serum of some patients with type II MPGN was capable of activating C3. This activation has been shown to result from an immunoglobulin, C3NeF, which binds to and stabilizes C3bBb, the alternative pathway C3 convertase, and prolongs its half-life, resulting in ongoing complement activation [8, 34–37].

The association of MPGN with disparate disorders such as type II MPGN, partial lipodystrophy, sickle cell disease, complement deficiencies, cryoglobulinemia, and infections with either hepatitis B or C suggests that this disorder is not a single pathogenic entity [18]. The recent recognition of a causal relation between hepatitis C infection and MPGN has led to the suggestion that this virus may be responsible for as many as 60% of cases previously deemed to be idiopathic [38].

C3NeF is an IgG autoantibody that prolongs the enzymatic half-life of the C3 convertase C3bBb, thus producing continuous C3 activation in plasma. Patients with positive C3NeF develop MPGN in 50% of cases. Although clinical manifestations, characterized by heavy proteinuria, progressive loss of renal function, hypertension, are similar, two major types of idiopathic MPGN have been recognized on the basis of difference in ultrastructural morphology: type I, characterized by subendothelial deposits, and type II (dense deposit disease), characterized by the deposition of dense deposits within the GBM.

In type I MPGN immunofluorescence microscopy reveals granular deposits of C3 in the mesangium and in peripheral capillary loops in all patients. Deposits of immunoglobulins and other complement components in capillary loops are present in some patients.

Type II MPGN differs from type I histologically because the dense deposits are localized homogeneously within GBM. C3 and other complement components are detected in the mesangium and capillary loops, but immunoglobulins are generally not seen on immunofluorescence microscopy. Electron microscopy of kidneys affected by type II MPGN reveals electron-dense deposits of unknown composition within the GBM.

Type I MPGN may be mediated by the deposition of immune complexes capable of activating complement both systemically and within the kidney. Serum complement concentrations tend to fluctuate. However, serial determinations reveal at least an intermittent decrease in the concentrations of C3, C1q, and C4 in the vast majority of patients, suggesting activation of complement through both the classic and alternative pathways.

In patients with type II MPGN serum concentrations of C3 tend to be persistently low, while concentrations of early components of the classic pathway are usually normal, suggesting that complement activation occurs primarily through the alternative pathway. Virtually all patients with type II MPGN have high serum concentration of C3NeF [39].

Partial lipodystrophy is a disfiguring condition that affects the body from the waist upward but spares the legs. Mathieson et al. [40] provided an explanation for the loss of fat in this condition. Adipose cells are the main source of Factor D, which completes the formation of the C3 convertase enzyme C3bBb by cleaving Factor B bound to C3b. There is a gradient in the concentration of Factor D in the fat cells of the body; more is present in the upper than the lower half of the body, which could explain the distribution of the fat loss. It is likely that the C3 nephritic antibody in partial lipodystrophy stabilizes the C3bBb C3 convertase that forms in the immediate vicinity of adipocytes. The abnormally stabilized enzyme may then cleave enough C3 to allow assembly of the membrane attack complex, which lyses adipocytes.

C3NeF is not usually connected with other conditions, but it is present in a few patients with SLE [41], post-streptococcal acute GN [42], and even in clinically healthy individual [43]. What triggers the production of C3NeF is unknown. It has been shown that about 50% of the patients positive for NeF do develop MPGN [3, 44, 45].

C3NeF:P has been found in sera from patients with types I and II MPGN and it displays the properties of properdin and IgG. C3NeF:P has been observed in patients with reduced serum concentrations of C3 and terminal complement components [46, 47].

An autoantibody with specificity to classical pathway convertase C4b2a, called C4NeF, stabilizes this convertase and prolongs the half-life [3, 36, 37, 47, 48]. It has been found in the sera of patients with SLE, MPGN and acute post-streptococcal GN. Chronic infections can perpetuate the formation of immune complexes, which in hepatitis C infection and bacterial endocarditis cause relentless activation and consumption of complement.

Defective regulation of C3 typically associated with GN may be due not only to C3NeF, which increases the stability of the C3 convertase enzymes, but also to reduced function of Factor H or Factor I. Other autoantibodies influencing the function of complement regulation have been described in relation to renal disease. Anti-factor H autoantibodies bind to Factor H and inhibit its function of enzymatic inactivation of C3b [49]. The alternative pathway is activated and depleted, leading to secondary C3 deficiency causing MPGN.

Anti-C1q autoantibodies have been described to be related to nephritis in SLE patients [50–52]. About one third of patients with SLE have high titers of autoantibodies against C1q. The presence of these autoantibodies is indicative of severe disease; they are strongly associated with severe consumptive hypocomplementemia and lupus nephritis. A rise in the titer of these anti-C1q autoantibodies has been reported to predict a flare of nephritis [53]. There also seems to be no overt nephritis in anti-C1q-negative SLE patients [54]. Immune deposits eluted from postmortem kidneys of SLE patients reveal the accumulation of these anti-C1q autoantibodies [55]. All these facts point to a pathological role of these

autoantibodies. However, not all patients with anti-C1q autoantibodies develop renal disease, and some healthy individuals also have low titer of anti-C1q autoantibodies [56].

Trouw et al. [3] found that anti-C1q antibodies deposit in the glomerulus, together with C1q, after injection of these antibodies in healthy mice, indicating that even in the absence of pre-existing immune complexes, as in SLE, these autoantibodies can target C1q to the glomerulus. The origin of these autoantibodies is unknown, but if C1q forms a molecular association with tissue debris, then it may itself become part of an autoantigenic complex [57].

Complement in SLE and lupus nephritis

There are many other observations that suggest the important role of complement in SLE. In human lupus nephritis, there is a large amount and diversity of immune reactants in glomerular deposits including IgG, IgA, C1q, C4, C3, C5b-9 ("full house" pattern). In addition, there is systemic consumption of complement with reduced concentrations of some components and the appearance of complement activation products in sera. Low serum concentrations of C3 and C4, low total hemolytic complement activity and elevated levels of antibodies to DNA or antinuclear antibody have been reported to correlate with the presence of active GN; serological evidence of increasing disease activity may precede the development of serious renal inflammation by months.

In addition, a number of mouse strains spontaneously develop lupus nephritis with immune complex and complement deposition in glomeruli, similar to the human disease, such as the New Zealand Black/White (NZB/W F1) and MRL/lpr strains.

Deficiencies of complement components are associated with renal disease, secondary to the development of SLE [58]. Deficiency of C1q, C4 and C2 predisposes strongly to the development of SLE via mechanisms relating to defective clearance of apoptotic material. In many of these SLE patients lupus nephritis occurs, characterized by the deposition of immune complexes. These immune complexes are primarily composed of anti-DNA antibodies and nucleosomes as antigen [59].

It has been widely accepted that the activation of complement by immune complexes is an important contributor to tissue injury in patients with SLE. The strength of the association of complement deficiency with SLE itself and with the severity of the disease is inversely correlated with the position of the deficient protein in the activation sequence of the classical pathway. Thus, hereditary homozygous deficiencies of C1q, C1r and C1s, and C4 are each strongly associated with susceptibility to SLE, with respective prevalence of 93%, 57% (since deficiencies of C1r and C1s are usually inherited together), and 75%. By contrast, the prevalence of SLE among persons with C2 deficiency is about 10%.

There is also an association between SLE, hereditary angioedema and GN [60, 61]. In patients with hereditary angioedema, excessive cleavage of C4 and C2 by C1s, caused by a heterozygous deficiency of C1 inhibitor, leads to an acquired deficiency of C4 and C2 that is sufficient to increase susceptibility to SLE and lupus nephritis.

IgA nephropathy and anti-mesangial cell proliferation

In IgA nephopathy serum complement levels are normal. On immunofluorescence of kidney biopsies, in addition to typical mesangial IgA deposits, C3 and C5b-9 in predominantly mesangial distribution are present, whereas C1 and C4 are uncommon, suggesting that IgA-mediated activation of the alternative complement pathway may be involved in the pathogenesis of this form of mesangioproliferative GN [62].

Much attention in recent years has focused on the role of the mesangial cell mediation of immune types of glomerular injury. Mesangial cell proliferation is a prominent feature of glomerular disease, including IgA nephropathy, lupus nephritis, some types of steroid-resistant nephritic syndrome and other lesions. *In vitro* studies demonstrate activation of mesangial cells by C5b-C9 [20].

Complement fixing IgG or IgA antibodies to mesangial cells have been reported in IgA nephropathy [63]. IgA can activate complement by the alternative pathway [64], and C5b-9 deposits are prominent in idiopathic IgA GN [65].

To test the role of C5-9 in immune diseases of the mesangium, anti-thymocyte serum model of mesangioproliferative GN was induced in C-6-deficient rats. There was a marked reduction in glomerular mesangiolysis, platelet infiltration, mesangial cell proliferation, macrophage infiltration and matrix expansion in C-6-deficient rats compared to control animals [66].

Nangaku et al. [67] compared a model of antibody to glomerular endothelial cell-induced thrombotic microangiopathy and found marked reduction in intracapillary thrombi and fibrin deposits, glomerular endothelial cell proliferation and macrophage infiltration in C6-deficient animals.

GN associated with infection

The prototype of this form of GN is the nephritis that follows infection with nephritogenic strains of group-A hemolytic streptococci by 14–21 days. Complement abnormalities include a large reduction in CH50 and C3 concentrations in many cases with normal C4, suggesting complement activation primarily via the alternative pathway [68]. Coarse granular pattern of deposits of C3 are seen by immunofluorescence in the mesangium and along capillary walls accompanied by lesser

amounts of IgG, and suggest that immune complex formation (either circulating or formed *in situ*) is involved [38].

Subendothelial immune deposits are probably responsible for local influx of inflammatory cells, but they are rapidly cleared and may not be seen on renal biopsy specimens obtained relatively late in the course of disease. Large subepithelial immune deposits referred as "humps" are best seen on electron microscopy during the first 2 weeks of the disease and tend to diminish by weeks 4–8.

Serial measurements of complement components can be helpful in the diagnosis of this disorder. Total hemolytic complement activity and C3 concentration are depressed early in the course of the disease and, in most cases, return to normal by 6–8 weeks [69]. The finding of persistently low concentrations of C3 more than 8 weeks after presentation should alert clinician to the possibility of lupus nephritis or MPGN.

Membranous nephropathy

MN disease is mediated primarily by the humoral immune response, which leads to deposition of IgG and complement on the outer, subepithelial surface of the GBM [70]. Although small complexes can cross the GBM and deposit at this site, experimental studies suggest that passive glomerular trapping of preformed immune complexes directly from the circulation is unlikely. Deposits are formed *in situ* by accretion of an antibody to intrinsic or planted antigens on the epithelial side of GBM.

Based on studies in animal models, the mechanism by which damage to the glomerular filtration barrier occurs that is sufficient to cause proteinuria appears to involve sublytic effects of complement C5b-9 on the glomerular epithelial cell. Complement activation and cleavage of C5 generates chemotactic factor C5a, which presumably is flushed by filtration forces into the urinary space and does not move backwards across the GBM to attract circulating inflammatory cells. The other product of C5 cleavage C5b combines with C6 to form a lipophilic complex that inserts into the lipid bilayer of the glomerular epithelial cells where C7, C8 and multiple C9 molecules are added to create a pore-forming complex C5b-9 [20].

Because the deposits form only on the outer, or subepithelial surface of the glomerular capillary wall, complement and immunoglobulin-derived chemotactic and immune adherence proteins are nor interactive with circulating cells, probably accounting for the non-inflammatory nature of the lesion. However, proteinuria is complement dependent and appears to be mediated primarily by the C5b-9 membrane attack complex of complement. In addition to other proteins, urinary excretion of C5-9 correlates to the immunological activity of disease [71].

Membrane insertion of C5b-9, although insufficient to cause cell lysis, does induce cell activation and signal transduction, with increased production of multi-

ple potentially nephritogenic molecules, including oxidants, proteases, cytokines, growth factors, vasoactive molecules, and extracellular matrix. This appears to occur in part through upregulation of glomerular epithelial cells production of transforming growth factor-β (TGF-β) isoforms II and III, as well as increased expression of TGF-β receptors in response to C5b-9. Glomerular injury mediated by C5b-9 induces a nonselective proteinuria through loss of both the size and the charge-selective properties of the glomerular capillary wall. Increased excretion of C5b-9 can be detected in urine.

Characteristic immunofluorescence or immunohistochemistry finding in MN are extensive subepithelial deposits of antibodies and complement components including C3 and C5-9. In 50% of cases, C3 deposits accompany deposits of IgG. They are of the similar diffuse granular pattern and are also localized subepithelially. Positive C3 staining (C3c) reflects active ongoing immune deposit formation and complement activation at the time of the biopsy. Staining for C5b-9 is also present, and C1 and C4 are often absent.

While the nature of the deposited antibody in human MN has not yet been established, many other aspects of the immunopathogenesis of MN are now understood based on studies of the Heymann nephritis models in rats, which closely simulate human lesion.

Tubulointerstitial disease and complement system

Proteinuria is now accepted to be not only a sign of glomerular lesions but also a contributory factor to the development of progressive tubulointerstitial changes. Excellent correlations between the degree of proteinuria and rate of decline of glomerular filtration rate have been demonstrated [72].

The complement system is being increasingly implicated in the pathogenesis of progressive renal disease resulting from persistent proteinuria. Under normal circumstances glomeruli (GBM and layers of endothelial and epithelial cells) restrict protein (including complement proteins) passage into urine and the tubular lumen. This barrier is impaired in GN and tubular cells are exposed to protein-containing urine. Activation of the complement system contributes to tubulointerstitial damage that invariably accompany glomerular diseases [73].

Data are now accumulating that proteins, including complement components derived from leak into the urine in the course of glomerular lesion, cause complement activation on the luminal surface of tubular epithelial cells. Damage of these cells results in fibrotic and inflammatory changes, leading to end-stage renal disease [74].

The complement system has a role in mediating these lesions. Most cells of human body are protected from autologous complement attack by expression of several membrane-bound complement regulatory proteins. The expression of com-

plement regulators is low in the tubular epithelial cells. Tubular epithelial cells express these complement regulatory proteins on their baso-lateral side and not on the luminal side [75, 76].

It has recently been established that renal tubular cells can produce complement proteins, activate complement, and respond to complement activation. Proteins in urine may cause direct activation of the tubular cells to overexpress complement proteins and contribute to local tissue injury [73]. Renal C3 production, mainly at the tubular level, may be induced by urinary excretion of C5-9 in idiopathic membranous glomerulopathy and may have a pathogenetic role in the tubulointerstitial damage. Local synthesis of complement components in the kidney may have a role both in host defense and in the promotion of interstitial inflammation and scaring. The most consistent and dramatic local expression of effectors molecules (e.g., C3) occurs in the proximal tubule. Such tubular complement may be mediator of interstitial damage [9].

Several bacteria have the capacity to colonize the urinary tract and cause infection. Most of these infections do not reach higher than the bladder but some are able to reach kidney and cause pyelonephritis. Various studies indicate that complement plays a role in the defense against bacteria, probably at all levels of infection. However, local production of C3 by tubular epithelial cells is very important in the colonization of the upper urinary tract, since C3-deficient mice exhibited less severe infections compared to C3-sufficient mice [77].

Recent data indicate that complement produced locally is very important in relation to transplant rejection and ischemia-reperfusion injury, since renal transplants from C3-deficient mice into wild-type C3-sufficient mice were not rejected, whereas C3-sufficient kidneys were rejected in this setting [78].

Complement, renal transplant and ischemia/reperfusion injury

Ischemia/reperfusion injury of the kidney is best explained by hypoxia damage of tubular epithelial cells that activate complement by alternative pathway. Tubular epithelial cells produce all the proteins of the alternative pathway. Most of the local injury is due to the assembly of the membrane attack complex [18].

The complement system plays a role in the rejection of xenotransplants [79]. Hyperacute rejection can be attributed to the reactivity of natural antibodies and activation of the complement system. Strategies to prevent or reduce complement activation include complement depletion or inhibition in the recipient or expression of natural complement regulatory proteins, such as decay-accelerating factor and membrane cofactor protein on donor cells, making them resistant to activation of recipient complement [80].

C4d deposits are found in 83% of patients with chronic allograft nephropathy. They are deposited mainly along peritubular capillaries, but they can be localized on

glomeruli as well [81]. The exact pathogenetic significance of these deposits is unknown, but they may indicate ongoing humoral immune reaction.

Complement activation in cholesterol crystal emboli disease

Cholesterol crystal emboli (CCE) is still an under-diagnosed condition causing renal dysfunction to the degree of acute renal insufficiency. Clinical observation of low serum complement, peripheral blood eosinophilia and eosinophiluria suggest that activation of complement system participate in inflammatory changes seen on histology specimens in patients with renal CCE [82, 83]. Activation of complement *in vivo* on trapped cholesterol crystals may result in complement cleavage products (C3a and C5a) causing chemotaxis for polymorphonuclear leukocytes and eosinophils with inflammation in small blood vessels.

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