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Mediation of immune glomerular injury

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Major advances in the basic sciences of immunology, cell biology, and molecular biology over the past decade have led to important new insights into the pathogenesis of kidney diseases. This review focusses on the current understanding of immunologic glomerular diseases, emphasizing insights derived from recent studies, particularly as they relate to clinical glomerular diseases. In reviewing this area, I focus primarily on the mechanisms which cause acute rather than chronic progressive disease and particularly on proteinuria as a marker of glomerular injury. I further subdivide mechanisms of glomerular tissue injury into those that are associated with inflammatory changes (by light microscopy) and those that are noninflammatory in nature. The major pathways of injury as they are currently understood are depicted schematically in Fig. 1. More detailed reviews of this subject have been published elsewhere [2, 3].

Noninflammatory mechanisms of glomerular injury

There are two major glomerular diseases in which a massive increase in glomerular permeability occurs in the absence initially of any morphologic alterations in glomerular structure. These are minimal-change/focal sclerosis and idiopathic membranous nephropathy (MN). Both of these lesions can be closely simulated in animal models in which the principal site of immune attack is at the level of the glomerular epithelial cell (GEC).

Glomerular injury due to noncomplement fixing anti-GEC antibodies

In minimal-change/focal sclerosis there is now increasing evidence that nephrotic syndrome results from glomerular effects of circulating permeability factors probably derived from immunocompetent cells. Thus, hybridomas of T cells from patients with active minimal-change disease secrete a factor which can transfer a similar lesion to the rat [11], and patients with active focal sclerosis, evidenced by the recurrence of disease in renal transplants, usually exhibit a serum factor which can induce an increase in albumin permeability in the isolated normal glomerulus [13].

While these circulating permeability factors are not immunoglobulins, lesions which closely simulate the structural and functional features of minimal-change/focal sclerosis can be induced in ani-

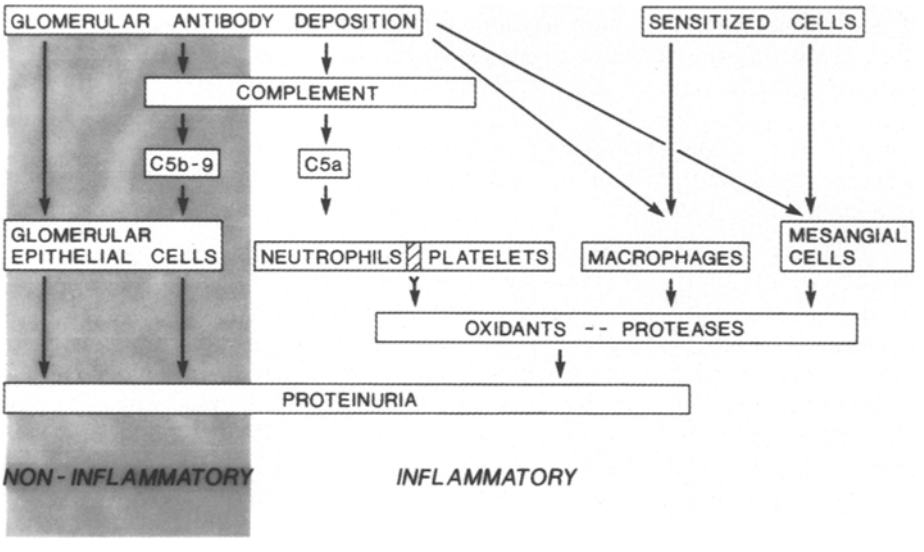

Fig. 1. Schema depicting the established mechanisms of immune glomerular injury which lead to proteinuria (Reprinted with permission from [3])

mals by a variety of antibodies that have in common the ability to bind to the membrane of the GEC without fixing complement. These antibodies include some antiglomerular antibodies, anti-Fx1A $F(ab')_2$, monoclonal antibodies K9/9 and 5-1-6 (all reviewed in [2, 3]), and all induce a dramatic change in the shape of the GEC, accompanied by areas of detachment of GEC from underlying glomerular basement membrane (GBM). It seems likely that better understanding of how these antibodies cause glomerular injury will also clarify how nonimmunoglobulin permeability factors damage the glomerulus as well. These models provide the opportunity to conduct such further studies. Possible mechanisms include stimulation of release by GEC of materials which directly damage underlying GBM, such as oxidants or proteases, or interference with molecules which regulate cell-matrix interaction leading to cell detachment from GBM, or both. Much has been learned recently regarding the molecular mechanisms which regulate the adherence of glomerular cells cell to GBM, and disorders of these processes may be particularly important in the pathogenesis of noninflammatory types of injury in diseases such as minimal-change disease [4].

Glomerular injury induced by complement fixing anti-GEC antibodies and C5b-9

As in minimal-change/focal sclerosis, the initial glomerular lesion in MN is a totally noninflammatory one. However, in MN there are extensive subepithelial deposits of antibody and complement components, including C3 and C5b-9. While the nature of the deposited antibody in human MN has not yet been established, many other aspects of the immunopathogenesis of MN are now understood based on studies of the Heymann's nephritis models in rats which closely simulate the human lesion. In Heymann's nephritis, subepithelial immune deposits result from antibody binding to antigens on the surface of the GEC, the best characterized of which is GP330 localized in the clathrin-coated pits. Antibody binding to the GEC membrane induces complement activation, probably via the alternative complement pathway. Because the deposits form only on the outer, or subepithelial, surface of the glomerular capillary wall, complement- and immunoglobulin-derived chemotactic and immune adherence proteins are not interactive with circulating cells, probably accounting for the noninflammatory nature of the lesion. Proteinuria, however, is a very complement-dependent phenomenon and appears to be mediated primarily by the C5b-9 membrane attack complex of complement (reviewed in [1, 5]. Thus, nephritogenic quantities of antibody fail to cause proteinuria in the intact animal, isolated perfused kidney, and isolated glomerulus if maneuvers to prevent C5b-9 formation are introduced. The mechanism by which C5b-9 causes proteinuria is still unclear. As with the permeability factors discussed above, the effect of C5b-9 in MN is on the GEC, where membrane insertion of C5b-9 occurs without inducing cell lysis. In vitro studies document that C5b-9 is a potent stimulus to production of several toxic metabolites by glomerular cells, including oxidants, proteases, prostaglandins, and various cytokines and growth factors. The currently available evidence suggests that oxidant production by the GEC in response to sublytic C5b-9 attack may be responsible for the alteration in basement membrane permeability that leads to nephrotic syndrome in MN.

Inflammatory mechanisms of glomerular injury

Most types of glomerulonephritis (GN) exhibit striking changes upon light microscopy, particularly hypercellularity, which may reflect infiltration by circulating inflammatory cells such as neutrophils, monocytes, or platelets or proliferation of resident glomerular cells, particularly mesangial cells. Examples include postinfectious GN, IgA nephropathy, rapidly progressive GN, lupus nephritis, and membranoproliferative GN. A plethora of recent studies have established that both circulating inflammatory cells and resident glomerular cells can mediate glomerular injury acutely by release of oxidants, proteases, and probably other chemoattractant and GBM-degrading molecules. Chronic injury is also augmented by release of various cytokines and growth factors that result in increased deposition of extracellular matrix leading to scarring and sclerosis. The following is a very brief summary of recent observations in this area.

Neutrophils and platelets

Neutrophil infiltration occurs early in any setting in which antibodies induce complement activation or immunoglobulins deposit at sites accessible to circulating inflammatory cells (e.g., subendothelial or mesangial immune complex deposits reviewed in [7, 9]. It has been known since the 1960s that neutrophils cause much of the antibody-induced injury which follows. Recent studies have substantially clarified how neutrophils localize in glomeruli through interaction with a variety of leukocyte adhesion molecules (selectins, integrins, intracellular adhesion molecules, and VCAM) which are dis-

played on cell surfaces. Many of these molecules are induced or overexpressed in response to cytokines and other inflammatory mediators. It has also been recently established that neutrophils localized in glomeruli induce injury by undergoing a respiratory burst that results in release of toxic oxygen metabolites, particularly H_2O_2, which is nephritogenic by virtue of its ability to interact with neutrophil-derived myeloperoxidase. This is a cationic molecule which localizes in glomeruli by interacting with negatively charged (anionic) sites and interacts with H_2O_2 and a halide to form hypohalous acids that directly damage GBM. Even more recently, it has been appreciated that in some settings platelets are essential for the occurrence of neutrophil-mediated injury and apparently augment this process. The nature of this platelet-neutrophil interaction is still under study.

Macrophages

Macrophages are also present in the early cellular infiltrate in several different inflammatory glomerular lesions [12]. Unlike neutrophils, they may localize in response to cytokines derived from cell-mediated immune reactions as well as antibody-mediated ones. They effect injury through several mechanisms, including release of oxidants and proteases which directly damage GBM, production of tissue factor which facilitates fibrin deposition and glomerular crescent formation, and release of other cytokines and growth factors including interleukin-1 and transforming growth factor-β (TGF-β) that are important stimuli to the production of extracellular matrix by glomerular cells.

Mesangial cells

Much attention in recent years has focused on the role of the mesangial cell in the mediation of both immune and nonimmune types of glomerular injury [6, 8, 10]. Mesangial cell proliferation is a prominent feature of glomerular diseases, including IgA nephropathy, lupus nephritis, some types of steroid-resistant nephrotic syndrome, and other lesions. Because of the relative ease with which mesangial cells can be grown in vitro, a large body of literature has evolved to document the activation of mesangial cells by a variety of inflammatory mediators. including C5b-9, certain types of immune complexes, endotoxin, and various other cytokines and growth factors. Additional in vitro studies demonstrate that activation or proliferation of mesangial cells can lead to the release of a host of proinflammatory materials, including oxidants, proteases, prostaglandins, growth factors, and extracellular matrix components.

To attempt to define which of these factors defined in vitro is operative in glomerular disease in vivo, we employed a model of mesangial proliferative GN induced by antibody to Thy 1.1 antigen on the mesangial cell membrane (ATS model). In this model, mesangial cell proliferation is initially associated with a complement-dependent platelet influx and may be mediated in part by the release of basic fibroblast growth factor (bFGF) by mesangial cells undergoing lysis. Subsequently there is a change in mesangial cell phenotype, with expression of α-smooth muscle actin and increased production of interstitial collagen simulating the properties of myofibroblasts. Proliferating mesangial cells exhibit increased protein and mRNA for platelet-derived growth factor (PDGF) B-chain and PDGF β-receptor, and proliferation can be significantly reduced by blocking PDGF, suggesting an autocrine mechanism for the maintenance of mesangial cell proliferation. Proliferation of mesangial cells is probably a process which contributes to, and augments, glomerular injury. Thus, mesangial cell proliferation is associated with increased production of mesangial cell derived proteinases that localize in areas of basement membrane injury. It is also associated with increased production of TGF-β and enhanced gene expression and deposition of normal mesangial matrix components leading to matrix expansion and sclerosis. A similar sequence of altered mesangial cell phenotype and cell proliferation preceding upregulation of genes for extracellular matrix component production leading to matrix expansion and sclerosis has now been documented in nonimmune models of progressive renal disease as well. These include the remnant kidney model and, recently, diabetic nephropathy.

Resolution of glomerular injury involving mesangial cell proliferation probably involves additional factors which regulate and attenuate the mechanisms that drive proliferation. These have not yet been systematically studied, but may include several factors such as TGF-β, SPARC, and nitric oxide, all of which are over-produced in this disease and have antiproliferative effects.

Summary

Although glomerular disease remains the most common cause of end-stage renal disease worldwide, major advances have been made recently in understanding the cellular and molecular mechanisms which mediate these disorders. Nephrotic syndrome in non inflammatory lesions such as

minimal-change/focal sclerosis and MN results from disorders of the GEC which can be simulated in animal models by antibodies to various GEC membrane epitopes. Clarification of how these antibodies effect the GEC to induce a loss of glomerular barrier function should substantially improve understanding of the pathogenesis of minimal change/focal sclerosis. In MN, proteinuria is mediated primarily by C5b-9 through similar mechanisms that also involve the GEC as a target.

Inflammatory glomerular lesions are induced by circulating inflammatory cells or proliferating resident glomerular cells. Understanding of how these cells induce tissue injury has also evolved considerably over the past decade. Neutrophil-induced disease involves leukocyte adhesion molecules in regulating neutrophil localization; proteases, oxidants, and myeloperoxidase in mediating injury and platelets in augmenting these processes. The activated mesangial cell exhibits altered phenotype and proliferation with release of oxidants and proteases. Mesangial cell proliferation may be initiated by basic fibroblast growth factor and is maintained by an autocrine mechanism involving PDGF. TGF-β is important in the subsequent development of sclerosis.

As understanding of these areas evolves, numerous new therapeutic strategies can now be devised, including agents which block or inhibit complement effects, oxidants, proteases, growth factors, and other cytokines. Appreciation of the role of several natural inhibitors of these mechanisms may also allow therapeutic manipulations that upregulate regulatory proteins, with a consequent therapeutic benefit. Thus these changes in basic understanding of the mechanisms of glomerular disease are likely to translate into new and more specific and effective forms of therapy in the next decade.

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