

SECTION VII ■ GLOMERULAR, INTERSTITIAL, AND VASCULAR RENAL DISEASES

CHAPTER

45

Mechanisms of Immune Glomerular Injury

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INTRODUCTION

This chapter reviews the mechanisms of tissue injury that result in immune glomerular diseases, including glomerulonephritis and nephrotic syndrome (when presenting as a primary glomerular disease). The chapter is organized by individual diseases rather than by mechanisms to allow readers to appreciate more readily how the processes of tissue injury described here translate into the clinical disease entities encountered by clinicians and pathologists and covered in other chapters in this section. The mechanisms described derive from several decades of studies done at the molecular and cell culture levels *in vitro* as well as in an array of well-characterized animal models of glomerular diseases and in man. Cell cultures are not glomeruli or kidneys, and mice and rats are not humans, but years of experience have taught us that mechanisms defined in these experimental settings can be translated into an improved understanding of the very similar processes seen in human disease. For more information, the reader is referred to other reviews of the immune mechanisms that lead to glomerular disease.^{1,2} A schematic overview of the major pathogenic sequences currently believed to be operative in human glomerulonephritis (GN), and their interactions, is presented in Figure 45.1.

BASIC IMMUNE MECHANISMS: AN OVERVIEW

The Innate Immune Response (Figure 45.1)

For many decades, studies of the pathogenesis of human GN have focused on the adaptive immune system involving antibodies and T cells. However, more recently, increased attention has been given to the more ancient and well-conserved elements of the innate immune response, which occurs immediately after an initiating event without the latent period involved in the processing of antigen, antigen presentation, and specific immune responses.³ The innate immune system has two major arms: Toll-like receptors (TLRs) and complement, both of which may be involved in adaptive immunity as well.

TLRs are ancient and ubiquitous pattern recognition receptors present on all cell membranes and intracellularly between cytoplasm and endosomes.³ Over 10 TLR isoforms have been characterized that recognize conserved molecular patterns like peptidoglycans, lipopolysaccharides, and bacterial and viral nucleic acids (pathogen-associated molecular patterns [PAMPs]). TLRs also respond to certain endogenous cell-derived patterns (danger-associated molecular patterns [DAMPs]). Another related cytoplasmic group of receptors called Nod-like receptors (NLR) has recently been described as well.⁴ TLR ligation is central to activating the non-antigen-specific innate immune system in the 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.^{3,4} TLRs activate multiple intracellular signaling pathways, primarily via nuclear factor kappa B (NF- κ B), that lead to the local release of a variety of cytokines, chemokines, and other inflammatory mediators by all cells, including inflammatory cells like neutrophils and macrophages, as well as all three resident glomerular cells (Fig. 45.1).^{3,4} Thus, TLRs and NLRs connect initiating pathogenic events like infection with a sequence of processes leading to immediate non-antigen-specific inflammation and tissue injury in GN that is associated with infections or autoimmunity or both (Fig. 45.1).

The Complement System (Figures 45.1 and 45.2)

The complement (C) system and its regulatory proteins are also ancient components of the innate immune system with multiple roles in human GN (Fig. 45.2).^{5,6} C activation products are the principal mediators of antibody-induced GN. Nonimmunoglobulin zymogens, such as damaged cells and bacterial and viral proteins, can also activate C. C1q binding to immunoglobulins in the form of antigen-antibody complexes leads to classical pathway activation through C1, C4, and C2. Activation of the mannose-binding lectin (MBL) pathway is usually a consequence of microbial pathogens or galactosyl immunoglobulin G (IgG) binding to circulating MBL and proceeds through C4. The alternative C pathway (AP) is activated at low levels spontaneously, as well as by

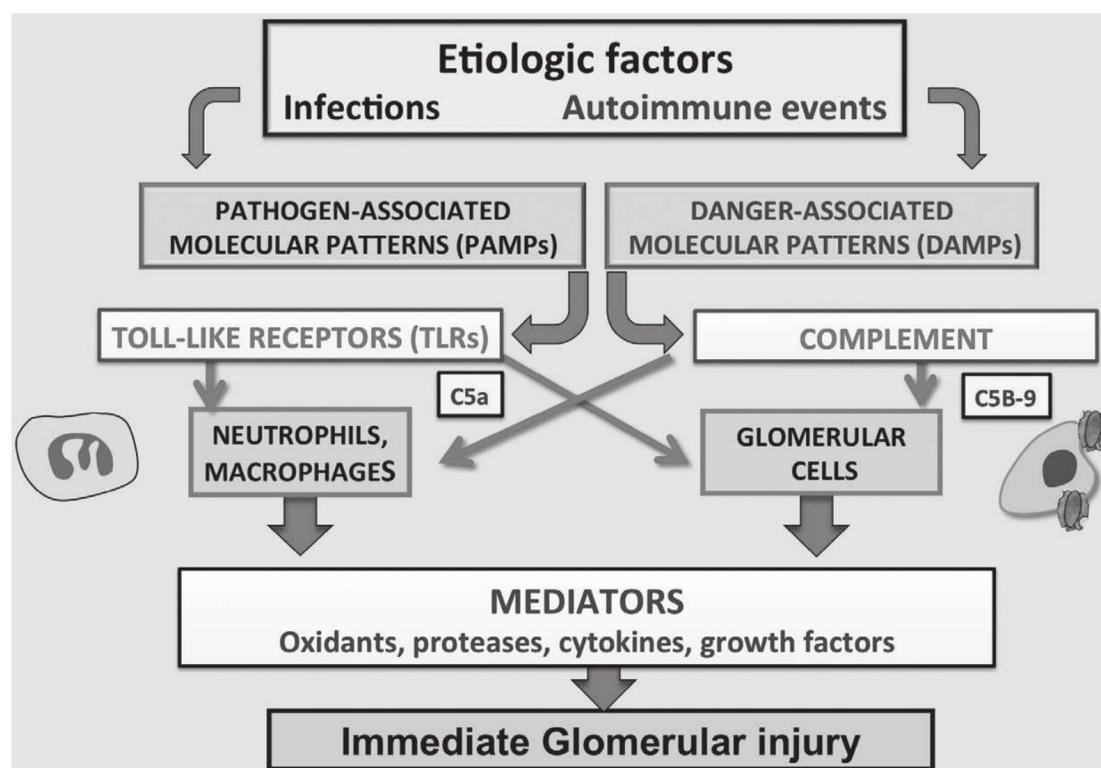


FIGURE 45.1 The innate immune system in glomerular disease. Etiologic factors, usually infections or autoimmune events, are presented to the immune system as pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). These interact with the two principal arms of the innate immune system, Toll-like receptors, and the complement system. Toll-like receptors are present on both circulating inflammatory cells like neutrophils and macrophages and on resident glomerular cells including endothelial and mesangial cells and podocytes. Toll-like receptor activation induces inflammation through release of multiple mediators including cytokines, growth factors, oxidants, proteases, eicosanoids, and others. Activation of complement also leads to the attraction of inflammatory cells through the generation of chemotactic factors such as C5a and to the conversion of resident glomerular cells to inflammatory cells following sublytic C5b-9 insertion into cell membranes. The mediators released by both infiltrating neutrophils and macrophages, and resident glomerular cells cause glomerular injury that leads to morphologic and functional changes in diseased glomeruli.

foreign surfaces such as some microbial products and damaged cells. AP activation begins at C3 without involving C1, C4, or C2. In individual complement-mediated diseases, several of these pathways may be involved.^{5,6} Among the immunoglobulins, IgG subclasses IgG₁ and IgG₃ and IgM are classical C pathway activators, whereas IgG₂ and IgG₄ and normally glycosylated IgA activate C poorly.⁷ However, C activation and its sequelae need not involve immunoglobulin deposits and may occur by other mechanisms even in the presence of immunoglobulin deposits. All C activation pathways lead to cleavage of C5 and release of chemotactic factors such as C5a that attract inflammatory cells (neutrophils, macrophages, platelets) when activation occurs within, or adjacent to, the circulatory compartment. Cleavage of C5 by C5 convertases also leads to the release of C5b and the addition of C6, C7, C8, and multiple C9 molecules to form the lipophilic terminal membrane attack complex (MAC or C5b-9) (Fig. 45.1).^{8,9} Sublytic quantities of C5b-9 can insert into lipid bilayers of adjacent glomerular cell membranes and act in a fashion similar to receptor agonists. Sublytic C5b-9 initiates several signaling pathways and thus converts endothelial cells, mesangial cells, and podocytes to local inflammatory effector cells that can proliferate; release a variety of cytokines, growth factors, eicosanoids, oxidants, proteases, and other acute inflammatory mediators; as well as upregulate genes that encode matrix components and contribute to

chronic overproduction of the extracellular matrix with scarring and sclerosis.⁹ Immunoglobulin-induced C activation products like C5a can also activate TLRs, thus linking the innate and adaptive immune systems (Fig. 45.2).¹⁰ C activation in vivo is tightly regulated by a number of circulating and cell-bound C regulatory proteins (CRPs) the functions of which, particularly those of CR1, factor H, membrane co-factor protein (MCP), and CD59, are also important in the development of several glomerular diseases (Fig. 45.2).^{5,6}

The Adaptive Immune Response

Immunoglobulins

CD4 T-helper cells, activated by antigen-presenting dendritic cells and macrophages, stimulate B cells and plasma cells to make antibodies specific for nephritogenic antigens. Antigenic peptides capable of inducing GN may represent only a few amino acids of much larger proteins. Based on older studies of serum sickness in rabbits induced by single (acute) or repeated (chronic) injections of bovine serum albumin (BSA), glomerular immune deposits have long been attributed to the passive trapping of circulating, soluble antigen-IgG antibody complexes (ICs).^{11,12} In acute serum sickness, a single exposure to BSA is followed by a latent period of 5 to 7 days and then the production of the IgG antibody. As antigen forms immune complexes and disappears from the circulation,

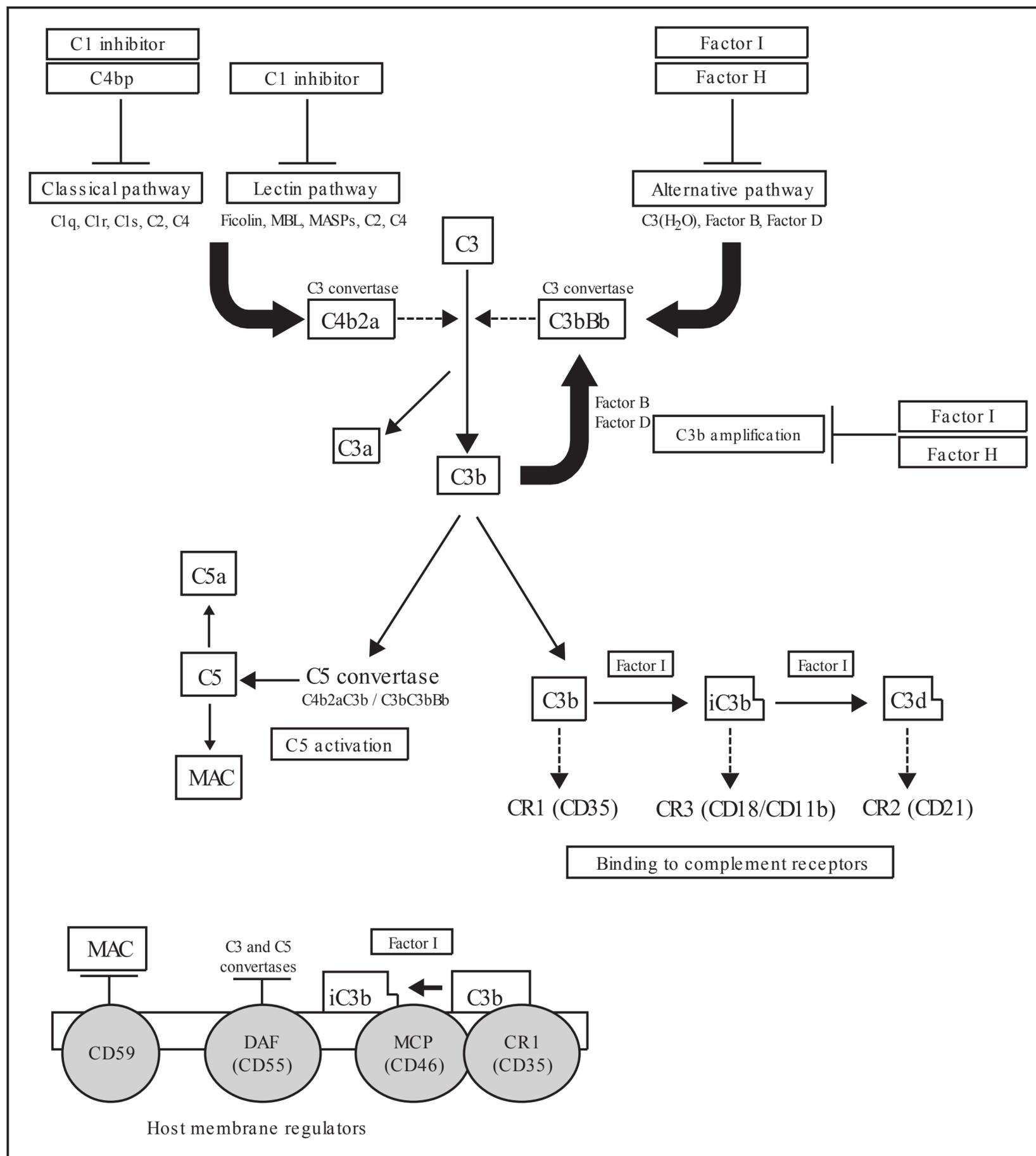


FIGURE 45.2 A schematic depiction of complement pathways and how they are activated as they relate to the pathogenesis of glomerulonephritis (GN). Activation via the classical, lectin, and alternative pathways leads to the formation of C3 convertases that cleave C3 to C3a and C3b. C3b can interact with complement receptors on cell surfaces such as CR1, CR2, and CR3 as well as contribute to the formation of C5 convertase. Cleavage of C5 results in the formation of the chemotactic factor C5a and C5b, which leads to the formation of the C5b-9 membrane attack complex (C5b-9) that is important in the mediation of several glomerular diseases. Factors H and I are circulating regulators of the alternative complement pathway, whereas CD59, decay accelerating factor (DAF), membrane cofactor protein (MCP), and complementary regulatory 1 (CR1) serve as membrane-bound regulators that protect cells from complement attack. *MBL*, mannose-binding lectin; *MASP*, MBL-associated serum protease; *MAC*, membrane attack complex (C5b-9) (Reproduced with permission from Pickering M, Cook HT. Complement and glomerular disease: new insights. *Curr Opin Nephrol Hypertens.* 2011;20(3):271–277.)

there is an initial phase of antigen excess leading to the formation of small, soluble immune complexes followed by equivalence with midrange size complexes that are believed to be trapped in tissues, and finally, to antibody excess with large complexes that are cleared through the mononuclear phagocyte system with eventual elimination of the antigen. Glomerular deposits of antigens and antibodies in acute serum sickness form primarily in the mesangium and in a subendothelial distribution. In chronic serum sickness, repeated antigen administration is provided to maintain slight antigen excess and is associated with more subepithelial deposits, again attributed to the passive glomerular trapping of small, preformed immune complexes that crossed the capillary wall to localize beneath podocytes.^{12,13} Attribution of the tissue injury that occurs in serum sickness to the passive trapping of circulating complexes followed from observations that inflammation occurred only during the period that complexes could be detected in the circulation, corresponded with appearance of immune deposits in glomeruli and that both the antigen and antibody components of the immune complexes were constituents of the deposits.¹³ However, later studies using passively administered preformed immune complexes did induce some glomerular deposits, but generally failed to replicate the tissue injury seen in either acute or chronic serum sickness.¹⁴ Moreover, later measurements of circulating immune complex levels in human disease found little correlation between circulating complex levels, sizes, and disease activity. Other studies done in anti-glomerular antibody (nephrotoxic nephritis [NTN]) models rather than in serum sickness demonstrated that antibody deposits activated C and other mediators that attracted circulating inflammatory cells—primarily neutrophils—which then caused tissue injury.¹⁵ Some of these discrepancies were resolved in 1978 when it was shown that the classic subepithelial immune complex deposits in the Heymann models of membranous nephropathy (MN) in rats formed in situ and were unrelated to circulating immune complexes. Instead, they resulted from antibody binding to endogenous glomerular components localized on the podocyte (see Membranous Nephropathy, which follows).^{14,16–18} Subsequent studies in both acute and chronic serum sickness using cationic BSA confirmed that deposits in these models involving exogenous antigens also formed locally and were unrelated to circulating immune complex levels or sizes.^{19,20} This new paradigm allowed the mediation of immune complex nephritis to be studied directly rather than by being extrapolated from findings in models of anti-GBM disease.

The variables that determine biopsy findings and clinical consequences in immune complex GN include: (1) where deposits form in the glomerulus (ICs of the same composition that form in a subendothelial distribution lead to exudative inflammatory cell infiltrates, in the mesangium to mesangial cell [MC] proliferation and matrix expansion, and in a subepithelial distribution to a noninflammatory lesion with podocyte injury, foot process effacement, and heavy proteinuria)^{18,21,22}; (2) the biologic properties of the antibody (or antigen) itself,

especially the capacity to activate complement, the Fc receptor affinity, the ability to form lattices that are necessary for complement activation to occur, or cryoprecipitability^{1,23}; (3) the mechanism of deposit formation (when ICs form in situ the process usually induces tissue injury at the site, whereas passive trapping of ICs formed in the circulation has not been shown to be nephritogenic)^{1,14,18}; and (4) the quantity of immune deposits formed (the more deposits that form, the more severe the disease).

T Cells (Figure 45.3)

Although the existence of T cells sensitized to glomerular antigens was first demonstrated in glomerular basement membrane (GBM) disease over 40 years ago,²⁴ experimental verification of the pathogenicity of T cells was delayed by several factors. The rapid expansion of immunopathology using fluoresceinated antibodies to visualize and characterize antibody deposits in human renal biopsies, the lack of good T-cell markers in both rodent models and in humans, and the conviction that all forms of GN were antibody mediated resulted in little research in this area for 2 decades.²⁵ In 1984, the hypothesis that T cells could mediate GN independent of antibody was confirmed in ingenious experiments using bursectomized chickens that had no B cells, and later, in more conventional rodent models.²⁶ In addition to providing help for B cells,²⁸ antigen-specific CD4 T cells alone, sensitized to either self or nonself antigens that are localized in glomeruli, can induce antibody-independent tissue injury.^{27,28} All subsets of T cells are now implicated in GN, including dendritic antigen-presenting cells (DC) and CD4 helper cells of the Th1, Th2, and T regulatory cell (Treg) lineages. The best-established mechanism of T-cell mediated glomerular injury involves the recruitment of macrophages, which then act as the inflammatory effector cells. However, interleukin 17 (IL-17) producing Th17 cells have attracted the most attention recently and now seem likely to account for much of the T cell-induced inflammation that occurs in GN.^{29,30} Th17 cells are attracted by mechanisms involving chemokines and their receptors, and they release cytokines such as IL-9, IL-17, IL-21, IL-22, and tumor necrosis factor alpha (TNF- α), which induce other cells to produce additional proinflammatory chemokines that attract neutrophils and monocytes and also activate resident glomerular cells.^{29,30} Th17 cells have now been demonstrated in renal biopsies in several forms of human GN.³¹ The T-cell component of the adaptive immune response is regulated by CD4-derived Tregs (Fig. 45.3).²⁶

DISEASES THAT USUALLY PRESENT AS GLOMERULONEPHRITIS

Postinfectious or Poststreptococcal Glomerulonephritis

The acute, diffuse exudative, and proliferative lesions of postinfectious or poststreptococcal glomerulonephritis (PSGN) were long regarded as the human equivalent of the acute

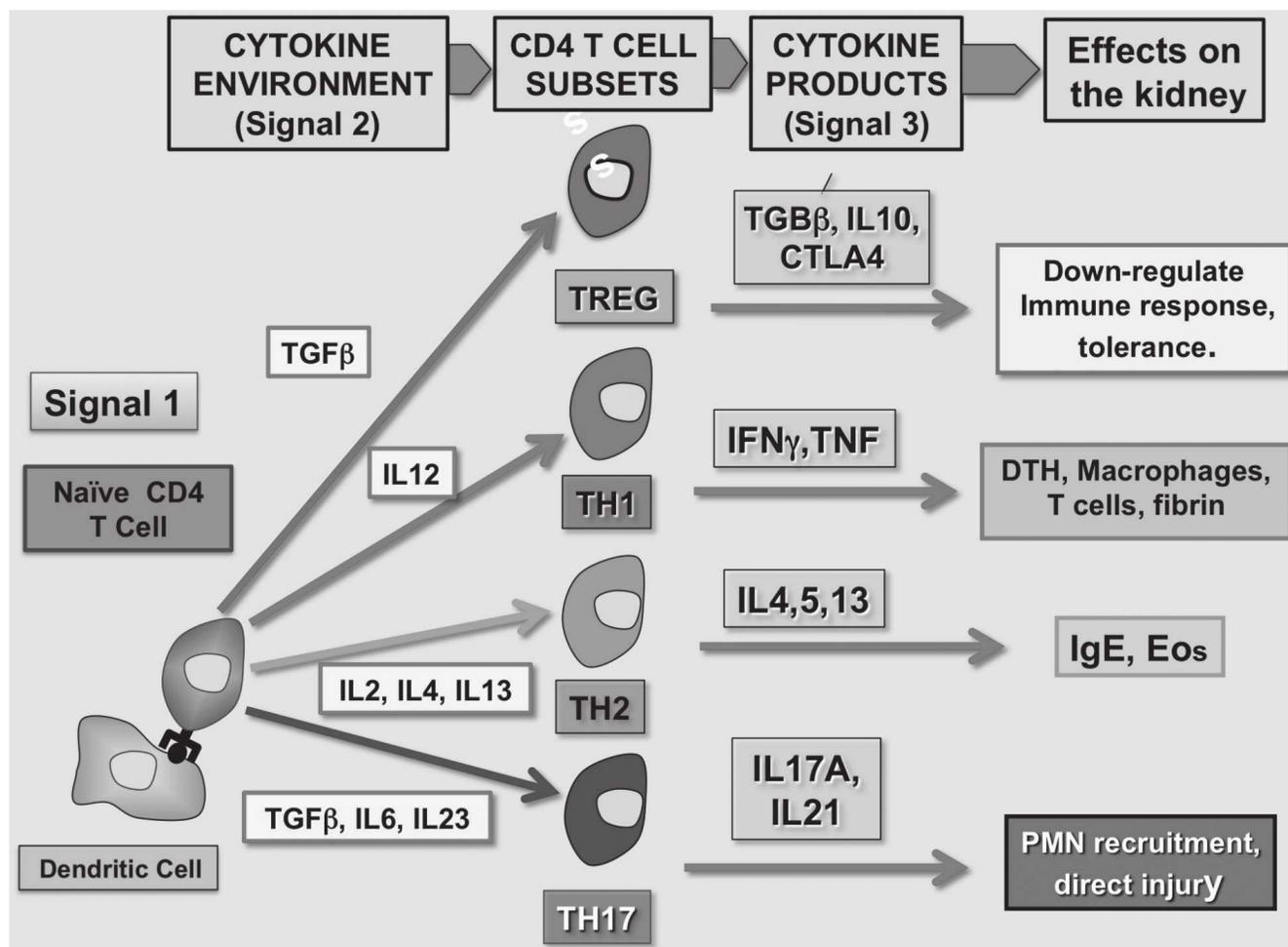


FIGURE 45.3 The T-cell component of the adaptive immune system in glomerulonephritis (GN). Antigen is presented to naïve CD4 T cells by dendritic cells (*Signal 1*). Depending on the predominant cytokine environment, T cells differentiate into CD4 T-cell subsets that play different roles in the pathogenesis of glomerular disease. In the presence of transforming growth factor beta (TGF- β), T regulatory cells (Tregs) develop that make TGF- β , interleukin 10 (IL-10), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) that downregulate and control the immune response. IL-12 stimulates differentiation into Th1 cells that make interferon gamma (IFN γ) and TNF and produce traditional T-cell/macrophage-mediated delayed-type hypersensitivity (DTH) reactions. IL-2, IL-4, and IL-13 favor the development of Th2 cells that make IL-4, IL-5, and IL-13, and lead to allergic-type hypersensitivity reactions involving immunoglobulin E (IgE) and eosinophils (Eos). The CD4 T cells most implicated in the pathogenesis of GN are Th17 cells that differentiate in the presence of TGF β , IL-6, and especially IL-17, and those that produce IL-17a and IL-21 that facilitate recruitment of other inflammatory cells such as neutrophils (PMNs) and also cause tissue injury directly.

“one shot” serum sickness model in rabbits, leading to a prolonged search for the “nephritogenic” streptococcal antigen that has extended over several decades. Although many candidate proteins have been proposed, most have failed to meet strict criteria for causality such as being demonstrable in deposits, particularly subepithelial “humps,” inducing antibody that correlated with clinical disease, and inducing a similar disease in animal models.³² However, streptococcal pyogenic exotoxin B (SpeB) meets most of these criteria. SpeB is a small (28 kDa), cationic (pK 9.3) cysteine protease with C activating and plasmin-binding properties and represents 90% of the secreted extracellular protein made in vivo by nephritogenic strains of group A streptococci.³² Antibody to SpeB correlates with disease activity in PSGN and colocalizes with IgG and C3 in subepithelial “humps.”^{32,33} However, the intense exudative glomerular inflammatory response and subepithelial humps are not well explained by the analogy to acute serum sickness because intact circulating ICs do not form subepithelial IC deposits directly, and subepithelial IC deposits do not produce inflammation, presumably because complement activation products like C5a go directly into the

urine and are not chemotactic for cells in the circulation.^{14,18} Moreover, IgG is sometimes absent, or only a minor constituent of the deposits, whereas C3 deposition has been reported to both precede and exceed detectable IgG.^{34,35} Several explanations for these apparent contradictions are plausible. They include observations that some subendothelial deposits are also present by electron microscopy (EM) in PSGN,^{34,35} perhaps because the antibody to SpeB exhibits molecular mimicry with endothelial cell antigens, and antiendothelial antibody deposits are generally rapidly cleared.³⁶ In addition, SpeB alone is a zymogen that can activate C directly through the MBL pathway independent of IgG.³² SpeB also exhibits plasmin-binding properties that can facilitate C activation and might cause proteolysis of GBM and facilitate the transit of dissociated subendothelial ICs to form subepithelial humps.³⁷ Finally, PSGN often exhibits autoimmune features including both IgM and IgG rheumatoid factors with cryoglobulin activity, antiendothelial antibodies, anti-DNA antibodies, and antineutrophil cytoplasmic antibodies (ANCA). Although the respective roles of these nonstreptococcal antibodies in mediating the disease, if any, remain undefined,

45.1 The Most Common Complement Profiles and Autoimmune Features in Glomerulonephritis

Disease	Serum C Profile	Autoimmune Features	References
Poststreptococcal GN	AP, MBL; normal C1q, Low C3-C9	Anti-C1q, IgG AECA, anti-DNA, ANCA, PDI, cardiac myosin	37, 42, 45–48
IgA nephropathy	Normal, lectin pathway activation	Anti-glycan, mesangial cell	52, 53
Anti-GBM nephritis	Normal, CP	Anti-GBM, ANCA (20%)	88,107,108
ANCA-positive GN	Normal, AP	Anti-MPO, PR3, cPR3, NET, DNA, endothelial cell, LAMP2	110, 123, 137, 138,152
Lupus nephritis	CP, low C1q-C9	Anti-dsDNA, annexin, MPO, PR3, nucleosome, IgG, C1q, cardiolipin, MBL, NET	110, 123, 152
MPGN I	CP, low C1q-C9	Anti-C3 convertase (C3Nef),C4Nef, C1q IgM anti-IgG	
MCD/FGS	Normal	None	
Membranous nephropathy	Normal	Anti-PLA2R, DNA, NEP, aldose reductase, enolase SOD2	
Dense deposit disease	AP, normal C1q, low C3-C9	C3Nef, C4Nef, anti-CFH, factor B, C1q	
C3 nephropathy	AP, normal C1q, low C3-C9	C3Nef, anti-CFH	

Most forms of GN exhibit major features of autoimmunity. GN, glomerulonephritis; AP, alternative pathway; MBL, mannose-binding lectin; IgG, immunoglobulin G; AECA, anti-endothelial cell antibodies; ANCA, antineutrophil cytoplasmic antibody; PDI, protein disulfide isomerase; anti-MPO, antimyeloperoxidase; PR3, proteinase 3; cPR3, complementary proteinase 3; NET, neutrophil extracellular trap; NEP, LAMP2, lysosomal membrane protein 2; C3Nef, C3 nephritic factor; CP, cofactor protein; MPGN, membranoproliferative glomerulonephritis; MCD/FGS, minimal change disease/focal glomerulosclerosis; anti-PLA2R, anti-phospholipase A2 receptor; SOD2, superoxide dismutase 2; anti-CFH, anti-complement factor H. NEP, neutral endopeptidase.

these findings suggest an autoimmune component to postinfectious GN that is consistent with current thinking about most other immune glomerular diseases (Table 45.1).^{38–40}

Other forms of postinfectious GN such as those associated with endocarditis, infected ventricular–atrial shunts, visceral abscesses, and *Staphylococcus aureus* infections with IgA deposits are clearly immunologically mediated, but the mechanisms involved in these diseases have been explored in much less detail.⁴¹

Immunoglobulin A Nephropathy

IgA nephropathy (IgAN) is the most common form of GN worldwide.⁴² IgAN is characterized by a focal proliferation of mesangial cells and mesangial matrix expansion accompanying diffuse mesangial aggregates of IgA, and often IgG, C3, and C5b-9.^{42–44} The disease is often associated with recurrent episodes of nephritis that immediately follow viral infections on mucosal surfaces of the upper respiratory

or gastrointestinal tracts.^{42–44} Although usually assumed to be mediated by a mesangial trapping of circulating ICs, no exogenous antigens have been consistently identified. Animal models of IgAN that closely mimic both the pathologic, immunopathologic, and the clinical features of IgAN have been challenging to produce, in part because of substantial differences between the rodent and human IgA immune systems. IgA in mesangial deposits, and in IC form in the circulation, is polymeric (mucosal) IgA₁ with a covalently linked secretory piece indicating a mucosal origin.^{45,46} In IgAN, a population of these IgA₁ molecules exhibits deficient O-linked glycosylation at five sites in the hinge region of the molecule.^{42–46} The failure to normally glycosylate IgA1 can be inherited and is commonly seen in family members without renal disease,⁴⁷ but the defect seems to occur epigenetically as well.⁴⁸ Although underglycosylated pIgA1 is produced by mucosal B cells and is usually assumed to originate from mucosal surfaces where it should not enter

the bloodstream, it might also reach the circulation if abnormal trafficking of these cells to the bone marrow occurs.⁴⁹ Underglycosylated IgA₁ undergoes conformational change and exhibits altered biologic properties compared to normal IgA₁, including increased tendencies to self-aggregate, to activate C, and to bind to other molecules like fibronectin, IgG, and collagen IV.^{45,46,50} In circulating macromolecular form, the underglycosylated IgA₁ aggregates lack the glycosylated sites necessary to interact with asialoglycoprotein and the CD 89 receptors in the liver and spleen, thus evading normal clearing mechanisms and facilitating mesangial localization.^{45,46,51} It is not yet known if the “lanthanic” mesangial IgA deposits seen in 6% to 16% of normal donor kidneys without disease contain underglycosylated or normal IgA.⁴²

Although IgG autoantibodies to MC antigens have been described in IgAN,⁵² Suzuki et al.⁵³ were the first to report IgG antibodies directed to cryptic GalNac antigenic structures in the hinge region of aberrantly glycosylated IgA₁ molecules (antiglycan antibodies). IgG antiglycan antibodies appear to correlate with disease activity in a way that has not been demonstrated with serum levels of IgA, IgA immune complexes, or IgA-fibronectin aggregates.⁵³ Antiglycan antibodies form circulating ICs with underglycosylated IgA₁ that can be passively trapped in the mesangium, although the mesangial trapping of ICs has not been demonstrated to be nephritogenic. Alternatively, IgG antiglycan antibodies could also lead to in situ IC formation with previously localized IgA aggregates. When IgG antibody does bind in situ to antigenic material in the mesangium⁵⁴ or on the MC membrane (the antithymocyte serum [ATS] model in rats),^{56–59} the mesangial response to acute immune injury closely simulates the clinical and histopathologic features of human IgAN.^{55,60}

In IgA nephropathy, MCs become activated through interactions between the IgA₁ deposits and IgA Fcα (CD89) receptors, TLRs (especially TLR4), and transferrin receptors (TfR, CD71).^{61,62} Innate immunity and 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.^{42,63} However, most experimental and clinical studies suggest a role for C in IgAN as well.^{5,6,63,64} C5b-9 generated from C activation induced by the interaction of IgA₁ aggregates with MBL, or the in situ formation of ICs containing IgG antiglycan antibodies can induce MC transformation to a smooth muscle actin-expressing myofibroblastlike cells, upregulate genes for collagen I, and increase production of cytokines and growth factors such as IL-1, IL-6, TNF-α, platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), fibroblast growth factor (FGF), connective tissue growth factor (CTGF), and hepatocyte growth factor (HGF), all resulting in MC proliferation and matrix expansion.^{5,6,8,9} Of these, the best-established mediators of the glomerular response to immune injury are PDGF, which is the principal growth factor involved in the proliferation of MC that follows immune

injury and the CTGF/TGF-β pathway that induces overproduction of mesangial matrix.⁶⁵ The pattern of glomerular C deposition seen in active IgAN includes MBL, C4d, and C5b-9 (but not C1q) that colocalize with IgA₁ and suggest the activation of both MBL and AP.^{66,67} Further evidence that C activation is important in IgAN includes observations that C deposits including MBL, C4d, and C5b-9 correlate with disease severity and prognosis.^{66–68}

Rapidly Progressive, Crescentic Glomerulonephritis

Anti-Glomerular Basement Membrane Nephritis

Anti-GBM (aGBM) nephritis is characterized initially by an acute, focal necrotizing GN with crescents and linear deposition of IgG, usually with C3, on the GBM.⁶⁷ With pulmonary alveolar hemorrhage it becomes Goodpasture syndrome (GPS). The role of aGBM antibody deposition inducing C activation, chemotactic factor release, and neutrophil-mediated injury was defined in NTN models in the 1960s,¹⁵ and the pathogenicity of human aGBM antibody was confirmed by the classic transfer studies of Lerner, Glasscock, and Dixon⁶⁹ in 1967. Studies in mice deficient in C3 and C4 primarily implicate the classical C pathway,⁵⁶ which is activated by IgG1 and IgG3 aGBM that correlates with disease activity and recurrence in transplants.^{57,58,67} Circulating and deposited aGBM antibodies are of the same specificity, indicating that available antigens to bind antibodies is limited, and they are primarily of the IgG1 and IgG3 subclasses.⁵⁸ Antibodies with apparently similar reactivity (but with lower titers, lower avidity, and primarily of the IgG2 and IgG4 subclasses) can be present in normal people.⁵⁹

GBM antigens are also expressed in several extrarenal tissues, where they are sequestered by an endothelial cell layer impermeable to IgG.^{70,71} The unique fenestrated endothelium in glomeruli allows for free access of IgG to GBM. The GBM antigen itself consists of two normally sequestered (“cryptic”) epitopes, E_A and E_B, residing on the noncollagenous domain of both the α3 and α5 chains of the noncollagenous (NC)1 hexamer of type IV collagen and is synthesized in the glomerulus exclusively by podocytes.^{70,71} Antibody directed to the α5 chain is associated with worse renal outcomes.⁷¹ Antibody deposition requires perturbation of the quaternary structure of the α3 45 NCI hexamer, possibly initiated by posttranslational modifications, proteolytic cleavage, or oxidant injury, which results in a conformational change in the α3 NC1 and α5 NCI subunits (“autoimmune conformeropathy”).^{70,71} In animal models, the nephritogenic GBM antigen has been mapped to as few as three amino acid sequences in a core residue,⁷² but both intermolecular and intramolecular epitope spreading occurs, suggesting immune reactivity may extend beyond the initial inducing autoantigen.⁷² Pulmonary toxins such as infections, smoke, and volatile hydrocarbons may damage the endothelium and expose the antigen in alveolar capillaries, thus accounting for the pulmonary manifestations in GPS.^{70,71} Whether such

extrarenal events have any role in autoimmunization is not known.

T-cell reactivity to GBM antigens was first demonstrated 4 decades ago, and a pathogenic role for GBM antigen-specific “sensitized cells” was proposed,²⁴ but the hypothesis was given little credence at the time.²⁵ However, many subsequent studies have confirmed these original observations with newer technologies⁷³ and documented that nephritogenic GBM antigens can induce a T-cell mediated GN with crescents, proteinuria, and decreased renal function in the absence of aGBM antibody.^{28,74,75} CD4 Th17 lymphocytes via the “IL-23/Th17 axis” have been shown to be central to the mediation of injury in aGBM models.^{31,76} 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. This may account for why recurrences of anti-GBM disease are so infrequent compared to other autoimmune GNs where Treg activity is often impaired.⁷⁷

The aGBM immune response in humans is strongly linked to human leukocyte antigen (HLA) DRB1 alleles 1501, 0701, and 0101 with DRB 1501 conferring a relative risk of over 8, whereas 0701 and 0101 are protective.⁷⁸ This HLA linkage is the strongest yet identified in any autoimmune disease. Preceding infections or environmental toxins that might expose antigenic determinants in extrarenal tissue are possible triggering events. The disease can also be induced experimentally with a small nephritogenic T-cell epitope, pCol28-40 of Col4alpha3NC1, which exhibits molecular mimicry with PAMPs in some gram-negative bacteria, especially *Clostridia botulinum*.⁷⁹ Finally, glomerular-derived antigenic peptides that have been demonstrated in 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.^{80,81} The occurrence of ANCA antibodies and signs of vasculitis in up to 20% of aGBM patients and examples of aGBM disease occurring with MN, suggest that some of the proposed etiologic factors in ANCA-associated GN or MN could be operative in aGBM disease as well (Table 45.1).^{82,83}

Antineutrophil Cytoplasmic Antibody-Associated Glomerulonephritis

Necrotizing crescentic GNs without immune deposits, later called “pauci-immune” GN, was first described in 1978,⁸⁴ and a decade later was linked to ANCA directed against myeloperoxidase (MPO) and proteinase 3 (PR3).⁸⁵ 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 extrarenal vasculitic disease.^{84,85} The major entities associated with ANCA and GN are Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis (MPA), which may be renal limited.⁸⁶ Explorations

of how anti-MPO and PR3 antibodies mediate GN without depositing in glomeruli have defined entirely new paradigms of immune glomerular injury.⁸⁷

In vitro studies have shown that cytokines, released in response to infections, can “prime” neutrophils and up-regulate adhesion molecules on neutrophils and endothelial cells (L and E selectins, respectively) to facilitate localization in glomerular capillaries.^{87,88} Cytokine-primed neutrophils redistribute MPO and PR3 contained in cytoplasmic primary granules to the cell surface by a mechanism involving CD177, thus permitting ANCA IgG to bind directly or through Fc or Fab’2 receptors.⁸⁹ ANCA binding induces a neutrophil respiratory burst with the release of cationic MPO and PR3 as well as other proteases and oxidants.^{86–88,90} Neutrophil activation and neutrophil–platelet interactions also release neutrophil extracellular traps (NETs) containing entrapped MPO, PR3, and MPO DNA in a chromatin web that can mediate injury directly through TLRs as well as modulate the immune response.⁹¹ In ANCA-GN, NETs are present in glomeruli and are colocalized with neutrophils and DCs, and anti-NET antibodies are present along with circulating MPO-DNA complexes (nucleosomes).⁹¹ Activation of TLR2 and TLR9 exacerbate experimental crescentic GN.⁹² Because of its highly cationic charge, MPO localizes readily in glomeruli by binding to endothelial cells on a charge basis, thus becoming a planted antigen that can form transient immune complexes in situ with the anti-MPO antibody or can interact with antigen-specific Th17 cells.⁹³ Finally, 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.⁹³

In 2002, Xaio et al.⁹⁴ provided the first compelling in vivo evidence for ANCA pathogenicity by transferring spleen cells and purified IgG from an MPO knockout mouse immunized with murine MPO to an immunologically compromised host to induce a T-cell-independent crescentic GN with proteinuria and reduced renal function. Other models have employed transfer of MPO+ bone marrow, adjuvants that enhance the immune response and increase cytokine levels, 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.^{87,95} Studies of the Xaio model have confirmed neutrophil dependence and, despite the absence of antibody deposits, a requirement for alternative C pathway activation involving C5a and C5a receptors.^{87,96} Both alternate C pathway proteins and C5b-9 deposits have been demonstrated in glomeruli in the human disease.⁹⁶ A model of crescentic GN induced by transferring spleen cells from PR3 immunized nonobese diabetic (NOD) mice to immune deficient controls has also been described recently.⁹⁷

Two other potentially nephritogenic ANCA antigens have also been identified. Lysosomal membrane protein 2 (LAMP2) exhibits molecular mimicry with the FimH group of adhesins on some gram-negative bacteria and is expressed on endothelial cells and neutrophils, and anti-LAMP2

antibodies have been correlated with disease activity and reported to induce a focal necrotizing and crescentic GN without immune deposits in animals.⁹⁸ However, these intriguing observations have not yet been confirmed. An antibody directed against complementary PR3 (cPR3)^{99–101} encoded by the antisense strand of PR3 cDNA, has been detected in a minority (20%) of ANCA patients.⁹⁹ Anti-cPR3 IgG elicits an anti-idiotypic antibody response that is reactive with native (sense) PR3, suggesting a role for auto-antigen complementarity in initiating the disease. Because amino acid sequences in cPR3 also have homologies with several infectious agents associated with PR3 disease including Ross River virus, *S. aureus*, and *Endamoeba histolytica*, this could represent another link to potentially etiologic infectious agents and the innate immune system.¹⁰⁰ Anti-cPR3 antibodies are also reactive, with plasminogen and might contribute to the delayed dissolution of clots in vitro potentially contributing to the prominent fibrin deposition seen in ANCA GN.¹⁰¹

Other groups have reasoned that the absence of antibody deposits in ANCA-positive GN, the limited correlation between ANCA levels and disease activity, and the absence of detectable ANCA in about 10% to 20% of patients with typical MPA¹⁰² suggest a primary role for antibody-independent, T-cell-mediated immune mechanisms.^{103,104} Consistent with this hypothesis is the persistent activation of T cells and the elevation of soluble T-cell products that correlate with disease activity,¹⁰⁵ the prominence of traditional Th1 delayed-type hypersensitivity markers like T cells, macrophages, fibrin, and occasional granulomas in ANCA-positive GN¹⁰⁴ and T-cell reactivity to ANCA antigens in some patients.^{106–108} T cells alone, including Th17 cells, can induce focal necrotizing and crescentic GN when sensitized to a “planted” glomerular antigen (as might occur with “planted” cationic MPO).^{27,109} A recent study using combinations of mice that were selectively deficient in T cells, B cells, or MPO demonstrated that active immunization with human MPO (in mice with subclinical glomerular injury) induced crescentic GN without immune deposits that required the presence of endogenous MPO and T-cell reactivity to MPO but did not require B cells or anti-MPO antibody.⁹⁵ Th17 cells and IL-17a, as well as TLRs 2 and 9, have recently been shown to be essential to the development of GN in a T-cell-dependent model.^{92,109} Abnormalities in T-cell regulation and Tregs have also been described in ANCA disease with decreased Tregs associated with disease and increased levels with remission.¹¹⁰

Proposed etiologic agents in ANCA disease include environmental toxins such as silica, infectious agents including gram-positive (*S. aureus*) and gram-negative (FimH H adhesins) bacteria, viral infections, and several drugs.^{86–88} There have also 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. The relatively frequent

observation of ANCA antibodies in other autoimmune glomerular diseases including anti-GBM disease, systemic lupus erythematosus (SLE), and MN suggests that common etiologic and susceptibility factors may be present (Table 45.1).^{82,111,112}

Lupus Nephritis

In lupus nephritis (LN), IgG, IgM, IgA, and C3 (“full house”) deposits develop in the mesangium associated with mild disease (mesangial LN, class I to II) and extend along the subendothelial aspect of the capillary wall associated with increasing proliferative/inflammatory lesions in <50% (focal) or >50% (diffuse) proliferative LN, class III to IV. When deposits are primarily in a subepithelial distribution the lesion is membranous LN (class V), which usually presents with nephrotic syndrome and exhibits fewer tendencies to progression.¹¹³ The autoimmune responses that underlie SLE have been extensively studied in mouse strains that develop the disease spontaneously and in humans, and are beyond the scope of this chapter.^{114,115} The best-established functional immune abnormalities in SLE include a loss of tolerance to numerous self-antigens, B-cell hyperactivity with overproduction of autoantibodies, and defective T-cell regulation.¹¹⁴

IgG anti-double-stranded DNA antibodies (aDNA) in serum and in glomerular deposits are the most prominent serologic features of SLE.^{114–116} The deposits are usually attributed to the passive trapping of DNA-aDNA ICs, although infusing aDNA or DNA-aDNA ICs has not achieved either significant glomerular localization or tissue injury in vivo.^{14,115} Several other mechanisms by which anti-DNA antibodies might be nephritogenic have been proposed. Some monoclonal aDNA antibodies exhibit cross-reactivity with capillary wall antigens, especially laminin and actinin.¹¹⁷ They may become internalized by cells within caveolae, achieve nuclear localization, and directly alter cell functions including apoptosis.¹¹⁸ Antibody to MC annexin, which colocalizes with glomerular IgG and C3 deposits, and correlates with disease activity, has also been identified with mesangial deposits.¹¹⁹ Most recent studies, however, suggest that deposited aDNA has reacted with extracellular DNA in the form of nucleosomes. Nucleosomes contain an anionic segment of DNA encircling a highly cationic histone core, giving the structure a net positive charge and thereby a high affinity for glomerular anionic sites along the endothelial surface of the capillary wall.^{115,116} Defective apoptosis in SLE, perhaps related to an acquired defect in DNase I, leads to necrosis and the release of chromatin debris from apoptotic blebs, thus facilitating access of nucleosomes to antigen-presenting DCs as well as entry into the circulation.^{114–116,120} Circulating nucleosomes are abundant in patients with lupus nephritis, antinucleosome antibodies correlate with disease, and both are present in membrane-associated electron dense deposits.^{114–116} Although this could represent an epiphenomenon, nucleosomes are essential for aDNA antibody localization

to occur in glomeruli.^{115,116} Whether they localize initially as free antigenic material or are already in IC form 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.^{121,122} In that capacity, they may mimic infectious nonself structures to generate DAMPs that could lead to both a loss of tolerance and local inflammation through both the innate and adaptive immune systems.¹²²

Other nonnucleosome autoantibodies have also been implicated in different aspects of the renal lesions in SLE, particularly lupus anticoagulant, anticardiolipin, antiphospholipid, and antibeta2 glycoprotein I antibodies in glomerular microthrombosis (Table 45.1).¹²³ Anti-C1q antibodies, mixed cryoglobulins containing rheumatoid factors, and others are also common (Table 45.1).^{114,123,124} Recent studies in both experimental and human SLE have also implicated the Th2 immune response with B-cell differentiation, the activation of basophils, and the production of IgE anti-DNA antibodies that deposit in glomeruli.¹²⁵ 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 SLE, may contribute to autoantibody production, and is one of several potential new therapeutic targets.¹²⁶

The subepithelial immune deposits in class V (membranous) LN¹²⁶ could form locally from dissociation of subendothelial ICs with transit across GBM to reform in a subepithelial location³⁷ or might represent reactivity of lupus autoantibodies to podocyte antigens analogous to the anti-PLA2R system identified in idiopathic MN and apparently operative in some patients with lupus MN (see the following).

C is believed to be a major mediator of tissue injury in LN through both intracapillary generation of neutrophil and macrophage chemotactic factors (classes 2 through 4) and the formation of C5b-9 (class V).^{60,127} Disease severity is reduced in murine models that lack selected C proteins and increased with deficient regulatory proteins.^{127,128} The observation that deficiencies of classical pathway proteins C1 > C4 > C2 are associated with an increased risk for SLE suggests protective roles for C as well.^{5,6,127} For example, C1q is produced by dendritic cells and is involved in tolerance induction and clearance of both apoptotic cells and ICs.^{5,6}

T cells exhibit several complex and abnormal phenotypes in SLE.^{114,115} In active LN, activated T cells are expanded, provide excess help to B cells, localize in renal cell infiltrates, and produce IL-17, which correlates with disease activity, all implying CD4 and Th17 cell involvement.^{114,115,129} Antigen-specific T-cell reactivity to nuclear antigens is well documented in LN,¹²⁹ and Th17 cells and IL-17 are increased in human and murine SLE and correlate with disease activity.^{114,115,130} IL-17-producing T cells, either Th17 or CD4⁻ CD8⁻ (double negative) T cells, are present

in nephritic kidneys and decreasing IL-17 production improves murine lupus nephritis.^{115,130} In addition to increased CD4 activity in SLE, most studies also suggest an accompanying defect in Treg cell activity that would augment an autoimmune response.^{114,115,131}

Epigenetic events, which might induce autoimmunity in SLE, include environmental exposures such as UV light and certain drugs and viral infections, especially Epstein-Barr virus (EBV).^{114,116} Some of these are believed to interact with the immune system through inhibition of DNA methylation that can result in hypomethylated CD4 cells, the overproduction of IgG by B cells, and the overproduction of some cytokines.¹³² Co-occurrences of LN with other GNs, including ANCA-positive GN,¹¹¹ IgA,¹³³ MN,¹¹³ and even a minimal change-like podocytopathy.¹³⁵ are also sufficiently well established to suggest etiologic factors in common (Table 45.1).

Membranoproliferative Glomerulonephritis, Type I

Membranoproliferative glomerulonephritis, type 1 (MPGN I) has many similarities to a renal-limited LN clinically and pathologically, including the presence of frequent autoantibodies including rheumatoid factors, antinuclear, anticardiolipin, anti-C1q, anti-C3 convertase (C3 nephritic factor [C3Nef]), and antiendothelial antibodies (Table 45.1).¹³⁶⁻¹³⁸ Hypocomplementemia with a classical pathway profile and increased disease susceptibility in the presence of C2 and C4 deficiency are also common to both entities.^{5,6,127,133} 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 LN and are also seen in a variety of chronic neoplasias (especially monoclonal gammopathies), infections, and other autoimmune processes.^{136-138,139} However, in contrast to LN, MPGN I in adults is seen almost exclusively (>90%) in association with hepatitis C viral (HCV) infections, and the glomerular deposits have prominent features of cryoglobulins.^{136,137,140,141}

The principal nephritogenic HCV antigen in MPGN I is believed to be a nonenveloped HCV E2 core protein, which can be demonstrated in circulating ICs and in glomerular deposits.^{142,143} An 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 the monoclonal IgM antibody to polyclonal anti-HCV IgG (rheumatoid factor).^{136-138,144} These soluble but cryoprecipitable aggregates of IgG, IgM, viral proteins/nucleic acids, and C1q make up the mesangial and subendothelial immune deposits characteristic of MPGN I. They 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 classical pathway C activation.^{136-138,145-147} As in SLE, 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, an antigen–antibody system involving a small cationic antigen or autoantibodies to as yet unidentified podocyte antigens.

As in SLE, C probably plays both nephritogenic and protective roles in MPGN I. C1q is important in mediating the initial interaction between IgM, IgG, HCV complexes, B cells, and TLRs,^{136,144} and C activation by immune deposits through the classical pathway likely aggravates tissue injury,^{5,6} although overexpression of a C regulatory protein, Crry, in a well-studied murine model did not significantly ameliorate the disease.¹⁴⁸

The role of the CD4 effector and Tregs in MPGN I have not yet been well defined in either animal models or in humans.

DISEASES THAT USUALLY PRESENT WITH NEPHROTIC SYNDROME

The Minimal Change Disease/Idiopathic Focal Sclerosis Spectrum

There are many clinical and pathogenetic observations in minimal change disease (MCD) and idiopathic focal glomerulosclerosis (FGS), which suggest that they reflect differences in the glomerular response to similar mechanisms. Some patients with MCD are steroid resistant and develop FGS, whereas some with biopsy-documented FGS are steroid responsive and behave like MCD.^{149–152} Both MCD and FGS can be triggered by multiple initiating events including infections, drugs, malignancies, and others.^{149–152} Both are diseases of the podocyte and both have been associated with “permeability factors.”^{151–155} MCD and FGS can both recur immediately in transplants,^{155,156} and can resolve when affected kidneys are placed in normal environments.^{157,158} Differences between MCD and idiopathic FGS in morphologic phenotype and clinical expression could reflect (1) differences in either quantity or biologic activity of a similar primary mediator or group of mediators, or (2) genetic or epigenetic differences in the target podocyte leading to differences in response to, or recovery from, a common primary mediator. Many genes are now established that regulate podocyte responses related to the glomerular barrier function. An epigenetic factor that might also contribute to different phenotypes resulting from similar pathogenetic mechanisms is low birth weight, which is associated with lower nephron numbers, and increased vulnerability of individual nephrons to sclerosis. Alternatively, the response of normal podocytes to two different mediators has not been excluded.

Evidence continues to mount that both MCD and idiopathic FGS reflect the effect on podocytes of circulating, probably T–cell-derived, nonimmunoglobulin “permeability factors,”^{151–155} a hypothesis first proposed by Shalhoub¹⁵³ in 1974. Studies by McCarthy and colleagues¹⁵⁵ over 15 years have demonstrated a factor in the serum of patients with recurrent FGS that can alter the albumin reflection

coefficient of normal glomeruli in vitro, thus increasing glomerular permeability to albumin. In MCD, Koyama et al.¹⁵⁴ demonstrated that factor(s) secreted by T-cell hybridomas derived from patients with active MCD transferred a MCD-like lesion to normal rats. However, these observations were not followed up to identify the factor itself. Despite these in vitro and in vivo observations, identification of the responsible factor(s) has proven frustratingly difficult.¹⁵⁵ Many cytokines and other mediators, including hemopexin, soluble urokinase receptor (suPAR), TNF- α , IL-13, angiopoietin-like 4, and cardiotropin-like cytokine 1 (CLC1), can be shown to be increased in MCD or FGS patients, and several also increase glomerular albumin permeability as measured using in vitro techniques.^{151,155} suPAR has been implicated in altering podocyte β 3 integrins leading to podocyte detachment and FGS,¹⁵⁹ and increased plasma levels of suPAR might contribute to proteinuria in both active and recurrent FGS through a similar integrin-related mechanism. Neutralization of CLC1 reduces permeability factor activity in FGS serum, as does galactose and normal serum and urine.¹⁵⁵

Human studies document Th2 polarization and elevated levels of IL-13, a Th2 cytokine with podocyte receptors, in active MCD.¹⁶⁰ IL-13 alters podocyte function through CD80, and overexpression of IL-13 induces albuminuria and foot process effacement.¹⁶¹ Transferring CD34+ stem cells from patients with active MCD also transfers proteinuria and causes podocyte foot process effacement, although the responsible factor has not yet been established.¹⁶² CD80 (B7.1) is a T-cell costimulatory molecule involved in antigen processing that is also expressed on podocytes. Podocyte CD80 activation through TLR4, independent of T cells, causes proteinuria and foot process effacement.¹⁶³ Recent studies by Garin et al.¹⁶⁴ have documented increased levels of CD80 expression in podocytes and CD80 protein in urine in active MCD (but not FGS), although measurement of urinary CD80 mRNA demonstrates higher levels in FGS than in MCD.¹⁶⁵ CD80 also functions as an inhibitory molecule in T cell–DC interaction and is downregulated by Treg-derived CTLA4, which is decreased in both serum and urine in active MCD.^{164,166} Thus, an initiating event, or “first hit,” such as an infectious process, might lead to the activation of podocyte CD80 via IL-13 or TLR4 leading to actin rearrangement and albuminuria with CD80 shedding in the urine.¹⁶⁶ The “second hit” would involve the defective CD80 regulation by either Tregs or podocyte-derived CTLA4.¹⁶⁶ Podocyte overexpression of angiopoietinlike-4, which, like CD80, is increased in serum and podocytes in MCD patients, induces a steroid-sensitive MCD-like glomerular lesion with heavy proteinuria, suggesting a role for this molecule in the podocyte response in MCD/FGS as well.¹⁶⁷

Membranous Nephropathy

Idiopathic MN is a noninflammatory glomerular lesion initially associated with essentially normal glomerular histology, accompanied by subepithelial deposits of IgG and C3 that are exclusively subepithelial in distribution and heavy

proteinuria.¹⁶⁸ Active and passive Heymann nephritis (HN) are rat models described over 50 years ago that very closely mimic the human disease.¹⁶⁹ Although the subepithelial deposits in the Heymann models were initially attributed to the passive trapping of circulating ICs containing a tubular antigen, studies have since shown that IgG antibodies form subepithelial immune deposits in situ by binding to a podocyte protein complex now called megalin.^{16,17,169} Unlike more inflammatory diseases in which the chemotactic factors generated by complement activation seem to play a primary role, proteinuria in experimental MN is complement dependent but mediated by sublytic C5b-9 attack on podocytes.^{9,170} Sublytic C5b-9 activates several signaling pathways, alters the actin cytoskeleton, upregulates the expression of TGF- β and TGF- β receptors and matrix production leading to GBM thickening and “spike” formation, and increases the production of oxidants and proteases believed to damage underlying GBM leading to proteinuria.⁹ C5b-9 also leads to podocyte DNA damage and impaired ability to complete the cell cycle, which may contribute to apoptosis, the shedding of podocytes in the urine, podocytopenia, and the development of glomerular sclerosis.^{9,171}

Proof of principle that MN in humans can also result from an autoimmune mechanism analogous to the one defined in the Heymann models was first provided by Debiec et al.¹⁷² who reported that alloimmunization of an infant to neutral endopeptidase (NEP) expressed on podocytes, resulting from a maternal NEP deficiency, leads to the transplacental transfer of anti-NEP IgG and typical MN in the newborn.¹⁷² However, the anti-NEP mechanism is not operative in most cases of adult idiopathic MN. Recently, Beck et al. and Hofstra et al.,^{173,174} using microdissection and proteomic technology, identified another antipodocyte autoantibody directed against the M-type phospholipase A2 receptor (PLA2R) in 70% to 80% of patients with idiopathic MN and showed that IgG anti-PLA2R is also present in the glomerular deposits and correlates with disease activity, response to therapy, and recurrence in transplants. Others have confirmed these findings.^{175,176} Antibodies reactive with aldose reductase, enolase, and superoxide dismutase, as well as PLA2R, have also been eluted from MN glomeruli, but these may represent secondary phenomena related to oxidant stress rather than primary pathogenic mediators.¹⁷⁵ Idiopathic MN apparently induced by an exogenous antigen, analogous to the chronic serum sickness model in rabbits induced by cationic BSA, has recently been described.¹⁷⁷ Four children had idiopathic MN associated with cationic BSA, thought to derive from an exposure to cows’ milk, with an antibody to it in the circulation and in the glomerular immune deposits. In this lesion, as well, subepithelial immune deposits appear to form locally independent of circulating immune complexes, and complement C3 and Cb-9 are present.¹⁷⁷

Whether the role of C5b-9 in mediating proteinuria established in HN (and in the chronic BSA serum sickness models of MN as well)^{178,179} mediates podocyte injury, and proteinuria in human MN is not established. C-independent

mechanisms of proteinuria have also been well described with IgG antipodocyte antibodies in several models,¹⁸⁰ including HN,^{181,182} although these models do not exhibit the prominent C3 and C5b-9 deposits seen in the C-dependent HN models and in humans. Despite the prominent C deposition in MN, deposited anti-PLA2R antibody is predominately of the poorly C-fixing IgG4 subclass, which induces poor C activation via the classical pathway. However, C activation might be induced by the lesser quantities of IgG1 and IgG3 usually present, as occurs with anti-NEP IgG.¹⁷² However, in both human MN and HN, classical C-pathway components are often absent in glomerular deposits, suggesting that IgG4 might induce C activation via the MBL or alternative C pathways. In the rat, C-mediated injury also requires the inhibition of podocyte C-regulatory proteins.^{9,183,184}

Once developed, the glomerular lesion in MN heals very slowly with proteinuria, often persistent for weeks or months after the immune response has abated and subepithelial deposits are no longer forming.¹⁸⁵ This likely explains why only 70% to 80% of patients with proteinuria and MN on biopsy have active disease as defined by elevated anti-PLA2R levels.^{173,174} Glomerular deposition of C3c and urinary excretion of C5b-9 have both been established experimentally as valid biomarkers of ongoing immune deposit formation in MN,^{185,186} but these should soon be supplanted by direct measurements of anti-PLA2R antibody.

Although a role for cytotoxic T cells has been proposed in C-independent models of HN,^{187,188} T cells generally do not have access to podocytes or the subepithelial space and are rarely seen in most HN models or human MN.^{183,189} No systematic studies of the role of T cells in human MN have been published.

No etiologic agents have been identified consistently in idiopathic MN. However, a genomewide association study has reported very strong associations with SNPs in genes that encode for HLA-DQA1 and PLA2R.¹⁹⁰ Whether these associations relate to rendering PLA2R antigenic or to altering its expression by podocytes is unclear. In secondary forms of MN, a number of potential etiologic agents have been identified, including hepatitis B virus (HBV) and HCV infections, several drugs, exposure to environmental toxins such as hydrocarbons, milk (in infants), formaldehyde, and solid organ tumors.^{183,191} To date, these secondary forms of MN have only rarely been associated with anti-PLA2R, although up to 30% of patients with lupus MN had an anti-PLA2R antibody in one study.¹⁹¹

C3 Nephropathies

Dense Deposit Disease

Dense deposit disease (DDD) was formerly referred to as type II MPGN because a minority of cases resemble type I MPGN by light microscopy and have a similar nephritic/nephrotic clinical presentation.^{192,193} However, DDD has little pathogenetic overlap with adult MPGN I and is probably better viewed as a C3 glomerulopathy, a form of GN characterized

by deposits of C without immunoglobulins, usually associated with abnormalities in C regulation.^{193–196} Thick linear deposits of C3, C5b-9, and other complement activation products without IgG characterize DDD along the contours of ribbon-like intramembranous electron-dense deposits within GBM and in the mesangium (“mesangial rings”).^{192,196} The C profile in serum and in glomerular deposits reflects alternative, or MBL, pathway activation.^{5,6,192} Normally, the alternative pathway C3 convertase, C3bBb catalyzes spontaneous low levels of C3 activation (C3 “tick over”), but is tightly regulated by circulating factor H (CFH), which binds the active Bb site on the convertase to inactivate the enzyme.^{5,6} Over 80% of DDD patients have an IgG autoantibody to the active site of the alternative pathway C3 convertase (C3 nephritic factor, C3Nef) that prevents normal CFH binding and, therefore, impairs regulation of the enzyme.^{5,6,192,193,197} DDD can also be associated with congenital absence or the mutation of CFH, neutralization by an anti-CFH antibody or antibody to factor B.^{197–200} Chronic unregulated C3 activation generates a variety of AP C activation products that accumulate, perhaps by charge interactions, along the inner GBM to form the classic dense deposits seen by EM.²⁰⁰ In turn, this accumulation of proteins modifies the filtration barrier structure and integrity leading to proteinuria and nephrotic syndrome.

DDD is associated with other similar disorders of C regulation such as partial lipodystrophy, but no specific etiologic factors have been identified.

Isolated C3 Glomerulopathy

Glomerular deposits of C3 without immunoglobulin also characterize another glomerulopathy, sometimes termed isolated C3 deposition glomerulopathy, but the electron-dense deposits are seen primarily in mesangial and subendothelial sites rather than within GBM.^{194,195} The lesion also may be associated with a spectrum of histologic abnormalities including MPGN I-like findings.^{194,195, 200} The disorder(s) seems to affect younger patients who often have hematuria and proteinuria, but less commonly exhibit hypocomplementemia, nephrotic syndrome, or progression compared to DDD.^{194,195} Evidence of disordered C regulation in the form of either mutated CRPs (H402 allele of factor H, factor I), anti-CFH, or antifactor B antibodies or C3Nef is also present in many of these patients.^{194,195,196,198, 200} A familial form of isolated C3 glomerulopathy due to mutations in the CFHR5 gene has also been described in Greek Cypriots that is more likely to progress (30%) and is worse in men than women.²⁰¹ The composition of the deposits and the reason for their different distribution compared to DDD are not known.

CLOSING COMMENTS

Recent advances in the understanding the pathogenesis of immune glomerular diseases now link infectious processes, especially chronic viral ones, with autoimmunity and GN. Once viewed primarily as human equivalents of the antibody-mediated serum sickness (IC) or NTN (aGBM)

models of GN in animals, most human GNs are now believed to be primarily autoimmune diseases involving both innate and acquired immune mechanisms, with distinction between the two becoming increasingly blurred. Moreover, T-cell as well as antibody-driven adaptive immune responses are considered of about equal importance (Fig. 45.1). Links to etiologic infectious agents more likely proceed through the recognition of PAMPs by TLRs and the triggering of autoimmune events 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 in 2011, clinicians still rely almost entirely on corticosteroids and toxic and nonselective immunosuppressive agents for therapy, as described in the clinical chapters, which follow.

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