REVIEW

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Experimental anti-GBM nephritis as an analytical tool for studying spontaneous lupus nephritis

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease that results in immune-mediated damage to multiple organs. Among these, kidney involvement is the most common and fatal. Spontaneous lupus nephritis (SLN) in mouse models has provided valuable insights into the underlying mechanisms of human lupus nephritis. However, SLN in mouse models takes 6–12 months to manifest; hence there is clearly the need for a mouse model that can be used to unveil the pathogenic processes that lead to immune nephritis over a shorter time frame. In this article more than 25 different molecules are reviewed that have been studied both in the anti-glomerular basement membrane (anti-GBM) model and in SLN and it was found that these molecules influence both diseases in a parallel fashion, suggesting that the two disease settings share common molecular mechanisms. Based on these observations, the authors believe the experimental anti-GBM disease model might be one of the best tools currently available for uncovering the downstream molecular mechanisms leading to SLN.

Key words: autoantibodies, mouse models, SLE, therapy, glomerular disease.

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ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE

Anti-glomerular basement membrane (anti-GBM) antibody disease is a well-studied cause of glomerulonephritis, characterized by the presence of anti-GBM antibodies (Abs) directed at specific antigenic targets within the glomerular and/or pulmonary basement membranes. This condition is also known as "Goodpasture's disease" or "Goodpasture's syndrome", named after the American pathologist who first described this clinical constellation of phenotypes in 1919 [36, 107]. However, the presence of anti-GBM antibodies in this disease was documented much later, in the 1960s, following the application of immunofluorescence microscopy to renal biopsies [27, 101]. In 1967, Lerner et al. [63] transferred antibodies eluted from the kidneys of patients with Goodpasture's disease to squirrel monkeys, which subsequently developed proliferative glomerulonephritis, demonstrating that the anti-GBM antibody was the central pathogenic mediator of this disease. Later, the antigenic epitopes recognized by anti-GBM antibodies were identified by successive studies [10, 16, 30, 125–127]. It is now appreciated that the NC1 domain of α3(IV) collagen is the main autoantigen recognized by the anti-GBM antibody [15,100]. The capacity of anti-GBM antibodies to bind to the recombinant α3(IV) NC1 domain was further confirmed by several *in vitro* studies [23, 76, 77, 120].

Anti-GBM nephritis (GBN) can be induced in various species by two different methods [89]. In experimental autoimmune glomerulonephritis, animals immunized with type IV collagen subsequently develop an autoimmune response that targets their own kidneys. In nephrotoxic nephritis, animals are injected with heterologous anti-GBM antibodies and the animal then initiate their own immune response to the foreign (i.e. xenogenic) antibodies. Among the various species studied, the Wistar-Kyoto (WKY) strain of rats is widely used as an experimental model of the human disease due to their sensitivity to experimental GBN. This model shares clinical features with human anti-GBM disease, including proteinuria, hematuria, and linear deposition of IgG along the GBM, with or without pulmonary hemorrhage [9, 32, 99]. Over the past decade, different mouse strains have also been used as an exper-

imental model for anti-GBM disease. Our previous work documented that the NZW, DBA/1, 129/sv, BuB/Bn, and C58 were the most susceptible mouse strains in terms of their sensitivity to GBN [130–132].

SHARED FEATURES BETWEEN EXPERIMENTAL ANTI-GBM NEPHRITIS AND SPONTANEOUS LUPUS NEPHRITIS

GBN and spontaneous lupus nephritis (SLN) share several features, as summarized in Table 1. Anti-GBM antibody is the key pathogenic mediator in GBN. In SLN, ANA, anti-dsDNA, anti-glomerular, and other autoantibodies play important roles in disease pathogenesis [61, 91, 110, 123]. Immune complex deposition can be seen in both diseases; however, its pathogenic role may differ. In GBN, immune complex deposition plays a secondary or negligible role, whereas it contributes to disease pathogenesis in SLN. Direct binding of anti-glomerular antibodies to glomerular antigens also contributes to disease development in both disease scenarios, especially in the GBN model.

Widespread crescent formation, with all glomeruli showing lesions of similar severity, is an important characteristic of GBN. On the other hand, the pathological changes in the glomeruli and tubulointerstitium are variable in SLN, with or without crescent formation, depending on the genetic background. Immunofluorescence analysis reveals linear deposits of IgG along the GBM in GBN, often accompanied by complement C3 deposits. In SLN, the typical immunoglobulin deposits consist of IgG, IgM, as well as IgA granular deposits in the mesangium, accompanied by complement deposition. Electron microscopy shows diffuse and irregular thickening of the GBM in GBN. In SLN, immune complexes are found typically deposited in the subendothelial, mesangial, and subepithelial regions. In both diseases settings, T cell and myeloid cell infiltration in the glomeruli and the tubulointerstitium can also be discerned.

THE ROLE OF T CELL IMMUNITY IN BOTH DISEASE MODELS

Besides their well-documented role in peripheral immune system, intra-renal T cells play at least two major pathogenic roles in the initiation and development of renal injury in both disease settings. One is through the overproduction of pro-inflammatory cytokines and the other is through increased cell-to-cell contact with other cells, ultimately leading to tissue injury [114]. T cell infiltration in the glomeruli and the tubulointerstitium is among the most common pathological changes seen in both GBN and SLN [26, 64, 81]. These glomerular infiltrating T cells appear to be autoactivated, as revealed by their capacity to induce intrinsic renal-cell proliferation [26], and to produce various cytokines, such as interleukin (IL)-12 and interferon (IFN)-γ [24, 26, 35, 64, 71].

The role of $CD4^+$ and $CD8^+$ T cells in glomerular injury and crescent formation in GBN has been elucidated using genetic tools such as $CD4^-$, $CD8^-$, or combined CD4/CD8-deficient mice [118]. Blocking helper T cells by anti-CD4 antibodies can also attenuate or prevent GBN [95]. Most interestingly, anti-CD8 therapy in GBN did not affect circulating antibodies, but improved glomerulonephritis [49, 94]. In SLN, CD4 knockout mice subjected to lupus-like graft-versus-host disease did not exhibit autoantibodies or nephritis [18]. Survival and glomerulonephritis were improved in (NZW×BXSB) F1 mice treated with anti-CD4 Abs and in graft-versus-host lupus mice treated with anti-T cell receptor Abs [1, 68]. These parallel findings implicate a very similar role for T cells in both GBN and SLN.

Two signals are necessary for productive T cell stimulation. One is the "synapse" between the T cell receptor and the major histocompatibility complex class II peptide complex on an antigen-presenting cell (APC), while the other mediates the costimulation provided by the APC. Therefore, genetic models lacking MHC or costimulatory molecules or the blockade of costimulatory pathways using antibodies can potentially provide clues concerning the pathogenic role of T cells in disease settings. Of relevance, mice lacking T cell receptors [47], CD28 [80], ICAM-1 [44], and MHC II [65] exhibited less disease when subjected to GBN. In MRL/*lpr* mice, a lupus-prone model, genetic absence of CD28 [83, 112], ICAM-1 [14], LFA-1 [50], MHC-1/MHC-II [45, 73], as well as both CD80 and CD86 [51] were all associated with reduction in most features of SLN. Blocking the costimulatory interaction of CD28/B7 [21, 29, 74, 79, 96], CD40/CD40L [72, 88, 93], and ICAM-1/LFA1 [59, 78] molecules can also alleviate the severity of GBN and SLN. The concordant results obtained in SLN and GBN involving these costimulatory pathways suggest that both disease settings share common T cell-mediated disease mechanisms.

Finally, in GBN a $CD4^+$ T cell-mediated mechanism has been implicated not only in initial glomerular injury, but also in triggering an anti-GBM antibody response to diverse GBM antigens [67, 128, 129]. In SLN, two congenic strains, NZM.C57Lc4 [124] and mIgM.MRL [17], characterized by the absence of circulating ANA, anti-dsDNA, and anti-nucleosome Ab, still developed lupus nephritis, implicating the potential role of T cells rather than antibodies in the pathogenesis of SLN.

GBN AND SLN SHARE COMMON MOLECULAR MEDIATORS IN PATHOGENESIS

Table 1 and Fig. 1 summarize the currently known molecular mediators which have been shown to play essential or important roles in both GBN and SLN. These molecules include cytokines, chemokines, adhesion molecules, as well as surface receptors. Only mole-

Table 1. Features and mediators affecting both anti-GBM nephritis and spontaneous lupus nephritis

	Anti-GBM nephritis	Spontaneous lupus nephritis
Inciting antibody	anti-GBM antibody	anti-nuclear/glomerular Ab
Autoantigen	α3(IV) NC1	chromatin/dsDNA/histone
Immune deposits		
direct Ig binding	yes	yes
IC deposition	minimal	yes
complement deposits	yes	yes
isotype of Ab	IgG	IgG, IgM, IgA
nature of deposits	linear	granular
site of deposits	GBM	GBM, mesangium
Renal pathology		
glomerular changes	variable[1]	variable[1]
tubulointerstitial changes	variable	variable
infiltrating cells	neutrophils, T cells, macrophages	neutrophils, T cells, macrophages
vascular changes	minimal	variable
Clinical spectrum		
urine analysis	proteinuria/hematuria	proteinuria/hematuria
renal function deterioration	rapidly progressive	variable
extra-renal manifestations	lung	multiple systems (skin, brain, joints)
Molecules affecting both diseases		
Complement		
C3/C4	pathogenic [41, 105]	ND
C5	pathogenic [42]	pathogenic [6]
Surface receptors		
FcR	pathogenic [85, 109]	pathogenic [19]
TLR2	pathogenic [13, 31]	ND
TLR3	pathogenic [31]	pathogenic [86]
TLR9	pathogenic [2]	pathogenic [3, 87]
Co-stimulatory molecules		
MHC I	pathogenic [73]	ND
MHC II	pathogenic [45]	pathogenic [66]
B7:CD28/CTLA4	pathogenic [79, 96]	pathogenic [22, 43, 51, 102]
CD40L	pathogenic [93]	pathogenic [46, 72]
Adhesion molecules		
ICAM-1/LFA-1	pathogenic [44, 78]	pathogenic [14, 50]
P-selectin	modulator [25, 69, 82]	protective [40]
Cytokines		
TNF-α	pathogenic [38, 48, 60]	pathogenic [12, 70]
IL-1	pathogenic [38, 115]	pathogenic [72, 108]
IL-6	pathogenic [38]	pathogenic [66]
IL-12	pathogenic [56, 117]	pathogenic [103]
IL-18	pathogenic [56, 58]	pathogenic [52]
CSF-1	pathogenic [52, 121]	pathogenic [62]
IFN-γ	modulator [37, 54, 57]	protective [104]
PDGF	pathogenic [84]	pathogenic [98]
Chemokines		
MCP-1	pathogenic [116]	pathogenic [106]
Others		
NO	pathogenic [11, 7]	pathogenic [92]

[1] Phenotype depends on the genetic background. ND – not done.

cules and studies that satisfied the following criteria were included in this table: 1) the molecule under investigation has been tested in both disease settings and 2) after augmenting or negating the effect of the molecule under investigation, the degree of nephritis was specially examined in either the GBN or the SLN disease setting.

Early complement proteins can clear immune complexes and apoptotic bodies, and their absence predisposes individuals to systemic lupus erythematosus (SLE). On the other hand, the activation of terminal complement components can lead to exacerbation of disease and damage to tissues and organs, in both GBN and SLN [28, 97]. Proteinuria and polymorphonuclear infiltration were significantly reduced in GBN in mice that were complement C3 or C4 deficient [41], although their roles were more complicated than expected [105]. Blocking complement activation in GBN following injection of Crry-Ig substantially diminished renal injury

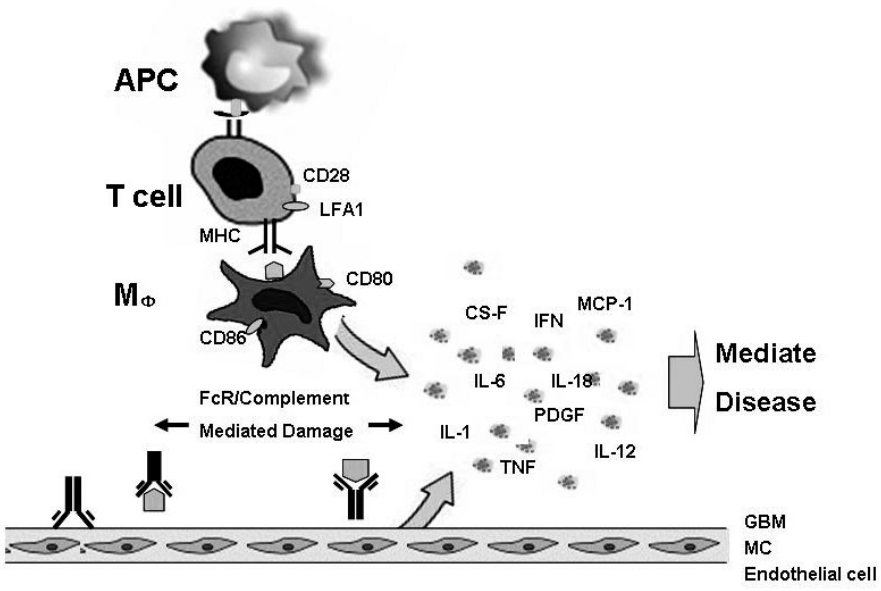

Fig. 1. T cell-mediated mechanisms and molecular mediators in the pathogenesis of GBN and SLN. FcR- and complement-mediated activation of intrarenal leukocytes and resident renal cells by deposited autoantibodies and immune complexes, together with T cell:macrophage and T cell:renal-cell interactions are envisioned to generate a large number of mediators in both GBN and SLN, as listed in the figure. Hence, nephritis in both disease scenarios appears to be dependent upon FcR, complement, various co-stimulatory molecules (e.g. CD80, CD28), as well as the released mediators shown, as detailed in Table 1.

[90]. Similarly, Crry-Ig treatment has been demonstrated to prevent MRL/*lpr* mice from developing proteinuria and renal failure, with less glomerulosclerosis and extracellular matrix component deposition [7]. Therefore, complement-mediated injury is instrumental in disease pathogenesis in both GBN and SLN. Like complement, the FcR serves an important role in antibody-triggered and IC-mediated inflammation [20, 39, 111, 113]. FcR-deficient mice subjected to GBN survived longer and the renal tissue was almost disease--free, whereas the wild-type controls died from nephritis with severe glomerular hypercellularity and thrombotic changes, although anti-GBM antibody and complement deposition were equally intense in both wild-type and knockout mice [85, 109]. Likewise, FcR-deficient NZB/NZW mice were protected from severe nephritis although they exhibited IC deposits and complement activation [19]. Taken together, Ab-directed complement activation and FcR-mediated injury appear to be necessary in both GBN and SLN.

Several cytokines have also been suggested to be involved in the pathogenesis of both diseases. Tumor necrosis factor (TNF), a pro-inflammatory cytokine, serves an important role in the recruitment of inflammatory cells and the subsequent development of proliferative GN [60]. In GBN, acute glomerular inflammation and crescent formation was decreased by blocking endogenous TNF-α [48], while TNF ablation prevented the development of proteinuria [60]. In SLN, administering rTNF-α worsened renal disease and mortality [12], with early up-regulation of adhesion molecules such as ICAM-1 and VCAM-1 [70].

IL-1, another pro-inflammatory cytokine, plays an important role in multiple inflammatory diseases. The severity of proteinuria and renal injury were reduced in SLN mice treated with IL-1 receptor antagonist [108], and similar findings were observed in mice with GBN as well [115]. IL-6 is one of the key factors in B cell differentiation, as well as Ab and acute-phase protein production. It is also a well-known pro-inflammatory cytokine that is critical for mesangial cell and macrophage/monocyte function [53]. Glomerular hypercellularity was inhibited in GBN through the use of IL-6 antagonists [38]. In SLN, renal injury was dampened by anti-IL-6 Ab treatment primarily through the inhibition of B and T cell activation [66]. To sum up, all three pro-inflammatory cytokines, TNF-α, IL-1, and IL-6, appear to play essential pathogenic roles in both diseases.

IL-12, a cytokine that is important in innate and adaptive immunity, induces the production of IFN-γ and the differentiation of T helper 1 (Th1) cells [119]. GBN was prevented in IL-12 deficient mice [117] and IL-12p40 deficient mice [56, 58], with decreased leukocyte infiltration. In MRL-Fas (*lpr*) mice, administering IL-12 increased IFN-γ-secreting lymphocyte infiltration within the kidney and elicited a cascade of events leading to autoimmune renal injury [103]. Thus, IL-12-dependent Th1 events worsen both GBN and SLN. IFN-γ is also critically involved in the pathogenesis of multiple autoimmune diseases as an inflammatory cytokine [4]. IFN-γ--deficient mice subjected to experimental GBN had less glomerular injury, glomerular crescents formation, and renal dysfunction than wild-type mice [54]. Similarly, IFN-γ receptor-deficient MRL/*lpr* SLN mice showed significant protection from renal damage, with prolonged survival as well as decreased intrarenal expression of TNF-α and colony-stimulating factor (CSF)-1 [104]. However, the role of IFN-γ is far more complex than that suggested by the above studies, as a recent report alluded to the protective role of IFN-γ in SLN [57].

Granulocyte-macrophage CSF (GM-CSF), granulocyte CSF (G-CSF), and macrophage CSF (M-CSF or CSF-1) trigger hemopoietic cells, particularly granulocytes and monocytes [33]. In both GM-CSF- and G--CSF-deficient mice, GBN was markedly improved [55]. On the other hand, administering M-CSF (CSF-1) exac-

erbated SLN through increased macrophage proliferation and differentiation within the glomeruli [8, 62]. Collectively, these reports draw a causal link between all myeloid cell growth factors and disease pathogenesis in both disease settings.

Platelet-derived growth factor (PDGF), a mitogenic factor, is involved in extracellular matrix metabolism, chemotactic and vasoactive processes, as well as inflammatory responses [34]. It is expressed on resident endothelial, mesangial, vascular smooth muscle, and interstitial cells as well as on immigrant mononuclear cells within the kidney. In SLN, imatinib, a small-molecule inhibitor of PDGF which works by binding to the PDGF-R signaling motif, can effectively alleviate glomerulonephritis [98]. Similarly, anti-PDGF-D therapy significantly ameliorates focal segmental glomerulosclerosis and podocyte and tubulointerstitial injury accompanied by reduced renal interstitial matrix accumulation and monocyte/macrophage infiltration in GBN [84]. Hence, PDGF signaling can trigger renal disease in both GBN and SLN.

Chemokines and their receptors mediate leukocyte recruitment to specific sites of inflammation; in particular, they actively partake in the development of renal inflammatory injury, both in the initiation and the progression phases. Hence they have been promoted as possible therapeutic targets in lupus nephritis [122]. In GBN, significant reduction in tubular injury has been reported in MCP-1-deficient mice, although the mice were not protected from glomerular injury [116]. In MRL/*lpr* SLN mice, the progression of nephritis was inhibited by Abs to MCP-1, possibly mediated by reduced intra-renal leukocyte infiltration [106].

In addition to the molecules discussed above, we have summarized in Table 1 additional molecules, such as Toll-like receptor ligands, P-selectin, and nitric oxide, all of which also show a concordant role in GBN and SLN [2, 3, 5, 6, 11, 13, 22, 24, 31, 37, 40, 42, 43, 46, 52, 57, 69, 75, 84, 86, 87, 92, 102, 121]. It should be pointed out that a substantial number of molecules have just been examined in one disease setting only, either GBN or SLN, and these molecules have not been included in the present review. Once these molecules get cross-evaluated in the reciprocal disease setting, the candidates listed in Table 1 should grow rapidly in the forthcoming years. As of now, when we review all of the molecules that have been examined in both GBN and SLN (as listed in Table 1), there is complete concordance with respect to how various molecules impact nephritis in both diseases. In other words, if a particular molecule turns out to play a pathogenic role in GBN, it is highly likely that it will have a similar pathogenic role in SLN.

CONCLUSION

In this article we have briefly compared the underlying pathology and molecular bases between GBN and SLN. Though there are some differences between these two diseases, increasing evidence indicates that both disease settings share common downstream molecular pathways that eventually compromise renal function. Complement, FcR, pro-inflammatory cytokines, chemokines, growth factors, and adhesion molecules all appear to determine the degree of tissue damage and renal dysfunction similarly in both disease settings. Considering the fact that GBN can be studied in a reproducible and rapid fashion, we believe the GBN model is an excellent analytical tool for exploring the molecular basis of SLN. This has two important clinical implications. First, with respect to genetic susceptibility, polymorphisms in genes encoding any of these "downstream" molecules may be considered as potential candidate genes for both diseases. Second, relating to the perspective of clinical therapeutics, treatment modalities that are effective in GBN may also prove efficacious in SLN.

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