Basic and Translational Concepts of Immune-Mediated Glomerular Diseases

William G. Couser
Division of Nephrology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington

ABSTRACT
Genetically modified immune responses to infections and self-antigens initiate most forms of GN by generating pathogen- and danger-associated molecular patterns that stimulate Toll-like receptors and complement. These innate immune responses activate circulating monocytes and resident glomerular cells to release inflammatory mediators and initiate adaptive, antigen-specific immune responses that collectively damage glomerular structures. CD4 T cells are needed for B cell–driven antibody production that leads to immune complex formation in glomeruli, complement activation, and injury induced by both circulating inflammatory and resident glomerular effector cells. Th17 cells can also induce glomerular injury directly. In this review, information derived from studies in vitro, well-characterized experimental models, and humans summarize and update likely pathogenic mechanisms involved in human diseases presenting as nephritis (postinfectious GN, IgA nephropathy, antiglomerular basement membrane and antineutrophil cytoplasmic antibody–mediated crescentic GN, lupus nephritis, type I membranoproliferative GN), and nephrotic syndrome (minimal change/FSGS, membranous nephropathy, and C3 glomerulopathies). Advances in understanding the immunopathogenesis of each of these entities offer many opportunities for future therapeutic interventions.

Recent reviews of the immune mechanisms that lead to glomerular disease have been published elsewhere. This review is organized by diseases rather than mechanisms to provide a translational overview of how immune responses mediate the glomerular injury seen by clinicians and pathologists. The processes described derive from studies done in vitro and in an array of animal models of glomerular diseases as well as in humans. Cell cultures are not glomeruli, and mice and rats are not humans, but experience has taught us that mechanisms defined in these settings often translate into better understanding of similar processes seen in human disease. Schematic overviews of the major pathogenic sequences currently believed to be operative in human GN and their interactions are presented in Figures 1 through 4.

OVERVIEW OF BASIC IMMUNE MECHANISMS

The Innate Immune Response

Toll-Like Receptors
Toll-like receptors (TLRs) are ancient and ubiquitous pattern recognition receptors present on all cell membranes and intracellularly between cytoplasm and endosomes (Figure 1). TLRs recognize conserved immunostimulatory molecular patterns (antigens) like peptidoglycans, LPSs, and bacterial and viral nucleic acids (pathogen-associated molecular patterns [PAMPs]) as well as endogenous cell-derived patterns (danger-associated molecular patterns [DAMPs]). Another related cytoplasmic group of receptors called Nod-like receptors (NLRs) has recently been described. TLR ligation is central to activating the non-antigen-specific innate immune system in immediate response to pathogens, but TLR activation is also required for adaptive, antigen-specific immune responses by facilitating conversion of dendritic cells to antigen-presenting cells. TLRs activate multiple signaling pathways that lead to local release of a variety of cytokines, chemokines, and other inflammatory mediators by all cells, including glomerular cells. Thus, TLRs and NLRs connect initiating events with mediation of tissue injury in GN associated with infections or autoimmunity or both.
Figure 1. Schematic overview of both the innate and adaptive immune mechanisms that mediate tissue injury in GN. Etiologic events expose immunostimulatory PAMPs or DAMPs that activate both the innate (red) and the adaptive (antigen specific, blue) immune systems, which also interact with each other. Activation of the innate immune system occurs immediately and involves TLRs or NLRs on both circulating inflammatory cells and resident glomerular cells. TLR activation results in release of inflammatory mediators that cause glomerular injury. Some PAMPs and DAMPs can activate complement directly through the innate immune system. TLRs are also required to activate the adaptive immune system through antigen-presenting cells that promote differentiation of CD4 helper cells, B cell activation, and antibody production. Antibodies lead to circulating complex trapping or in situ formation of immune complexes that can activate both the TLR and complement components of the innate immune system. Complement activation generates the chemotactic factor C5a that attracts circulating inflammatory cells (including neutrophils, macrophages, basophils, and natural killer cells), which release mediators and damage glomeruli. C5b-9 that activates resident glomerular cells to do the same. CD4 Th1 and Th2 cells cause tissue injury primarily through macrophages and basophils, respectively, whereas Th17 cells can mediate glomerular damage directly. CD4 regulatory cells (Tregs) downregulate the adaptive immune response.

When MBL binds to mannose residues on pathogens and activates the serine proteases, MASP-1 and MASP-2, leading to activation of C4 and C2. The alternative pathway is activated spontaneously by hydrolysis of C3 and amplified by defects in complement regulation. Non-Ig zymogens such as damaged cells and bacterial and viral proteins can also activate the alternative pathway beginning directly at C3. The same initiating event may activate more than one pathway.

Complement activation products are the principal mediators of antibody-induced GN (Figures 1 and 2). Usually this involves C1q binding to Ig that leads to classic pathway activation through C4 and C2; however, some Igs, depending on their level of glycosylation, can also bind MBL. IgG subclasses 1 and 3 and IgM are classic complement pathway activators, whereas IgG 2 and 4, IgA, IgD, and IgE activate complement poorly.1,12

All complement activation pathways proceed through cleavage of C3 and C5 leading to release of chemotactic factors such as C5a that attract inflammatory cells (neutrophils, macrophages, and platelets) at abutting the circulation as well as formation of the terminal membrane attack complex (C5b-9) (Figure 2).7–9 Sublytic quantities of C5b-9 can insert into lipid bilayers of adjacent glomerular cell membranes, initiate several signaling pathways, and convert these cells to effector cells, which may proliferate; release a variety of cytokines, growth factors, eicosanoids, oxidants, proteases, and other acute inflammatory mediators; as well as upregulate production of matrix components that contribute to chronic scarring and sclerosis (Figure 1).1,12,13 Complement activation products like C5a can also activate TLRs.14

Complement activation in vivo is tightly regulated by a number of circulating and cell-bound complement regulatory proteins (CRPs), whose functions, mutations and deficiencies are also important in the development of several glomerular diseases.8,9 Abnormalities in serum complement profiles are sometimes helpful in assessing the nature of the underlying disease and its activity, but significant complement-mediated injury may occur locally without alterations in circulating complement components (Table 1).

The Adaptive Immune Response

Ig

CD4 T helper cells stimulate B cells and plasma cells to make antibodies specific for particular antigens (Figure 3). On the basis of older studies of serum sickness in rabbits induced by single (acute) or repeated (chronic) injections of BSA, glomerular immune deposits have long been attributed to the passive trapping of circulating, soluble antigen–IgG antibody complexes (ICs).15,16 Other studies done in antiglomerular antibody models (nephrotoxic nephritis; NTN) demonstrate that antibody deposition activates complement through the classic complement pathway generating chemotactic factors that attract circulating inflammatory effector cells, which then cause tissue injury (Figures 1 and 3).17 Typical granular IC deposits can also form locally, or in situ, due to antibody binding to either exogenous planted antigens or endogenous glomerular components (Figure 3).18–23 There are several variables that determine the biopsy findings and clinical consequences in IC GN: (1) where the deposits form—ICs of the same composition in a subendothelial distribution lead to exudative inflammatory cell infiltrates, in the mesangium to mesangial cell proliferation and matrix expansion, and in a subepithelial distribution to a
The acute, diffuse exudative and proliferative lesion of poststreptococcal GN (PSGN) was long regarded as the human equivalent of the acute, one-shot serum sickness model in rabbits leading to a prolonged search for the nephritogenic streptococcal antigen. Although many candidate proteins have been proposed, most have failed to meet strict criteria for causality.

**Figure 2.** Schematic depiction of the three pathways of complement activation as they relate to GN. In the adaptive immune system, complement-fixing antibodies (IgG1, IgG3, IgM) in immune complexes and CRP initiate classic pathway activation through C1q, C4, and C2 to form C4b2a, the classic pathway C3 convertase. In the innate immune system, PAMPs and DAMPs activate complement through the MBL or alternative pathways. Some infectious PAMPs and DAMPs bind MBL leading to activation of MBL-associated serine proteases (MASPs), which activate C3 via C4, C2 and the classic pathway C3 convertase. In the alternative pathway, direct activation of C3 occurs spontaneously ("C3 tickover") and by foreign surfaces, damaged cells, and IgA. Cleavage of C3 produces C3b, which combines with factor B and properdin to form the alternative pathway C3 convertase that is regulated by factors H and I to prevent excess C3 activation. Both classic and alternative pathway C3 convertases cleave C3 leading to release of C3b, which allows C5 convertase formation. Cleavage of C5 produces the chemotactic factor C5a and C5b, which combines with C6, C7, C8, and multiple C9 molecules to form the lipopholic C5b-9 membrane attack complex that can activate resident glomerular cells to become effector cells. C5b-9 formation is regulated by cell-bound CRPs such as CD59.

**T Cells**

In addition to providing help for B cells, T cells alone, sensitized to either self or nonself antigens that are localized in glomeruli, can induce antibody-independent tissue injury. Although all subsets of T cells are now implicated in GN, including dendritic antigen-presenting cells (DCs) and CD4 helper cells of the Th1, Th2, and T regulatory (Treg) lineages, IL17-producing Th17 cells likely account for much of T cell–induced inflammation (Figure 4). Th17 cells are attracted by mechanisms involving chemokines and their receptors, and release cytokines such as IL9, IL17, IL21, IL22, and TNFα, which induce other cells to produce additional proinflammatory chemokines that attract neutrophils and monocytes and also activate resident glomerular cells. Th17 cells are found in renal biopsies in several forms of human GN. The T cell component of the adaptive immune response is regulated by Tregs.

**Diseases Usually Presenting as GN**

**Postinfectious or Poststreptococcal GN**

The acute, diffuse exudative and proliferative lesion of poststreptococcal GN (PSGN) was long regarded as the human equivalent of the acute, one-shot serum sickness model in rabbits leading to a prolonged search for the nephritogenic streptococcal antigen. Although many candidate proteins have been proposed, most have failed to meet strict criteria for causality. However, streptococcal pyogenic exotoxin B (SpeB) meets most of these criteria, although it has not been implicated in all cases of epidemic PSGN. SpeB is a small (28 kD), cationic (pK 9.3) cysteine protease with complement-activating and plasmin-binding properties and represents 90% of the secreted extracellular protein made in vivo by nephritogenic strains of group A streptococci. Antibody to SpeB correlates with disease activity in PSGN and co-localizes with IgG and C3 in subepithelial humps. However, the intense exudative glomerular inflammatory response is not well explained by a serum sickness analogy and humps because circulating ICs do not form subepithelial IC deposits directly and subepithelial IC deposits do not produce inflammation. Moreover, IgG is sometimes absent or is only a minor constituent of the deposits, whereas C3 deposition often both precedes and exceeds detectable IgG.

Possible explanations for these apparent contradictions include observations that some subendothelial deposits are also present in PSGN, perhaps because antibody to SpeB also exhibits molecular mimicry with endothelial cells. In addition, SpeB alone can activate complement directly through the MBL pathway independent of IgG. SpeB also exhibits plasmin-binding properties that facilitate complement activation and might cause proteolysis of glomerular basement membrane (GBM), facilitating...
Table 1. Most common complement profiles and autoimmune features in GN

<table>
<thead>
<tr>
<th>Disease</th>
<th>Serum C Profile</th>
<th>Autoimmune Features</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Poststreptococcal GN</td>
<td>AP or MBL normal C1q, low C3-C9</td>
<td>Anti-C1q, IgG Aeca*, anti-DNA, ANCA, protein disulfide isomerase (PDI), cardiac myosin</td>
<td>38,44,47-50</td>
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<tr>
<td>IgAN</td>
<td>Normal</td>
<td>Antiglycan, endothelial cell, mesangial cell, IgG, C1q</td>
<td>54,56,59</td>
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<tr>
<td>Anti-GBM nephritis</td>
<td>Normal</td>
<td>Anti-GM, ANA (20%), anti-C1q</td>
<td>87,90,94,96</td>
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<tr>
<td>ANCA-positive GN</td>
<td>Normal</td>
<td>Anti-MPO, PR3, cPR3, NET, DNA, endothelial cell, LAMP2</td>
<td>119-122,124,133,134</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>C1q, low C3-C9</td>
<td>Anti-dsDNA, annexin, MPO, PR3, nucleosome, IgG, C1q, C1s, C1-1NH, C4, cardiolipin, MBL, NET, H-ficolin, C3Nef</td>
<td>17,171-173</td>
</tr>
<tr>
<td>MPGN I</td>
<td>CP, low C1q-C9</td>
<td>Anti-C3 Nef, C4 Nef, C1q</td>
<td>199,282</td>
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<tr>
<td>MCD/FSGS</td>
<td>Normal</td>
<td>None</td>
<td>216,246,217,215</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Normal</td>
<td>Anti-PLA2R, DNA, NEP, aldose reductase, SOD2, C1q</td>
<td>83,268,255,257,260,281</td>
</tr>
<tr>
<td>DDD</td>
<td>AP, normal C1q, low C3-C9</td>
<td>Anti-C3Nef, C4 Nef, CFH, factor B, C1q</td>
<td>7,198,283,284,290</td>
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<tr>
<td>C3 nephropathy</td>
<td>AP, normal C1q, low C3-C9</td>
<td>C3Nef, CFH, factor B</td>
<td>7,286</td>
</tr>
</tbody>
</table>

CP, classic pathway; AP, alternative pathway; MBL, mannose binding lectin pathway; LAMP2, lysosomal membrane protein 2.

the transit of dissociated subendothelial ICs to form subepithelial humps.37,45,46 Finally, PSGN often exhibits autoimmune features including both IgM and IgG rheumatoid factors with cryoglobulin activity, antineutrophil cytoplasmic antibodies, anti-DNA antibodies, and antineutrophil cytoplasmic antibodies (ANCA), although their respective roles in mediating the disease, if any, remain unclear (Table 1).47-50 Other forms of postinfectious GN such as those associated with endocarditis, infected ventricular-atrial shunts, visceral abscesses, and Staphylococcus aureus infection with IgA deposits are clearly mediated immunologically; however, the mechanisms involved have been explored in much less detail.39,41,51,52

**IgA Nephropathy**

IgA nephropathy (IgAN) is the most common form of GN worldwide and is characterized by focal mesangial proliferation and matrix expansion accompanying diffuse mesangial deposits of IgA, and often IgG, C3, and C5b-9, usually associated with recurrent episodes of GN that often immediately follow mucosal viral infections.53-57 Although assumed to be mediated by mesangial trapping of circulating ICs, no exogenous antigens have been identified consistently.55,56 IgA in mesangial deposits, and in IC form in the circulation, is polymeric (mucosal) IgA1 that exhibits deficient O-linked glycosylation at five sites in the hinge region of the molecule.55,56,58,59 The failure to normally glycosylate IgA1 can be inherited in IgA nephropathy and Henoch-Schönlein purpura,60,61 but the defect also seems to occur epigenetically.62 Underglycosylated pIgA1 is produced by mucosal B cells and might also reach the circulation if abnormal trafficking of these cells to the bone marrow occurs.63,64 Underglycosylated pIgA1 predicts progression and exhibits altered biologic properties compared with normal IgA1 including increased tendencies to self-aggregate, unmasking of MBL binding sites and autoimmune features in GN.

In IgAN, mesangial cells become activated through interactions between the IgA1 deposits and IgA Fcα (CD89) receptors, TLRs, and transferrin receptors (TR, CD71).78,79 TLR activation by IgA aggregates, perhaps containing or accompanied by PAMPs, may account for the recurrent episodes of acute injury with hematuria, particularly those that immediately follow infections.55,56,80 However, most experimental and clinical studies suggest a role for complement as well.7,9,81,82 C5b-9 generated from complement activation induced by interaction of IgA1 aggregates with MBL, or in situ formation of ICs by IgA antiglycan antibodies, induces mesangial cell transformation to α-smooth muscle actin–expressing myofibroblast-like cells, upregulates genes for collagen type I, and increases production of cytokines and growth factors such as IL1, IL6, TNFα, PDGF, TGFβ, EGF, FGF, CTGF, and HGF, all resulting in mesangial...
cell proliferation and matrix expansion. The pattern of glomerular complement deposition in IgAN includes MBL, C4d, and C5b-9 (but not C1q) that co-localize with IgA and suggests both MBL and AP rather than classic pathway activation. Complement deposits correlate with both disease severity and prognosis.

**Rapidly Progressive, Crescentic GN**

Anti-GBM Nephritis

Anti-GBM nephritis is characterized initially by an acute, focal necrotizing GN with crescents and linear deposition of IgG, usually with C3, along the GBM. When associated with pulmonary alveolar hemorrhage, it is called Goodpasture’s syndrome. The role of anti-GBM antibody deposition inducing complement activation, chemotactic factor release, and neutrophil-mediated injury was defined in NTN models in the 1960s, and the pathogenicity of human anti-GBM antibody was confirmed by the classic primate transfer studies of Lerner et al. in 1967. Studies in C3−/− and C4−− mice implicate primarily the classical complement pathway activated by IgG1 and IgG3 anti-GBM antibody that correlates with disease activity and recurrence in transplants. Antibodies with apparently similar reactivities but with lower titers, lower avidity, and primarily of the IgG2 and IgG4 subclasses can be present in healthy humans.

GBM antigens are also expressed in several extrarenal tissues where they are sequestered by an endothelial cell layer impermeable to IgG. The unique fenestrated endothelium in glomeruli allows free access of IgG to GBM. The GBM antigen itself consists of two normally sequestered or cryptic epitopes, EA and EB, residing on the noncollagenous domain of both the α3 and α5 chains of the NC1 hexamer of type IV collagen. Antibody deposition requires perturbation of the quaternary structure of the α3, α4, α5NC1 hexamer, possibly initiated by oxidant injury, which results in a conformational change in the α3NC1 and α5NC1 domains (an autoimmune conformeropathy). In rodent models, the nephritogenic GBM antigen has been mapped to as few as three amino acid sequences in a core residue, but both intermolecular and intramolecular epitope spreading occur, suggesting that immune reactivity may extend beyond the initial inducing autoantigen.

Pulmonary toxins such as infections, smoke, and volatile hydrocarbons may damage endothelium and expose antigen in alveolar capillaries accounting for the pulmonary manifestations of Goodpasture’s syndrome. Whether such extrarenal events have any role in autoimmunization is not known.

T cell reactivity to GBM antigens was first demonstrated 40 years ago, and a pathogenic role for GBM antigen-specific sensitized T cells was proposed but given little credence at the time. However, many subsequent studies have confirmed these original observations with newer technologies and documented that nephritogenic GBM antigens can induce a T cell–mediated GN with crescents, proteinuria, and decreased renal function in the absence of anti-GBM antibody. The IL23/Th17 axis is central to the mediation of injury in anti-GBM models. Another unique feature of the T cell response to GBM is the appearance of long-lived Tregs and inversion of the T cell effector/regulatory cell ratio later in the disease that may account for why recurrences of anti-GBM disease are uncommon compared with other autoimmune glomerulonephritides in which Treg activity is often impaired.

The anti-GBM immune response in humans is strongly linked to HLA DRB1 alleles 1501, 0701, and 0101 with 1501 conferring a relative risk ratio >8, whereas 0701 and 0101 are protective. Possible triggering events include preceding infections or environmental toxins that might expose antigenic determinants in extrarenal tissue. Most patients have anti-GBM antibodies in the circulation that precede clinical disease. The disease can also be induced experimentally with a small nephritogenic T cell epitope, pCol28-40, from the α3NC1 domain, which exhibits molecular mimicry with PAMPs in some Gram-negative bacteria, especially Clostridia botulinum. Finally, recent studies indicate that glomerular-derived antigenic peptides that enter the urine can be taken up and degraded by tubular cells and then presented to interstitial dendritic cells leading to induction of an immune response in regional lymph nodes. The occurrence of ANCA antibodies and signs of vasculitis in up to 20% of anti-GBM patients, and examples of anti-GBM disease occurring with membranous nephropathy, suggest that some of the proposed etiologic factors in these diseases are operative in anti-GBM disease as well (Table 1).

ANCA-Associated GN

Necrotizing crescentic GN without immune deposits, later called pauci-immune GN, was described in 1979 and a decade later linked to ANCA directed against myeloperoxidase (MPO) and proteinase 3 (PR3). It is characterized by a focal necrotizing and crescentic GN with large gaps in the capillary wall associated with a smoldering, nephritic clinical course, usually in older individuals who may also exhibit extra-renal vasculitic disease. The major entities associated with ANCA and GN are granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis), Churg-Strauss syndrome, and microscopic polyangiitis, which may be renal-limited. Explorations of how anti-MPO and PR3 antibodies mediate GN without depositing in glomeruli have defined entirely new paradigms of immune glomerular injury.

In vitro studies show that cytokines, released in response to infections, prime neutrophils and upregulate adhesion molecules on neutrophils and endothelial cells (L and E selectins, respectively) to facilitate localization in glomerular capillaries. Cytokine primes by redistributing cytoplasmic primary granules containing MPO and PR3 to the cell surface where ANCA IgG binds directly or through Fc, Fab’2, or neutrophil-specific Mac-1 receptors.

activating a respiratory burst with release of cationic MPO and PR3 as well as other proteases and oxidants.\textsuperscript{129–135} Neutrophil extracellular traps (NETs) are also formed containing entrapped MPO, PR3, and MPO DNA in a chromatin web and these can mediate injury directly through TLRs as well as modulate the immune response.\textsuperscript{134,136} In ANCA-GN, NETs are present in the circulation and in glomeruli co-localized with neutrophils and DCs, and anti-NET antibodies are present along with circulating MPO-DNA complexes (nucleosomes).\textsuperscript{134} Activation of TLR2 and TLR9 exacerbate experimental crescentic GN.\textsuperscript{136} MPO can also cause glomerular injury directly through oxidative mechanisms involving the MPO-H2O2-halide system resulting in halogenation of glomerular structures and severe glomerular injury.\textsuperscript{137}

In 2002, Xaio et al. provided the first compelling \textit{in vivo} evidence for ANCA pathogenicity by transferring spleen cells from an MPO null mouse immunized with murine MPO to an immunologically compromised host to induce a T cell–independent crescentic GN with proteinuria and reduced renal function.\textsuperscript{138} Similar studies implicate an immune response to PR3 in pathogenesis.\textsuperscript{139} Other models have utilized transfer of MPO\textsuperscript{−} bone marrow,\textsuperscript{140} adjuvants that enhance the immune response and increase cytokine levels,\textsuperscript{141} and mice with subclinical GN immunized to human MPO in which the crescentic GN that follows is mediated by the immune response to endogenous MPO.\textsuperscript{142} Studies of the Xaio model confirm neutrophil dependence and, despite the absence of antibody deposits, a requirement for alternative complement pathway activation involving C5a and C5a receptors.\textsuperscript{7–10,143–147} Both alternative complement pathway proteins and C5b–9 deposits are found in glomeruli in human disease.\textsuperscript{147}

Two other ANCA antigens have also been studied. Lyosomal membrane protein 2 exhibits molecular mimicry with the Fim H group of adhesins on some Gram-negative bacteria and is expressed on endothelial cells and neutrophils.
Lysosomal membrane protein 2 antibodies correlate with disease activity and induce a focal necrotizing and crescentic GN without immune deposits in animals. However, these intriguing observations require further confirmation. An antibody directed against a 13 amino acid sequence in complementary PR3 DNA, encoded by the antisense strand of PR3 DNA, has been detected in a minority (20%) of ANCA patients. Anti-cPR3 IgG elicits an antibody response in a minority (20%) of ANCA-positive GN patients. Anti-cPR3 antibodies are also reactive with plasminogen and delay dissolution of clots in vitro, potentially contributing to the prominent fibrin deposition seen in ANCA GN.

Other groups reason that the absence of antibody deposits in ANCA-positive GN, the limited correlation between ANCA levels and disease activity, and the absence of any detectable ANCA in approximately 10%–20% of patients with typical microscopic polyangiitis suggest a primary role for antibody-independent, T cell–mediated immune mechanisms. Consistent with this hypothesis are persistent activation of T cells and elevation of soluble T cell products that correlate with disease activity. The prominence of traditional Th1 delayed-type hypersensitivity markers like T cells, macrophages, fibronectin, and occasional granulomas in ANCA-positive GN and T cell reactivity to ANCA antigens in some patients. T cells alone, including Th17 cells, induce focal necrotizing and crescentic GN when sensitized to a planted glomerular antigen as might occur with planted cationic MPO. A recent study used combinations of mice selectively deficient in T cells, B cells, or MPO to demonstrate that active immunization with human MPO (in mice with subclinical glomerular injury) induces crescentic GN without immune deposits that requires the presence of endogenous MPO and T cell reactivity to MPO, but does not require B cells or anti-MPO antibody. Th17 cells and IL17α, as well as TLRs 2 and 9, are also essential to the development of GN in a T cell–dependent model.

Proposed etiologic agents in ANCA disease include environmental toxins such as silica and infectious agents, including Gram-positive (S. aureus) and Gram-negative (Fim H adhesins) bacteria, viral infections, and several drugs. There also have been significant but low-level associations with potential susceptibility genes and their polymorphisms, including ANCA antigens, HLA, immune response proteins, Fc receptors, cytokines and others, but no high-level associations have been described, other than DRB1*15 in African Americans. The relatively frequent observation of ANCA antibodies in other autoimmune glomerular diseases including anti-GBM disease, lupus, and membranous nephropathy suggests that common etiologic or susceptibility factors may be present.

Figure 4. The T cell component of the adaptive immune system in GN. Antigen is presented to naive CD4 T cells by dendritic cells (signal 1). Depending on the predominating cytokine environment, T cells differentiate into CD4 T cell subsets that play different roles in the pathogenesis of glomerular disease. In the presence of TGFβ, Tregs develop that downregulate and control the immune response. IL12 stimulates differentiation into Th1 cells that make IFNγ and TNF and produce traditional T cell/macrophage–mediated delayed-type hypersensitivity reactions. IL2, IL4, and IL13 favor development of Th2 cells that make IL4, IL5, and IL13 and lead to allergic-type hypersensitivity reactions involving IgE and eosinophils. The CD4 T cells most implicated in the pathogenesis of GN are Th17 cells that differentiate in the presence of TGFβ, IL6, and especially IL17 and produce IL17a and IL21 that facilitate recruitment of other inflammatory cells and can also cause tissue injury directly.

Lupus Nephritis
In lupus nephritis, IgG, IgM, IgA (full house), and C3 deposits are localized primarily in the mesangial in mild disease (mesangial lupus nephritis, class I and II), along the subendothelial aspect of the capillary wall with increasing proliferative/inflammatory lesions (focal or diffuse proliferative lupus nephritis, class III and IV), or in the subepithelial space with membranous lupus nephritis (class V). The autoimmune responses that underlie lupus have been extensively studied in humans and in mouse strains that spontaneously develop the disease and are beyond the scope of this review. The best-established...
functional immune abnormalities in lupus are loss of tolerance to numerous self-antigens, B cell hyperactivity with overproduction of autoantibodies, and defective T cell regulation.170

The most prominent serologic feature of lupus is the presence of IgG anti-double-stranded DNA antibodies (anti-DNA) in serum and in glomerular deposits.170,174 The deposits are usually attributed to DNA–anti-DNA ICs trapped from the circulation, although infusing anti-DNA or DNA–anti-DNA ICs has not achieved either significant glomerular capillary wall localization or disease expression in vivo.22,170,175 Some monoclonal anti-DNA antibodies exhibit cross-reactivity with capillary wall antigens, especially laminin and α-actinin176,177 and may become internalized by cells within caveola, achieve nuclear localization, and directly alter cell functions including apoptosis.178 Mesangial deposits have also been associated with antibody to mesangial cell annexin, which co-localizes with IgG and C3 and correlates with disease activity.179 However, most recent studies conclude that deposited anti-DNA reacts with extracellular DNA in the form of nucleosomes that consist of an anionic segment of DNA wound around a highly cationic histone core, giving the structure a net positive charge and thereby a high affinity for glomerular anionic sites.171,172 Defective apoptosis in SLE, perhaps related to an acquired defect in DNase I, leads to necrosis and release of chromatin debris from apoptotic blebs allowing access of nucleosomes to antigen-presenting DCs as well as entry into the circulation.170–172,180 Circulating nucleosomes are abundant in patients with lupus nephritis, anti-nucleosome antibodies correlate with disease, and both are present in membrane-associated electron-dense deposits.170,172 Although this could represent an epiphenomenon, nucleosomes are required for anti-DNA antibody localization to occur in glomeruli.171,172 Whether they localize initially as free antigenic material to initiate in situ IC formation or are trapped as preformed ICs is not known. Nucleosomes exhibit several other relevant biologic properties, including the ability to activate dendritic cells through binding to TLRs 2 and 9, and they likely directly activate resident glomerular cells through TLRs as well.181,182 In that capacity, they may mimic infectious non-self structures to generate DAMPs that could lead to both loss of tolerance and local inflammation.182

Other non-nucleosome autoantibodies have also been implicated in different aspects of the renal lesions in lupus, particularly lupus anticoagulant, antiphospholipid, and anti-β2 glycoprotein I antibodies in glomerular microthrombosis, as well as anti-C1q antibodies, mixed cryoglobulins containing rheumatoid factors, and others (Table 1).170,183,184 Recent studies in both experimental and human lupus also implicated the Th2 immune response with B cell differentiation, activation of haplophil, and production of IgE anti-DNA antibodies that deposit in glomeruli.183 B cell activating factor (BAFF or BlyS), a cytokine of the TNF ligand superfamily that activates B cells and modulates the immune response by inhibiting B cell apoptosis, is increased in lupus, likely contributes to autoantibody production, and has recently become a potential therapeutic target.186

The subepithelial immune deposits in class V (membranous) lupus nephritis could result from dissociation of subendothelial ICs with transit across GBM to reform in a subepithelial location or from deposition of other lupus autoantibodies with specificity for podocyte antigens as occurs in idiopathic membranous nephropathy (see below). Complement activated by IC deposits is a major mediator of tissue injury in lupus nephritis through both intracapillary generation of neutrophil and macrophage chemotactic factors (class II–IV) and formation of C5b–9 (class V).7,9,10,187 Disease severity is reduced in murine models that lack selected complement proteins and is increased with deficient regulatory proteins.184,187,188 Blocking studies in murine models suggest that the AP of complement is more important in mediating kidney damage than the classic pathway.189 The observation that deficiencies of classic pathway proteins C1r>C4> C2 are associated with increased risk for lupus suggests protective roles for complement as well.9,10,187 For example, 90% of patients with inherited C1q deficiency develop lupus, and C1q is produced by dendritic cells and involved in tolerance induction and clearance of both apoptotic cells and ICs.9,10

T cells exhibit complex and abnormal phenotypes in lupus.170,171,173 Activated T cells are expanded, provide excess help to B cells, localize in renal cell infiltrates, and produce IL17, which correlates with disease activity, all implying CD4 and Th17 cell involvement.170,171,190 Antigen-specific T cell reactivity to nuclear antigens is well documented in lupus nephritis, and Th17 cells and IL17 are increased in human and murine SLE and correlate with disease activity.170,171,173,191 IL17-producing T cells, either Th17 or CD4+CD8+ (double negative) T cells, are present in nephritic kidneys, and decreasing IL17 production improves murine lupus nephritis.170,191 In addition to increased CD4 activity in SLE, most studies also suggest an accompanying defect in T regulatory cell activity.170,171,173,192

The epigenetic events that induce autoimmunity in lupus include environmental exposures such as ultraviolet light and certain drugs and viral infections, especially Epstein–Barr virus.170–173 Some of these interact with the immune system through inhibition of DNA methylation, which can lead to overexpression of some genes resulting in hypomethylated CD4 cells, overproduction of some cytokines and Mdm2, and overproduction of IgG by B cells.193 There also are sufficiently well-established co-occurrences of lupus nephritis with other GNs, including ANCA-positive GN,166 IgA194 membranous nephropathy, and even a minimal change-like podocytopathy195 to suggest common etiologic factors (Table 1).

**Type I Membranoproliferative GN**

Type I membranoproliferative GN (MPGN I) has many clinical and pathologic similarities to a renal-limited lupus
nephritis, including frequent autoantibodies such as rheumatoid factors and antinuclear, anticardiolipin, anti-C1q, anti-C3 convertase (C3NeF), and anti-endothelial antibodies (Table 1).196–199 Hypocomplementemia with a classic pathway profile, and increased disease susceptibility in the presence of C2 and C4 deficiency, is also common to both entities.7,9,10,188,200

The histologic features of capillary wall thickening, cellular proliferation, and infiltrating inflammatory cells associated with primarily mesangial and subendothelial deposits of IgG, IgM, and C3 are similar to lupus nephritis and are also seen in a variety of chronic neoplasias (especially monoclonal gammopathies), infections, and other autoimmune processes.196–199,201 However, in contrast to lupus, MPGN I in adults is seen almost exclusively (>90%) in association with hepatitis C viral (HCV) infection, and the glomerular deposits often have prominent ultrastructural features of cryoglobulins.202–204

The principal nephritogenic HCV antigen seems to be non-enveloped HCV E2 core protein, which is demonstrable in circulating ICs and in glomerular deposits.205–207 IgG3 antibody bound to HCV E2 can interact with the globular domain of C1q, engage B cells through both B cell receptors and TLR7, and elicit production of monocolonal IgMκ antibody to polyclonal anti-HCV IgG (rheumatoid factor).196–199,208 These soluble, but cryoprecipitable, aggregates of IgG, IgM, viral proteins/nucleic acids, and C1q constitute the mesangial and subendothelial immune deposits found in glomeruli and cause local inflammation through direct interaction with TLRs 3, 7, and 9 on both infiltrating inflammatory cells and/or resident glomerular cells as well as by inducing more classic pathway C activation.196–198,209–213 As in lupus, the subepithelial deposits often seen in MPGN I (and sometimes referred to as type III MPGN) may represent subendothelial deposits that dissociate and reform in situ or autoantibodies to as yet unidentified podocyte antigens.45,46

As in lupus, complement likely plays both nephritogenic and protective roles in MPGN I. C1q seems to be important in mediating the initial interaction between IgM, IgG, HCV complexes, B cells, and TLRs,196,197,212 and complement activation by immune deposits through the classic pathway likely aggravates tissue injury,7,10 although overexpression of a complement regulatory protein, Crry, in a well studied murine model did not significantly ameliorate the disease.214 The roles of CD4 effector cells and Tregs in MPGN I are not yet well defined in either animal models or in humans.

**Diseases That Usually Present with Nephrotic Syndrome**

**Minimal Change Disease/Idiopathic FSGS Spectrum**

There are many clinical and pathogenetic observations in minimal change disease (MCD) and idiopathic FSGS, which suggest that they may represent different points on the same disease spectrum. Some patients with MCD are steroid resistant and develop FSGS, whereas some patients with biopsy-documented FSGS are steroid responsive and behave like MCD.215–217 Both can be triggered by multiple initiating events, including infections, drugs, malignancies, and others.215–217 Both are diseases of the podocyte that have been associated with circulating permeability factors,215,217–220 can recur immediately in transplants,221,222 and can resolve when affected kidneys are placed in normal environments.223 Thus, differences in disease phenotype and clinical expression could reflect variation in the quantity of a common mediator or group of mediators.

Alternatively, mutations or epigenetic differences in podocyte genes that alter response to, or recovery from, such circulating mediators might also account for differences between MCD and FSGS. Mutations in podocyte genes that regulate the slit diaphragm, cell membrane, and cytoskeleton are increasingly recognized, not only in FSGS but in other forms of GN as well.224 African Americans with nondiabetic nephropathy express variants in the gene encoding APOL1.225–229 Both clinical and experimental studies document the importance of several other genes, especially ones that regulate the podocyte actin cytoskeleton, in modulating the development of proteinuria, foot process effacement, and sclerosis, including RhoA, urokinase receptor, Pdlim2, and connective tissue growth factor.230–234 Experimentally, podocyte expression of angiopoietin-like-4 is upregulated in experimental MCD and responds to steroids.235 Alternatively, the possibility that MCD and FGS could involve entirely different pathogenetic mechanisms acting on normal podocytes has not been excluded.

Some evidence suggests that both MCD and idiopathic FSGS reflect the effect on podocytes of circulating, perhaps T cell–derived, non-IgG permeability factors.215,217–220 As suggested first by Shalhub in 1974,218 Studies by McCarthy et al. demonstrate a factor in the serum of patients with recurrent FSGS that alters the albumin reflection coefficient of normal glomeruli in vitro.220 In MCD, Koyama et al. showed that factors secreted by T cell hybridomas derived from patients with active MCD transfer a MCD-like lesion to normal rats.219 Despite these in vitro and in vivo observations, identification of the responsible factor(s) has proven frustratingly elusive.220 Many cytokines and other mediators—including hemopexin, soluble podocyte urokinase receptor, TNFα, IL13, angiopoietin-like 4, and cardiotrophin-like cytokine 1—are increased in patients with MCD or FSGS and several also increase glomerular albumin permeability in vitro.231,236–238 Soluble urokinase receptor has been implicated in activating podocyte β3 integrins leading to FSGS,231 and mounting evidence suggests that increased plasma levels of soluble podocyte urokinase receptor mediate proteinuria in both active and recurrent FSGS (but not MCD) through a similar integrin-related mechanism.230 Neutralization of cardiotrophin-like cytokine 1 reduces permeability factor activity in FSGS serum as does galactose and normal serum and urine.213–217

Human studies document Th2 polarization and elevated levels of IL13, a Th2 cytokine with podocyte receptors, in active MCD.236,237 IL13 alters podocyte function238,239 and overexpression of IL13 induces albuminuria and foot process effacement.240 Transfer of CD34+
CD80 demonstrates higher levels in measurement of urinary mRNA encoding proteinuria.250,251 Heymann nephritis is a IgG and complement and heavy proteinuria, suggesting a role for this molecule in the podocyte response.235 Finally, proteinuria, shedding of podocytes in the urine, and development of glomerular sclerosis.254

Proof of principle that membranous nephropathy in humans can also result from an analogous autoimmune mechanism was first provided by Debiec et al., who reported alloimmunization of an infant to neutral endopeptidase (NEP) expressed on podocytes, resulting from a maternal NEP deficiency, which led to transplacental transfer of anti-NEP IgG and typical membranous nephropathy in the newborn.255 However, the anti-NEP mechanism is not operative in most cases of adult idiopathic membranous nephropathy.256 Recently, Beck et al., using microdissection and proteomic technology, identified another antipodocyte autoantibody directed against the M-type phospholipase A2 receptor (PLA2R) in 70%–80% of patients with primary membranous nephropathy and showed that IgG anti-PLA2R was present in the glomerular deposits and correlated with disease activity, response to therapy, and recurrence in transplants.257,258 Others have confirmed these findings.259,260 Antibodies reactive with aldose reductase enolase and SOD as well as PLA2R have also been eluted from membranous glomeruli, but these may represent secondary phenomena related to oxidant stress rather than primary pathogenic mediators.259

Membranous Nephropathy
Idiopathic membranous nephropathy is a noninflammatory glomerular lesion with exclusively subepithelial deposits of IgG and complement and heavy proteinuria.250,251 Heymann nephritis is a rat model that closely mimics the human disease.252 Studies in both active and passive Heymann nephritis models show that IgG antibodies form subepithelial immune deposits in situ by binding to a podocyte protein complex now called megalin,18,19,253 and that proteinuria is mediated by sublytic C5b-9 attack on podocytes.1,2,83 Sublytic C5b-9 activates several signaling pathways, alters the actin cytoskeleton, and upregulates expression of TGFβ and TGFβ receptors and matrix production leading to GBM thickening and spike formation. Increased podocyte production of oxidants and proteases damages underlying GBM leading to proteinuria.83 C5b-9 also leads to podocyte DNA damage and impaired ability to complete the cell cycle, which may contribute to apoptosis, podocyte necrosis, shedding of podocytes in the urine, and development of glomerular sclerosis.254

Whether the role of C5b-9 in mediating proteinuria as established in Heymann nephritis, and in the chronic serum sickness models of membranous nephropathy as well,261,262 mediates podocyte injury and proteinuria in human membranous nephropathy is unclear. Complement-independent mechanisms of proteinuria are also well described with IgG antipodocyte antibodies in several models,263–265 including Heymann nephritis,266,267 although these models do not exhibit the prominent C3 and C5b-9 deposits seen in the complement-dependent Heymann models and in humans.268,269 Despite the prominent complement deposition in membranous nephropathy, deposited anti-PLA2R antibody is predominately of the poorly complement-fixing IgG4 subclass, although complement activation might be induced by the lesser quantities of IgG1 and IgG3 usually present as occurs with anti-NEP IgG.256 However, in both human membranous nephropathy and Heymann nephritis, classic complement pathway components are often absent in glomerular deposits.260

Membranous nephropathy can spontaneously remit,271 but once developed, the glomerular lesion heals very slowly resulting in persistent proteinuria for weeks or months after the immune response has abated and subepithelial deposits no longer are forming.272 This likely explains why only 70%–80% of patients with proteinuria and membranous nephropathy on biopsy have active disease as defined by elevated anti-PLA2R levels.257,258 Glomerular deposition of C3c and urinary excretion of C5b-9 have both been established experimentally as valid biomarkers of ongoing immune deposit formation in membranous nephropathy,272,273 but these should soon be supplanted by direct measurements of anti-PLA2R antibody in serum,274 which correlates with disease activity and response to therapy.275

Although a role for cytotoxic T cells is proposed in complement-independent models of Heymann nephritis,276,277 T cells do not have access to podocytes or the subepithelial space and are rarely seen in most Heymann nephritis models or human membranous nephropathy.269,278 No systematic studies of the role of T cells in human membranous nephropathy have been reported.
No etiologic agents have been identified consistently in idiopathic membranous nephropathy. However, a genome-wide association study reports very strong associations with single nucleotide polymorphisms in genes that encode for HLA-DQA1 and PLA2R.279 Whether these associations relate to rendering PLA2R antigenic or to altering its expression by podocytes is unclear.

A number of potential etiologic agents have been identified in secondary forms of membranous nephropathy, including hepatitis B and C virus infection, several drugs, exposure to environmental toxins such as hydrocarbons, formaldehyde, cat-ionic BSA in cows’ milk (in infants),280 and solid organ tumors.269 Although 30% of patients with tumor-associated membranous were found to be positive for anti-PLA2R in one study,281 these secondary forms of membranous nephropathy, including class V lupus membranous nephropathy, have generally not been associated with anti-PLA2R, and their pathogenesis remains unknown.

**C3 Glomerulopathies**

*Dense Deposit Disease*

Dense deposit disease (DDD) has been referred to as type II MPGN because a minority of cases resemble MPGN I by light microscopy and can have a similar nephritic/nephrotic clinical presentation.199,282–284 However, DDD lacks Ig deposits and has little pathogenic overlap with adult MPGN I, which is an immune complex disease. DDD is now best viewed as a C3 glomerulopathy, a form of GN characterized by deposits of complement without Ig and usually associated with abnormalities in complement regulation.285,286 DDD is a disorder of alternative complement pathway regulation characterized by linear deposition of alternative pathway and terminal complement proteins including C5b-9, without IgG, along the contours of ribbon-like intramembranous electron-dense deposits within GBM and in the mesangium (mesangial rings).282–284,287

The complement profile in serum and in glomerular deposits reflects alternative, or MBL, pathway activation.7–10,198,199,282–284 Normally, low-level spontaneous hydrolysis of C3 to produce C3b leads to formation of the alternative pathway C3 convertase, C3bBb, which then catalyzes more C3 activation (C3 tickover). C3bBb is tightly regulated by circulating complement factor H (CFH), which binds the active Bb site on the convertase to impair degradation of the enzyme and prolong its half-life, leading to hypercatabolism of C3.7–10,198,282–284,288 Over 80% of DDD patients have an IgG autoantibody to the Bb active site of the alternative pathway C3 convertase (C3 nephritic factor, C3Nef) exposed after interaction of factor B with C3b that prevents normal CFH binding.282–284

However, DDD can also be associated with other loss of CFH function conditions independent of C3Nef, including congenital absence or single nucleotide polymorphisms of CFH, neutralization by an anti-CFH antibody288–290 or antibody to factor B,291 and, less commonly, with gain in function mutations in C3 that lead to C3 convertases resistant to CFH regulation.284 In mice, CFH deficiency induces massive complement activation and a DDD phenotype that is ameliorated by administration of CFH or properdin.292,293 Chronic unregulated C3 activation generates a variety of alternative pathway complement activation products that accumulate, perhaps by charge interactions, along the inner GBM to form the classic dense deposits seen by electron microscopy.284,287,290 In turn, this accumulation of proteins modifies filtration barrier structure and integrity, leading to proteinuria and nephrotic syndrome. DDD is associated with other similar disorders of complement regulation such as partial lipodystrophy, but no specific etiologic factors have been identified.

**C3 Nephropathy**

Glomerular deposits of C3 without Ig also characterize another C3 glomerulopathy variant, sometimes termed C3 nephropathy or C3 deposition glomerulopathy; however, the electron-dense deposits are primarily at mesangial and subendothelial sites rather than within GBM.7,285,286 These lesions also may be associated with a spectrum of histologic abnormalities including MPGN I–like findings.285,286 The disorder seems to affect younger patients who often have hematuria and proteinuria but less commonly exhibit hypocomplementemia, nephrotic syndrome, or progression compared with DDD.288 Evidence of disordered complement regulation in the form of either mutated CRPs (H402 allele of factor H, factor I), anti-CFH or anti-factor B antibodies, or C3Nef is also present in most of these patients.285,286,288–291 A familial form of the disease in people of Cypriot origin due to mutations in CFHR (CFHR5 nephropathy) has recently been described.294 The composition of the deposits and the reason for their different distribution compared with DDD are not known, although studies in murine models of MPGN suggest that abnormalities in complement factor I may play a role.295

**OVERVIEW OF IMMUNE MECHANISMS**

Recent advances in understanding the pathogenesis of immune glomerular diseases now link infectious processes, especially chronic viral ones, with autoimmunity and GN. Although once viewed primarily as human equivalents of the antibody-mediated serum sickness (IC) or NTN (anti–GBM) models of GN in animals, most human glomerulonephritides are now believed to be primarily autoimmune diseases. They involve both innate and adaptive immune mechanisms, with distinction between the two becoming increasingly blurred, and T cell as well as antibody-driven adaptive immune responses (Figures 1 through 4). Links to etiologic infectious agents more likely proceed through recognition of PAMPs by TLRs and triggering of autimmune processes than through direct effects of ICs containing exogenous antigens trapped from the circulation. However, progress in translating these scientific advances to better therapies has been slow, and clinicians currently still rely almost entirely on corticosteroids and toxic, nonsselective immunosuppressive agents for treatment.

As the relevant sciences have evolved, three things have remained constant—the
patients, the utility of well characterized animal models of their diseases, and the contributions of physician-scientists who have accounted for most of the advances described above. The patients and the animal models will remain and the technology to study them will advance dramatically in the years ahead. However, the future supply of qualified physician-scientists is threatened. In closing, it is worth noting that continued progress in this area will require the continuous availability and dedication of investigators who fully understand both the tools of basic science and the clinical and pathologic manifestations of human renal diseases, for knowledge of both will be required to generate and test new hypotheses that can lead to improvements in therapy. Perhaps this review can serve as an encouragement to some who might follow that path.

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DISCLOSURES

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REFERENCES

75. Emancipator SN: Prospects and perspectives on IgA nephropathy from animal models. Nephron Dial Transplant 182, 2004
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membrane glomerulonephritis into membra-

119. Stilmant MM, Bolton WK, Sturgill BC, Schmitt GW, Couser WG: Crescentic glo-

120. Falk RJ, Jennette JC: Anti-neutrophil cyto-


125. Jennette JC, Xiao H, Falk R, Gamis AM: Experimental models of vasculitis and glo-


127. Wilde B, van Paassen P, van Rossum AP, Rarok AA, Huitema MG, Fassina G, Limburg PC, Kallenberg CG: Constitutive membrane expression of proteinase 3 (PR3) and neutrophil activation by anti-

128. Falk RJ, Terrell RS, Charles LA, Jennette JC: Anti-neutrophil cytoplasmic autoanti-
bodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci USA 87: 4115–4119, 1990


130. Bosch X: LAMPs and NETs in the patho-


134. Van Timmeren MM, Chen M, Heeringa P: Review article: Pathogenic role of com-
plement activation in anti-neutrophil cyto-


137. Pendergraft WF 3rd, Preston GA, Shah RR, Tropscha A, Carter CW Jr, Jennette JC, Falk RJ: Autoimmunity is triggered by cPR-3 (105-201), a protein complementary to hu-

138. Heuwings P, Belmonte F, Charles Jennette J, Falk RJ, Preston GA: Longitudinal studies of patients with ANCA vasculitides demonstrate concurrent reactivity to complementary PR3 protein segments cPR3m and cPR3C and with no reactivity to cPR3N. Autoimmunity 44: 98–106, 2011


141. Chen M, Kallenberg CG, Zhao MH: ANCA- negative pauci-immune crescentic glomer-


175. Raz E, Breizis M, Rosenmann E, Eilat D: Anti-DNA antibodies bind directly to renal anti-DNA antibodies different from other SLE autoantibodies. J Autoimmunity 44: 1–57, 2010


IgA nephropathy—no support of an overlap. PloS ONE 5: e10559, 2010


Sequential study of immune complex deposition, ultrastructural changes, proteinuria, and alterations in glomerular sialoprotein. Lab Invest 34: 23–30, 1976


