Complement in Lupus Nephritis

The complement cascade consists of a series of plasma proteins that not only play a vital role in destroying pathogens but also mediate humoral and cellular interactions within the immune system (Figure).

Recent work, driven particularly by the availability of gene-targeted mice, has considerably increased our understanding of the links between the complement system and glomerular disease. In this presentation I shall discuss recent insights into the role of the complement system in the pathogenesis of lupus nephritis.

Complement activation products typically deposit in glomeruli in systemic lupus erythematosus (SLE), where they are thought to contribute to injury but, paradoxically, deficiencies of early components of the classical pathway in man are amongst the strongest predisposing factors to lupus\(^1\). In addition low copy number of the gene for C4 also predisposes to SLE\(^2\). It has previously been shown that the classical pathway component C1q and mannose binding lectin (MBL) bind to apoptotic cell surface blebs, which contain high concentrations of lupus autoantigens. Deficiency of C1q leads to autoimmunity associated with impaired clearance of apoptotic cells by phagocytes and the appearance of glomerular apoptotic bodies\(^3;4\). These data led to the formulation of the ‘waste disposal’ hypothesis which proposes that dying cells provide the source of autoantigens responsible for driving autoantibody production in SLE and that defects in the clearance mechanisms for these dying cells increases the risk of developing autoimmunity\(^1\). It is increasingly recognised that classical pathway activation by C1q and subsequent C3 deposition on the surface of apoptotic cells occurs in a predominantly IgM-dependent manner\(^5\). This is consistent with the finding that serum IgM deficient mice develop autoimmunity\(^6\).

Dendritic cells (DC) play a central role in the control of immune responses. Immature DC (iDC) are able to induce tolerance whereas DC, which have matured in response to inflammatory signals, are stimulatory. Importantly, therefore, opsonisation of apoptotic cells with C1q (or MBL) enhances the uptake of apoptotic material not only by macrophages but also by iDC\(^7\). In addition, iDC are a rich source of C1q the production of which is down-regulated on iDC maturation\(^8\). Thus, secretion of cytokines such as interferon alpha, which lead to maturation of dendritic cells and
reduced secretion of C1q, may potentially thereby impair clearance of apoptotic cells and thus predispose to inflammation and autoimmunity. C1q may also regulate the threshold for DC activation.

Autoantibodies that bind to the collagenous tail of C1q are well described in SLE. There is a strong correlation between anti-C1q antibodies and renal disease in SLE; titres of anti-C1q antibodies may predict lupus nephritis flares and they can be eluted from kidney biopsies in lupus nephritis. A series of papers by Daha’s group have elucidated the role of these autoantibodies in lupus nephritis. His group demonstrated that lupus prone mice develop circulating anti-C1q antibodies that deposit in the kidney before the development of overt nephritis. This suggested that anti-C1q antibodies were present in the right place and at the right time to be involved in the pathogenesis of glomerular injury but did not provide proof of their pathogenicity. They then injected rabbit-anti-mouse C1q antibodies into a non-autoimmune strain of mouse. This caused C1q and anti-C1q and in addition C3 to deposit in glomeruli but only caused mild albuminuria. Most recently this same group synthesised mouse anti-mouse C1q antibodies which when injected into non-autoimmune strains of mice, depleted circulating C1q levels and led to the deposition of C1q and IgG within glomeruli but again caused only minor renal injury. The same antibodies were then administered to Rag2-/- (immunoglobulin deficient) mice. This led to a reduction in circulating C1q but no glomerular C1q deposition implying that IgG in the glomerulus acts as a target for the attachment of C1q which can then bind anti-C1q antibodies. Most importantly, it was demonstrated that if anti-C1q antibodies were given together with complement-fixing antibodies directed against glomerular basement membrane, marked C1q and immunoglobulin deposition occurred together with significant glomerular inflammation that did not occur if either antibody was administered alone. This study provides the definitive evidence that anti-C1q antibodies can exacerbate antibody-mediated glomerular injury. The JL-1 antibody used by the authors recognises the same collagen-like domain as do human anti-C1q antibodies suggesting that this murine study is likely to be relevant to human SLE. Using gene targeted mice it was shown that injury in this model was dependent on C3, C4 and Fc receptors. The authors hypothesised that activation of the classical pathway by anti-C1q antibodies led to generation of chemotactic complement fragments, inflammatory cell influx and stimulation of these cells via Fc receptors. An alternative mechanism
for the action of anti-C1q may be related to C1q depletion which may lead to autoimmunity as described earlier.

More information on the role of the lectin pathway in the pathogenesis of lupus is also starting to appear. MBL variant alleles associated with lower functional levels of MBL are common and may predispose to SLE and in particular to nephritis. In patients with SLE these variant alleles are associated with anti-C1q and antiphospholipid antibodies but not with anti-MBL antibodies. Anti-MBL antibodies are however present in a number of patients with idiopathic SLE but unlike anti-C1q antibodies do not correlate with nephritis or disease activity. MBL has been shown to bind predominantly to late apoptotic cell blebs, and thereby to activate complement in a similar fashion to C1q. The resultant C4 deposition is able to enhance the non-inflammatory phagocytosis of apoptotic cells by macrophages and immature dendritic cells which may help maintain tolerance.

In contrast to the role of the classical pathway in protecting from the development of autoimmunity, activation of the alternative pathway may contribute to tissue damage via the formation of the anaphylatoxins or the membrane attack complex. It was previously shown that lupus-prone (MRL/lpr) mice deficient in the alternative pathway protein Factor B were protected from renal disease compared to wild-type controls. However, this study was flawed as there were important differences in MHC haplotype between the mice which may have accounted for some of the phenotypic variability. In order to clarify this, the same investigators have studied the effect of deficiency of another component of the alternative pathway, Factor D. In this study they confirmed a role for alternative pathway activation in the pathogenesis of nephritis in SLE. Factor D deficiency had no effect on serum IgG levels or glomerular IgG deposition, but significantly reduced glomerular hypercellularity, reduced glomerular C3 deposition and improved renal function. This is in contrast to mice deficient in C3 which were not protected from renal injury and in fact developed more proteinuria and greater glomerular IgG deposition than controls. These results highlight the important differences between the protective effects of the classical pathway and the damaging effects of the alternative pathway in the pathogenesis of lupus nephritis. However, in spite of the improvement in renal injury, the lifespan of factor D deficient mice was not increased indicating the importance of factors other
than complement, such as Fc receptor-mediated processes, in causing glomerular injury in lupus\textsuperscript{20}.

In order to examine the effect of the terminal pathway of complement activation on the pathogenesis of lupus nephritis Ravirajan et al\textsuperscript{21} utilised a murine model of SLE induced by human monoclonal anti-dsDNA antibodies that is characterised by proteinuria and glomerulonephritis. They demonstrated that the administration of neutralising antibodies to C5 significantly reduced proteinuria and treated animals had less mesangial expansion and podocyte foot process effacement. This confirms previous findings that anti-C5 antibodies reduce renal disease in another murine lupus model (NZB/W)\textsuperscript{22}. These studies suggest important therapeutic strategies for human lupus nephritis using agents that inhibit the terminal pathway whilst leaving the potentially beneficial effects of the classical pathway and C3 unaffected.

In summary there is evidence that elements of the classical pathway of complement activation protect against the development of SLE. Animal models suggest that mechanisms involved include clearance of apoptotic cells and other cellular debris, alteration of the activation threshold of dendritic cells and clearance of immune complexes. Complement activation occurs in glomeruli in lupus nephritis. Animal models indicate an injurious role for the alternative and terminal pathways of complement activation and also for anti-C1q antibodies in amplifying glomerular inflammation.
Figure. The complement system can be activated by the classical, mannose-binding lectin or alternative pathways. In each case this results in the formation of a C3 convertase enzyme which activates C3 and culminates in the synthesis of the anaphylatoxins C3a and C5a, the opsonin C3b, and the membrane attack complex (MAC). The complement system is very tightly regulated at the levels of C1, the C3 or C5 convertases and within the terminal pathway by both membrane bound and circulating factors (marked in black).

Reference List


for and high copy number is a protective factor against SLE susceptibility in European Americans. Am.J.Hum.Genet. 80:1037-1054, 2007


