The etiology of glomerulonephritis: roles of infection and autoimmunity

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Despite major advances in understanding genetic predispositions ('first hits'), pathogenic immune responses, and the mediators of tissue injury in glomerulonephritis (GN), there remains a dearth of knowledge about the etiologic events, or 'second hits', which trigger these diseases. This paper reviews evidence that infections initiate most forms of GN through numerous simultaneous and/or sequential pathways that begin with activation of the innate immune response and lead to autoimmunity. These pathways include immune dysregulation, adjuvant or bystander effects, epitope spreading, molecular mimicry, epitope conformational changes, and antigen complementarity that, in genetically susceptible individuals, result in the nephritogenic autoimmune responses that underlie GN. Infections may also have direct effects on glomerular cells. Rapid expansion in knowledge of the microbiome and its role in health and disease, as well as systems biology approaches to glomerular disease offer the potential to develop preventive approaches to GNs that can now be treated only with immunosuppression.

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Nearly 200 years ago, Richard Bright first described glomerular disease, diagnosing proteinuria in his patients by using a candle to heat urine on a spoon to determine whether it precipitated with heat.[1] Bright also first recognized the relationship of scarlatina (due to streptococcal infection) to subsequent glomerulonephritis (GN) in the 1800s. With the advent of immunopathology, studies of serum sickness models in rabbits by Germuth and Dixon provided seminal insights into the immune mechanisms that underlie most forms of (GN).[2,3] A relationship was demonstrated between the immune response to exogenous protein antigens, as would be presented by infectious agents, the appearance of immune complexes in the circulation, and the development of immune complex deposits in glomeruli that induced inflammation and replicated the clinical and pathologic features of acute and chronic GN in man.[2–4] This paradigm has stood the test of time with some modifications—i.e., the recognition that most immune complexes that cause tissue injury are likely formed *in situ*.[5]

Most studies over the subsequent 50 years have moved on with advances in biomedical science to focus primarily on defining the downstream mediators by which immune complexes induce tissue injury and the glomerular response to those mediators. What has emerged is a detailed understanding of the roles of the innate and adaptive immune responses in producing both the pathologic and clinical manifestations of GN.[5] Moreover, the factors that regulate risk for most types of GN in humans ('first hits') now appear to be genetically determined. However, with rare exceptions, the processes involved have proven to be primarily autoimmune in nature rather than serum sickness–like.[5,6] Despite a half century of research devoted to identifying 'nephritogenic' antigens, most of these studies in man have been negative or unconfirmed and little correlation has been found between circulating immune complex levels and clinical GN. Thus, little progress has actually been made over the past half century in elucidating the primary etiologic events that initiate most types of GN.

In this paper, we review currently available evidence to support the hypothesis that the etiology of most forms of GN are likely infections, and review how the immune response to infectious agents, modified by both genetic and epigenetic factors, could lead to the autoimmune processes that we

Table 1 | Most forms of primary GN exhibit features that support a role for autoimmunity in their pathogenesis

Disease	Autoimmune features	References
Post-streptococcal GN	Anti-C1q, IgG	40,70–74
	AECA, anti-DNA, ANCA, protein disulfide isomerase (PDI), cardiac myosin, C3Nef	
IgA nephropathy	Anti-glycan, endothelial cell, mesangial cell, IgG	83-84,86,88
Anti-GBM nephritis	Anti-GBM, ANCA (20%)	50,57,58,89
ANCA-positive GN	Anti-MPO, PR3, cPR3, NET, DNA, endothelial cell, LAMP2	35,92
Lupus nephritis	Anti-dsDNA, annexin, MPO, PR3, nucleosome, IgG, C1q, cardiolipin, MBL, NET	
MPGN I	Anti-C3Nef, C4Nef, C1q	116,119
MCD/FGS	None identified	
Membranous nephropathy	Anti-PLA2R, DNA, NEP, aldose reductase, SOD2	61,121,122
Dense deposit disease	C3Nef, C4Nef, anti-CFH, factor B, C1q	126,127
C3 nephropathy	C3Nef, anti-CFH	125–127

Abbreviations: AECA, anti-endothelial cell antibody; ANCA, antineutrophil cytoplasmic antibodies; C3Nef, C3 nephritic factor; CFH, complement factor H; dsDNA, double-stranded DNA; FGS, focal glomerular sclerosis; GN, glomerulonephritis; GBM, glomerular basement membrane; LAMP2, lysosome-associated membrane protein-2; MBL, mannose-binding lectin; MCD, minimal change disease; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PLA2R, phospholipase A2 receptor; PR3, proteinase 3; SOD, superoxide dismutase.

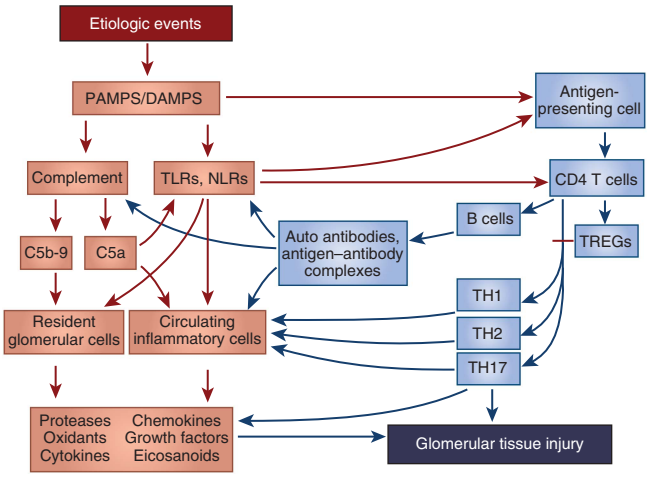

Figure 1 | Schematic overview of both the innate and adaptive immune mechanisms that mediate tissue injury in glomerulonephritis (GN). Etiologic events expose immunostimulatory pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) that activate both the innate (orange color) and the adaptive (antigen specific, blue) immune systems, which also interact with each other. Activation of the innate immune system occurs immediately, and involves Toll-like receptors (TLRs) or nod-like receptors (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, and 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. (Reprinted with permission from Couser.[5])

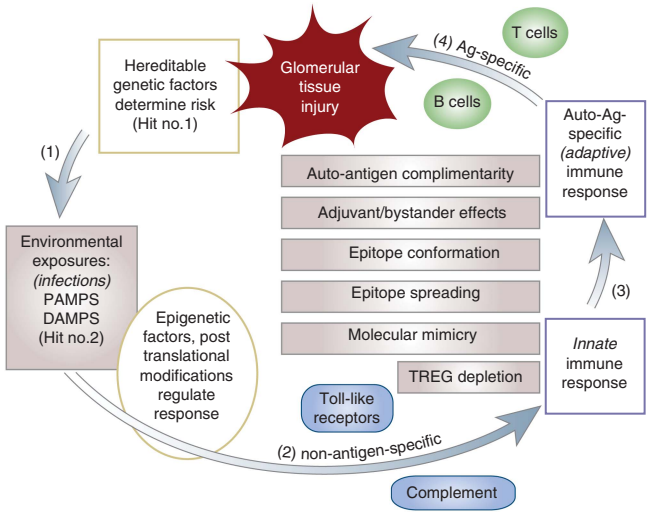

Figure 2 | Schematic overview of the mechanisms linking initial exposure to an infectious etiologic agent in a genetically susceptible individual to an autoimmune response and to glomerular tissue injury. (1) Hereditable risk factors predispose certain individuals to respond to environmental factors in ways that can lead to a nephritogenic autoimmune response (Hit#1). (2) Exposure to infectious etiologic agents in the environment occurs (Hit#2), which may be modified by epigenetic factors, and activates the innate immune system through interactions with TLRs and complement. (3) Conversion of a non-antigen-specific innate immune response to an antigen-specific adaptive immune response directed at specific autoantigens can occur through several pathways that may operate simultaneously and in concert. These include defects in regulation of existing natural autoimmunity, molecular mimicry, epitope spreading, epitope conformational changes, adjuvant/bystander effects, and autoantigen complementarity. (4) The adaptive immune response generates antigen-specific T and B cells, usually directed at antigens that are fixed or 'planted' in the glomerulus. These immune reactants, usually through inflammatory effector cells and/or complement, mediate tissue damage.

now know mediate GN (Table 1, Figures 1 and 2). We acknowledge that these observations are conceptual and do not meet strict criteria for causality.[7,8] However, a better understanding of the mechanisms and correlations between altered immune responses to environmental pathogens, particularly infectious agents, and initiation of the autoimmune processes that lead to GN could help guide the discovery of new biomarkers and stimulate more effective approaches to both prevention and therapy of renal disease.

HOW DO INFECTIONS INDUCE AUTOIMMUNITY?

Many chronic infections are known to be associated with the development of autoantibodies, including cryoglobulins (IgM antibodies directed against IgG), rheumatoid factors, antinuclear antibodies, and even antineutrophil cytoplasmic antibodies (ANCAs).[9–11] There are a number of factors that can promote the transition from an initial immune response to an exogenous agent into an autoimmune response (Figure 1). First, the infection needs to elicit an immune response. Although this can occur with local infection (such as skin or sinus), the likelihood increases if the antigens can gain access to the circulation. This may result from the properties of the infection itself, but may also be expected to occur more readily in the airways, if there is chronic irritation/inflammation (such as from smoking or hydrocarbon exposure), or in the intestines, if there is increased intestinal permeability (such as from gastrointestional inflammation or the excessive intake of fructose-containing sugars).[12]

The first line of defense is the innate immune response, mediated by neutrophils, monocyte/macrophages, natural killer cells, complement, and cytokines, which is triggered by the binding of pathogen-associated molecular patterns to germline-encoded receptors known as pattern recognition receptors[13,14] that include Toll-like receptors (TLRs) and C-type lectin receptors capable of complement activation through the mannose-binding lectin pathway.[13] The innate immune system acts by identifying pathogen-associated molecular patterns, which include bacterial carbohydrates and peptides, mannose, and lipopolysaccharide.

If the antigenic stimulus persists, the adaptive immune response follows, with the presentation of antigens to dendritic and other antigen-presenting cells leading to an orchestrated T- and B cell–mediated, antigen-specific immune response. Normally, the immune system is directed solely at the invading pathogen and autoimmunity does not occur as deletion of self-reactive T cells has largely occurred during thymic development (central tolerance). If self-reactive T and B cells escape into the circulation, other mechanisms are available to delete or suppress them and maintain tolerance to potentially nephritogenic antigens (peripheral tolerance). Loss of tolerance, when it occurs, relates to several factors, including the nature of the infectious agent and its antigens, genetic factors, the lack of ability of the innate immune system to eliminate the infection, and the nature of the target host antigen. The major mechanisms by which an initial immune response to an environmental pathogen can induce autoimmunity leading to GN are reviewed below.

Abnormalities of immune regulation

Abnormalities in the normal regulatory mechanisms that help prevent the development of autoimmunity[14] are believed by many to initiate clinical autoimmune disease in susceptible individuals.[14] Low levels of pathogenic autoantibodies may be present in asymptomatic individuals before the development of autoimmune disease.[15] Regulation and suppression of activation of these autoimmune phenomena is mediated largely by T regulatory cells (Tregs).[16] Control of Treg function is in part mediated by genetic polymorphisms in various genes, including *CTLA-4*, a molecule that is both expressed on Tregs as well as secreted by them, which blocks the costimulatory activation of T cells.[17,18] Other molecules such as dicer and sialyl acetyl esterase regulate B-cell development and peripheral tolerance, and epigenetic dysregulation of sialyl acetyl esterase has been demonstrated in 50% of patients with systemic lupus erythematosus (SLE).[19] In GN, evidence for impaired activity of Tregs has been shown in a number of diseases, including anti-glomerular basement membrane (GBM) disease,[20,21] SLE,[19,22,23] ANCA-associated vasculitis (AAV),[24,25] and minimal change disease.[26] Thus, defects in immune regulation may predispose certain individuals to both infection and autoimmunity.

Although defects in autoregulatory function may often have a genetic basis, there are well-established conditions in which infections can modulate the general immune response. For example, infection with the measles virus results in specific immunity to the measles virus, but is followed by a generalized immunosuppression driven by a viral-mediated increase in Treg cells.[27] One potential mechanism may be by the production of viral microRNA that can act to enhance or block host immune regulatory systems.[28]

Molecular mimicry

Molecular mimicry is a type of antigen-specific immune response that elicits autoimmunity. The most classic autoimmune reaction is generated when a pathogen has antigens that are similar enough in amino-acid sequence or structure to self-antigens that T cells or antibodies activated in response to the pathogen are also reactive with self.[29] This may occur even when only a small peptide sequence, or 'hot spot', shared between self and microbial antigens binds to the T-cell receptor.[30] A classic example is the finding that certain streptococcal M proteins elicit an antibody response that cross-reacts with cardiac myosin and may have a role in the development of rheumatic fever.[31,32] Examples related to GN also exist, including similarities between clostridial antigens and GBM resulting in anti-GBM antibodies,[33] some Staphylococci and Ross River virus with proteinase 3 (PR3) leading to ANCAs,[34] fimbriated *Escherichia coli* antigens that cross-react with human lysosome–associated membrane protein-2 in endothelial cells, neutrophils in AAV,[35] viral nucleoproteins and lupus autoantigens,[36–38] Tn antigens (which contain *N*-acetylgalactosamine glycans) and underglycosylated IgA_1 in IgA nephropathy (IgAN),[39] and streptococcal pyogenic exotoxin B and a cross-reacting antigen expressed on endothelial cells in post-streptococcal GN.[40]

Generalized activation of preexisting autoreactive T and B cells (adjuvant or bystander effects)

Infections may stimulate autoimmune reactions nonspecifically. For example, some bacteria and viruses express

superantigens that do not require internalization and processing by antigen-presenting cells, but rather can directly engage T cells that express particular T-cell receptor V_β chains. Superantigen stimulation can induce polyclonal IgG stimulation and nonspecific T-cell activation that results in the generation of autoantibodies and T cells with reactivity to self-antigens.[41,42]

Another way in which antigens and superantigens can elicit disease manifestations caused by autoimmunity is to expand a preexisting population of autoreactive T cells that are normally present in numbers too small to cause disease.[15,16,21] Biomarkers for immunity to self-antigens are known to be present in several glomerular diseases long before clinical manifestations occur, including SLE, AAV, and anti-GBM disease.[15,16]

Local injury with death of the infecting organism or 'bystander' cells can also result in the release of proteins, uric acid, or DNA, which can act as an adjuvant to stimulate activation of immune cells.[43] The known ability of *Staphylococcus aureus* infection to trigger flares of AAV may relate to this adjuvant, or bystander effect,[44] owing to the release of CpG motifs in the bacterial DNA[45] or possibly the presence of superantigens, which are common in this particular bacteria. The extracellular release of nucleic acids and double-stranded DNA may also be important in the initiation and enhancement of the antinuclear antibody response in SLE.[16,19,23,46,47] Indeed, infections with viruses such as polyoma virus can result in marked stimulation of antinuclear antibodies in NZB/W mice, likely via the release of DNA and nucleic acids that stimulate autoimmune responses.[48]

Epitope conformational changes

Epitope conformation refers to another process in which local injury leads to a change in the conformation of a protein that results in the exposure of previously hidden components that can then become the target of an autoimmune response. The oxidative stress induced by smoking, for example, has been reported to alter the conformation of the noncollagenous region of the αIII chain of type IV collagen in the alveoli, thereby exposing cryptic Ea and Eb antigens that may be seen as foreign, thus initiating an autoimmune response and facilitating binding of anti-GBM antibody.[49,50] The ability of infections to unmask sequestered antigens in GN is best understood in the hemolytic uremic-like syndrome observed with pneumococcal pneumonia. In this condition, neuraminidase A that is produced by the Pneumococcus cleaves *N*-acetylneuraminic acid (a sialic acid) from the cell surface of red blood cells and glomeruli, resulting in the exposure of the Thomsen–Friedenreich antigen, a glycan to which natural antibodies are normally present. This results in a hemolytic uremic syndrome often with prominent renal failure.[51]

A closely related mechanism may involve antigen modification. For example, there has also been interest in a potentially causal role for an anaerobic bacteria, *Porphyromonas gingivalis*, in some cases of rheumatoid arthritis.[52] *P. gingivalis* carries an enzyme (peptidylarginine deiminase), which citrullinates proteins that may lead to neoepitopes that increase the risk for the development of autoantibodies present in rheumatoid arthritis.[52,53]

Epitope spreading

Epitope spreading is another mechanism for inducing autoimmune responses and is well established in both experimental and human GN.[54,55] In this situation, an initially very specific immune response broadens to include responses to a different epitope on the same protein (intramolecular spreading) or on different proteins (intermolecular spreading). For example, in the anti-GBM disease, glomerular eluates contain an antibody that is reactive not only with the primary autoimmune target (a 13 amino-acid fragment of the NC1 domain of the α3 chain of type IV collagen)[50,56,57] but also with epitopes on the αV chain.[50] Circulating anti-GBM antibodies in patients with nephritis show reactivity with epitopes of all five chains of type IV collagen, and this expansion of anti-GBM reactivity increases with disease severity, suggesting spreading of reactivity with worsening disease.[58,59] In the Heymann models of membranous nephropathy (MN) in rats, intramolecular B-cell epitope spreading has been documented by inducing disease through immunization with one nephritogenic megalin epitope and by demonstrating antibodies to three additional recombinant epitopes 8 weeks later that correlated with increased severity of disease.[60] Epitope spreading may also occur in primary MN in man as some glomerular eluates contain not only antibodies to the primary target antigen, phospholipase A2 receptor (PLA2R), but also to other podocyte antigens.[61]

Antigen and antibody complementarity

Autoimmunity can also be induced by the development of antibodies to the antigen-binding region (idiotype) or Fc portion of an antibody, resulting in the development of anti-idiotypic antibodies and anti-Fc antibodies, such as the IgM cryoglobulins/rheumatoid factors. The latter are especially common with chronic bacterial infections such as subacute endocarditis. In addition, nonpathogenic autoantibodies can also develop to complementary peptides of target antigens, such as to PR3 (one of the target antigens in AAV), followed by the development of pathogenic anti-idiotypic antibodies that are reactive with the native self-protein.[62] In this scenario, an infectious agent such as the Ross River virus might induce an antibody response to shared epitopes of the complementary peptide of PR3. Although this initial antibody is not pathogenic, it leads to production of a pathogenic anti-idiotypic antibody that recognizes native PR3.[34]

HUMAN GLOMERULAR DISEASES: INFECTION AND AUTOIMMUNITY

Infections are well-established mechanisms for inducing autoimmunity.[54,63,64] Humans inherit about 20,500 genes, a number dwarfed by the one million genes expressed by the microbes within us, and 90% of the genes in our bodies are of

microbial origin.[16] It is known, for example, that a single microbial species can induce autoimmunity and that elements of the microbiome can drive autoimmune arthritis and type I diabetes.[65,66] Increasing recognition of the role of the innate immune system, the first line of defense against invading infectious agents, in several forms of GN also adds evidence for an etiologic role of infectious agents.[67] Thus, in any quest to identify etiologic agents in GN, it is tempting to postulate that infections are likely the most common. What follows summarizes current evidence to support this hypothesis in humans GNs.

ANTIBODY-ASSOCIATED GN

Post-infectious GN

Post-infectious GN (PSGN) is currently thought to be caused by infection with certain group A Streptococci that contain streptococcal pyogenic exotoxin B, which circulates and binds to glomeruli, initiating activation of the alternative pathway of complement through the mannose-binding lectin pathway and inducing an antibody response.[68,69] Autoimmune manifestations are common in PSGN, and may include IgG anti-IgM rheumatoid factors, ANCA, anti-DNA, anti-C1q, and the C3 nephritic factor (C3Nef), an autoantibody to the active site on the alternative pathway C3 convertase.[70–72] Pyogenic exotoxin B also exhibits molecular mimicry with endothelial cells, although the biologic significance of this is unclear.[73] Although the role of autoimmunity in mediating this usually self-limited illness remains uncertain,[68] the only antibody identified to date in glomerular eluates in PSGN is IgG rheumatoid factor.[74]

However, a variant of a PSGN-like syndrome has recently been recognized following upper respiratory tract infection in which patients display hypocomplementemia with the typical diffuse proliferative lesion, including subepithelial 'humps', but show an unusually prolonged clinical course.[75] Many of these patients have abnormalities in complement regulatory protein (CRegP) function, with some due to autoantibodies, particularly C3Nefs,[75] which are believed to account for the GNs referred to as 'C3 nephropathies'. The role of such post-infectious, autoantibody-induced CRegP dysfunction in the pathogenesis of this and other forms of GN is only now being investigated (see C3 nephropathy below).

IgA nephropathy

IgAN and its systemic variant, Henoch–Schönlein purpura, result from the formation of circulating, underglycosylated IgA_1 aggregates that are poorly cleared and preferentially localize in the glomerular mesangium.[76–78] A genetic predisposition has been linked with polymorphisms involving innate and adaptive immunity and the alternative complement pathway.[78] However, many people, especially first- and second-degree relatives of IgAN patients, exhibit these abnormalities in IgA_1 glycosylation without disease, and it remains unclear what constitutes the 'second hit' that leads to glomerular inflammation.

Infections may have a role as the second hit, especially as upper respiratory and gastrointestinal infections are known to induce immediate (synpharyngitic) episodes of hematuria.[76,79] Viral antigens derived from human hepatitis B virus, cytomegalovirus, Epstein–Barr virus (EBV), herpes simplex virus 1 or 2, and adenoviruses have all been detected in the mesangial deposits of a few IgAN patients, but not consistently, and a role for circulating complex trapping involving exogenous antigens seems unlikely.[76,79] Connections between celiac disease and other autoimmune inflammatory diseases of the small bowel (in which molecular mimicry with bacterial pathogens results in an immune response to GI mucosa in patients with anti-gliadin antibodies) and IgAN have been reported,[76,80] and there appears to be an increased prevalence of infection with *Helicobacter pylori*, as well as antibodies to it, in IgAN and Henoch–Schönlein purpura.[81,82]

Additional evidence for the role of infection in the pathogenesis of IgAN includes genetic links to single nucleotide polymorphisms in *DEFA* genes that encode for α-defensins—neutrophil proteins that protect from infections—and in the *THSF13* gene that encodes for APRIL—a tumor necrosis factor ligand involved in the response to mucosal infections and in the production of IgA in gut-associated mucosal lymphoid tissue.[78] Some bacteria can stimulate intestinal dendritic cells to produce polymeric IgA and induce mesangial deposits of IgA.[79] Bacterial lipopolysaccharide (endotoxin) is a TLR4 natural ligand that also reduces the activity of galactosyltransferase due to methylation of its chaperone Cosmc, suggesting another possible role of infections in the defective glycosylation that later leads to autoimmunity.[83]

Of particular interest with regard to an infectious etiology for IgAN is the finding of IgG anti-glycan autoantibodies reactive with the hinge region of abnormally glycosylated IgA_1, which correlate with clinical manifestations[83,84] and progression[85] of the disease. These IgG anti-glycan antibodies also recognize other poorly glycosylated proteins, particularly the ubiquitous Tn antigen,[86] which is expressed by many bacterial pathogens.[87] In turn, antibodies to Tn may also be expected to bind the polymeric IgA1, as the underglycosylated hinge region has components antigenically identical to Tn.[86,88]

Thus, one might postulate that an infection with a pathogen expressing the Tn antigen may induce, in genetically predisposed individuals, elevated levels of circulating (and perhaps mesangial) underglycosylated IgA_1. IgG antibodies directed to the Tn antigen may then react with the underglycosylated IgA_1 via molecular mimicry, generating both circulating and *in situ*–formed immune complexes of IgA_1 and IgG that localize in the mesangium. Such deposits would injure mesangial cells through direct interaction with mesangial TLRs and other receptors, and also activate complement through the mannose-binding lectin pathway leading to C5b-9 formation, thus producing the clinical and pathologic manifestations of IgAN.[5]

Anti-GBM disease

The pathogenesis of anti-GBM nephritis is known to be due to T-cell- and antibody-mediated reactivity to a 13 amino-acid peptide in the α3 chain of type IV collagen, and is associated with expression of certain *HLA-DR* genes.[50,57,58,89] Consistent with other autoimmune diseases, existence of anti-GBM antibody in normal individuals is well established.[90] Defects in immune regulation are also described.[21] Initial reports of the disease,[91] and considerable clinical experience since then, suggest a possible association with preceding viral infections such as influenza, although this has not been definitively established. An interesting observation is that the nephritogenic T-cell epitope ($pCOL_{28–40}$) is very similar to seven bacterial peptides derived from a GenBank search. Three of these bacterial peptides could induce crescentic anti-GBM nephritis, the most potent one derived from *Clostridia botulinum*,[33] providing proof of principle and a plausible link to preceding infection as a triggering etiologic event, in at least some patients.

AAV with GN

AAV is thought to be mediated by activation of neutrophils in the microvasculature in glomeruli and other organs by autoantibodies to different neutrophil enzymes (myeloperoxidase and PR3) or to human lysosome–associated membrane protein-2 present in the vascular endothelium and neutrophils.[35,92] Neutrophil extracellular traps are also formed as a consequence of neutrophil–platelet interactions, and contain entrapped myeloperoxidase, PR3, and myeloperoxidase DNA in a chromatin web. Neutrophil extracellular traps can mediate injury directly through TLRs as well as modulate the immune response.[93] In AAV, neutrophil extracellular traps are present in the circulation and in glomeruli colocalized with neutrophils and dendritic cells, and anti-neutrophil extracellular trap antibodies are present along with circulating myeloperoxidase–DNA complexes (nucleosomes). Depending on which TLR is activated, Th1 (TLR 9) or Th17 (TLR 2) autoreactive T cells may be generated.[94] As in most autoimmune diseases, there is also evidence for both preexisting autoimmunity in the form of ANCA antibodies, defects in immune regulation, and genetic predisposition.[24] Infections, including sinusitis and upper respiratory tract infections, are common with the initial clinical presentation. Indeed, the original report of this disease described patients with likely acute Ross River virus infection.[95–97] ANCA-positive serology has been reported in many infections including suppurative lung disease, subacute bacterial endocarditis, and infections with *Pseudomonas*, *Klebsiella*, *E. coli,* and Ross River virus.[98] The connection between a *S. aureus* infection or carrier state and a relapse in PR3-associated AAV (relative risk 7.2) are well established.[99]

Several autoimmune mechanisms may be operative. Molecular mimicry has been demonstrated between PR3 and Staphylococci,[98] and between FimH-expressing uropathogenic *Klebsiella* or *E. coli* and human lysosome–associated membrane protein-2.[35,100] In the example of *S. aureus* and PR3, antigen complementarity can lead to development of an anti-idiotypic antibody with reactivity to cPR3, which is present in some 30–40% of AAV patients.[35] Epigenetic upregulation of ANCA autoantigen-encoding genes by environmental stimuli including infection has also been described,[101] as has a markedly enhanced nephritogenic effect of influenza virus infection (in mice).[102]

Lupus nephritis

SLE remains the prototypical systemic autoimmune disease, and the mechanisms that may connect infections, primarily viral, to the etiology of the disease are well defined, although the specific viruses have not been identified.[103,104] As in other autoimmune diseases, preexisting subclinical immunity to nuclear antigens[105]and defects in immune regulation are well documented.[19,23,104,106] Multiple genes have been incriminated as risk factors, particularly ones that normally assure low levels of DNA or nucleotides in extracellular compartments through opsonization of dead cells, or apoptosis, and genes coding for components of the classical complement pathway.[104,106,107]

There is a remarkable similarity between the immune environment in SLE and that stimulated by viral infections, which initiate type I interferon (IFN-α) or IFN-γ.[16,38,103,108] In brief, many viruses can induce an immune response by the release of viral ribonucleoprotein and U1 small ribonucleoprotein, which is similar to that observed in SLE.[19,23] These ligands bind TLRs, particularly TLR3, TLR7, and TLR9, to activate the innate immune system and induce type I IFN release by plasmacytoid dendritic cells.[104,108] Uridine-rich endogenous mammalian RNA sequences can also activate autoreactive B cells through TLRs.[109] Activation of the type I IFN pathway results in a 'signature' of specific gene expression that is observed with both viral infections and SLE.[19,23,106,107] Indeed, IFN-α has been shown to be essential for development of SLE in both spontaneous and induced animal models.[106,107]

Of the potential viral etiologies that may trigger the disease, the best studied is the EBV.[110,111] This virus infects B cells via binding of its viral envelope glycoprotein 350 to the B-cell type 2 complement receptor and remains latent for the life of the individual.[38] About 99.5% of lupus patients have serologic evidence of prior EBV infection compared with 95% of controls, a highly significant difference with an odds ratio of 9.5, and they also have a 10-fold increase in EBV-infected B cells.[110] The titer of anti-EBV antibodies is also higher in SLE, and the EBV viral load is 10–100 times higher than that in controls.[110,111] There is also evidence of impaired T-cell reactivity to EBV viral proteins.[110,111] Biomarkers of latent EBV activation correlate with exacerbations of SLE.[111] With regard to a mechanism for the association, EBV nuclear antigens (EBVNA1) exhibit molecular mimicry with Sm and Ro protein epitopes, and immunization with these epitopes produces a lupus-like disease in mice.[108] Although none of these observations alone establish causality, together they provide strong support for the hypothesis that SLE may be

triggered by specific viral infections occurring in certain genetically susceptible individuals.

Membranoproliferative GN (type I)

The relationship between hepatitis C viral (HCV) infection and adult type I MPGN has become well established since we first described it two decades ago.[112] Classic immune complex formation mechanisms involving HCV antigen and anti-HCV antibody, probably in the form of cryoglobulins/rheumatoid factors, have been invoked to explain the extensive subendothelial and mesangial immune complex deposits that induce complement-mediated inflammation. In addition to producing immune deposits, the globular domain of C1q protein and viral core proteins activate the innate immune system through TLRs on B cells to stimulate clonal B-cell expansion and production of IgG anti-IgM rheumatoid factors.[113–115] A similar pattern of immune glomerular injury is seen in several other chronic infectious processes.[116]

A link between HCV infection and autoimmune phenomena is well established in viral hepatitis.[113] It involves pathways similar to those described above for EBV virus and SLE, including strong activation of the innate immune system through TLRs, a viral gene signature pattern, B-cell clonal expansion, and defects in the complement system.[117,118] In fact, in both clinical and renal pathologic manifestations, SLE and type I MPGN have much in common. In MPGN I, both IgM and IgG rheumatoid factors (type II cryoglobulins) are present in 70–80% of patients, C3Nefs are seen in 20–30% of patients, and antiendothelial cell antibodies have been reported as well, thus documenting the existence of autoimmunity in HCV-associated MPGNI.[116,119] Whether these autoimmune phenomena are of pathogenetic relevance compared with antiviral immune responses is unclear. However, recent descriptions of patients presenting with MPGN I who then develop hemolytic uremic syndrome with autoantibody-induced CRegP dysfunction suggest that at least C3Nef can have a pathogenic role in some patients.[120]

Membranous nephropathy

Long considered a prototype of chronic serum sickness induced with a foreign protein antigen, primary MN has now been shown to be an autoimmune disease induced by glomerular deposition of IgG_4 antibodies to a podocyte membrane protein, PLA2R.[121,122] Genome-wide association studies have shown strong linkage between primary MN and HLA DR, as well as single nucleotide polymorphisms in *PLA2R* genes, confirming both an autoimmune pathogenesis and a role for PLA2R in regulating the development of autoimmunity in MN.[123]

Many secondary forms of MN are well established to be induced by infections, especially hepatitis B virus and HCV, and are anti-PLA2R negative.[121,124] Among the secondary forms of MN, only the class V membranous lesion associated with lupus has been documented to have an autoimmune pathogenesis.[5,19,23] To date, no evidence has emerged to suggest an infectious etiology for primary, PLA2R-positive, MN.

NON-ANTIBODY-MEDIATED GLOMERULAR DISEASES

C3 nephropathies

C3 nephropathies refer to a type of GN in which C3 deposition without immunoglobulin characterizes the renal biopsy and in which the cause appears to be dysfunction of CRegPs that leads to persistent activation of the alternative pathway of complement, resulting in clinical and pathologic features of GN.[125–127] C3 nephropathies include dense deposit disease, C3 deposition glomerulopathy, and CFHR5 nephropathy and their variants.[125–127] Although some of these involve hereditary defects in CRegP structure and function, others reflect epigenetic dysregulation of these proteins owing to autoantibody formation.[125–127] The best example is dense deposit disease in which 80% of patients have an IgG autoantibody, C3Nef, which prevents regulation of the alternative pathway C3 convertase by complement factor H, leading to persistent C3 activation, deposition of alternative pathway activation products in glomeruli, and chronic GN.[126–127]

Earlier literature on what was previously termed MPGN type II is replete with reports of onset of clinical disease following infectious episodes.[128] As in other autoimmune GNs, C3Nef autoantibodies have been reported in normal individuals in whom acquired defects in immune regulation could initiate disease.[129] Recent studies have now shown that some patients with 'atypical PSGN' demonstrate dysregulation of the complement system and a prolonged clinical course owing to the presence of C3 and C5 nephritic factors, consistent with the hypothesis that infection-induced autoimmunity resulted in chronic, progressive GN (see PSGN above). GNs related to these mechanisms also predispose patients to thrombotic microangiopathies, many of which are also infection-induced autoimmune disorders of complement regulation.[120] Indeed, there is substantial pathogenetic overlap between MPGN I, with or without HCV infection, dense deposit disease, and thrombotic microangiopathies, with all three involving infection as an initiating event, autoimmunity, and complement alternative pathway dysregulation.

CONCLUSIONS

Despite major advances in understanding the genetic predispositions, the autoimmune responses, and the mediators of tissue injury in immunologically mediated GN, there remains a remarkable dearth of knowledge about the etiologic events, or 'second hits', which actually trigger the onset of these diseases. Current evidence suggests that infections may initiate many of the autoimmune or other reactions in genetically susceptible individuals, which lead to glomerular disease through numerous simultaneous and/or sequential pathways that begin with activation of the innate immune response. These pathways vary depending on the nature of the infectious pathogen and the genetically regulated

immune response of the host. These mechanisms include immune dysregulation, adjuvant or bystander effects, epitope spreading, molecular mimicry, epitope conformational changes, and antigen complementarity. Infections may also have direct effects on podocytes and other glomerular cells, either due to direct infection or the induction of innate immune responses.

Continued efforts are essential to clarify the genetic basis for susceptibility to GN, as are efforts to improve therapy with new agents directed against the immune response and the myriad mediators it activates in the glomerulus. However, most therapeutic initiatives continue to target downstream events rather than causes. New technologies involving systems biology approaches and the rapidly expanding understanding of the diverse roles of the human microbiome in health and disease are now scientifically feasible and clinically necessary if we are to supplement the existing information reviewed here to further define the infectious triggers of GN. Achieving this goal will allow approaches toward prevention to be added to our currently inadequate therapeutic armamentarium.

DISCLOSURE

All the authors declared no competing interests.

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