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Experimental Pathology Resources

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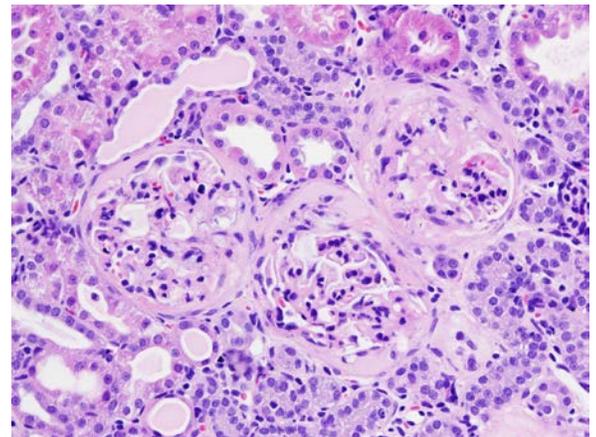
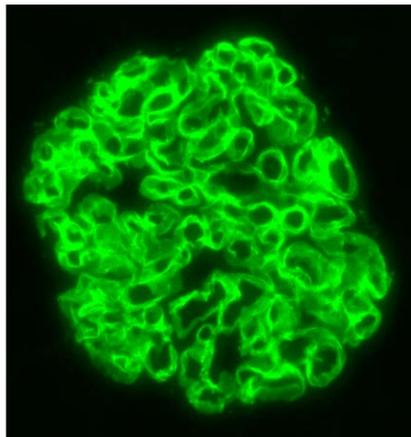
## Descriptions of Classical Models of Glomerulonephritis

### 1. Models of Immune-Mediated Glomerular Disease:

Two widely used rat models to investigate mechanisms of immune glomerulonephritis involving glomerular capillary immune deposits are anti-GBM nephritis and Passive Heymann Nephritis (PHN). Location of immune complexes in the GBM determines the resultant glomerular injury and renal syndrome (reviewed in 3, 28, and 29). Immune complexes that tend to accumulate along the inner surface of the glomerular capillary wall on the endothelial cell surface and in subendothelial space (like anti-GBM antibody and antigen-antibody complexes) are directly accessible to circulating inflammatory cells and mediators and often associated with crescent formation (28,29). The consequent activation of complement, infiltration of inflammatory cells and release of cytokines, growth factors and oxidants is injury to the glomerular capillaries and development of proliferative glomerulonephritis, alterations to the permeability barrier and development of crescents (28,29). Immune complexes that tend to localize in the subepithelial region, away from the capillary lumen (as in Anti-Fx1A, PHN) lead to minimal infiltration and proliferation (30,31) but rather glomerular epithelial injury and proteinuria.

#### a. Anti-GBM disease:

Administration of antibodies to whole glomeruli or to isolated glomerular basement membrane (GBM) induces a glomerulonephritis involving early leukocyte adhesion molecules in regulating neutrophil and platelet localization; proteases, reactive oxygen species and eicosanoids mediating injury in augmenting these



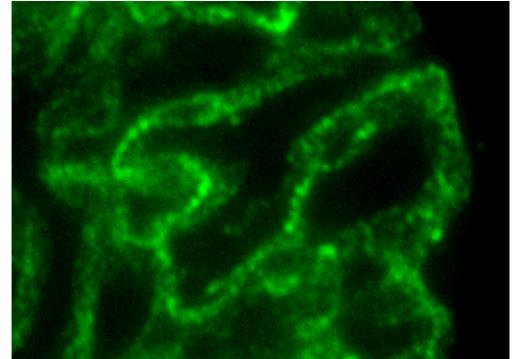
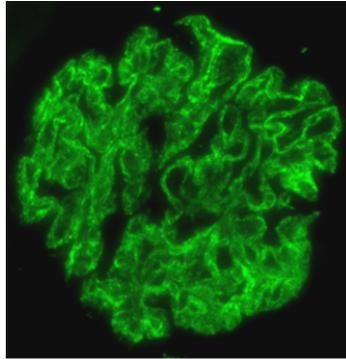
Anti-GBM disease induced by sheep antibody to whole rat glomeruli. The disease is characterized by linear deposits of sheep and rat IgG by immunofluorescence (A) and moderate mesangial hypercellularity, inflammatory infiltrates, glomerulosclerosis, and crescents in Bowman's space (H&E section).

processes (3,28) leading to a crescentic glomerulonephritis and interstitial nephritis (32,33). Preimmunization of rats with IgG before passive

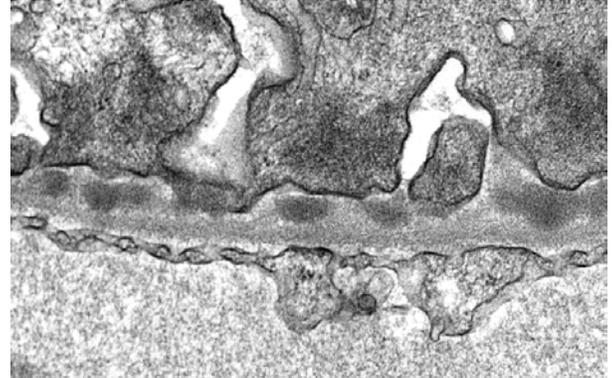
injection of nephritogenic antibody induces an accelerated disease model. The model has been heavily used to examine cellular and immune-mediated mechanisms of glomerulonephritis (3,34-37), and pathogenesis of crescents (32,33,38-40), mesangial hypercellularity (41), interstitial fibrosis (3,33,42-44) and proteinuria. Complement and neutrophil-dependent injury, macrophages, T-cells, and platelets, procoagulant signals and matrix accumulation are just a few of the many cellular mediators of anti-GBM disease. A variety of therapeutic interventions have been used to ameliorate the disease and define pathogenic mechanisms (45-49). *Product # PTX-001S.*

b. Membranous Nephropathy, (Passive Heymann Nephritis, PHN): Membranous nephropathy (MN) is a slowly progressive glomerular disease characterized by subepithelial immune complex deposits associated with increased protein excretion (50) without associated glomerular hypercellularity in acute injury. Subepithelial deposits, generalized thickening of the basement membrane, sclerosis and interstitial changes can occur depending on the severity and duration of the disease. The disease has been associated with an extensive list of other immune diseases, infectious or parasitic diseases, drugs and toxins tumors and other secondary diseases (50).

Immunization of rats with a proximal tubular epithelial fraction (Fx1A) induces an immune complex “membranous” nephritis characterized by subepithelial immune deposits and proteinuria with striking resemblance to human disease (51,52). Fx1A contains a large glycoprotein gp330 (megalin) a nephritogenic antigen produced by glomerular epithelial cells (53-56). Passive administration of anti-Fx1A antibody produces a nephritis defined by two phases: 1) a heterologous phase representing an acute nephritis induced by exogenously administered antibody, and 2) a chronic autologous phase characterized by the production of the hosts own response to the exogenous (heterologous) sheep immunoglobulin planted within glomerular structures. All variants of the model produce subepithelial deposits and proteinuria. Among the many uses of the model, have been studies to investigate



Membranous nephropathy induced by sheep antibody to rat Fx1A. The disease is characterized by finely granular staining of sheep and rat IgG by immunofluorescence (A&B) and subepithelial deposits by EM (C).



mechanisms of glomerular permeability and immune complex deposition (56-59), role of complement-induced glomerular epithelial injury (56,60,61), and mechanisms of glomerular epithelial cell response to injury (56,62-67). Several therapeutic interventions including statins (68, ACE inhibition (68) and inhibition of cyclooxygenase (69), cyclin dependent kinase (70) and heparanase (71) have been successful in the amelioration of epithelial cell injury and proteinuria. *Product # PTX-002S*.

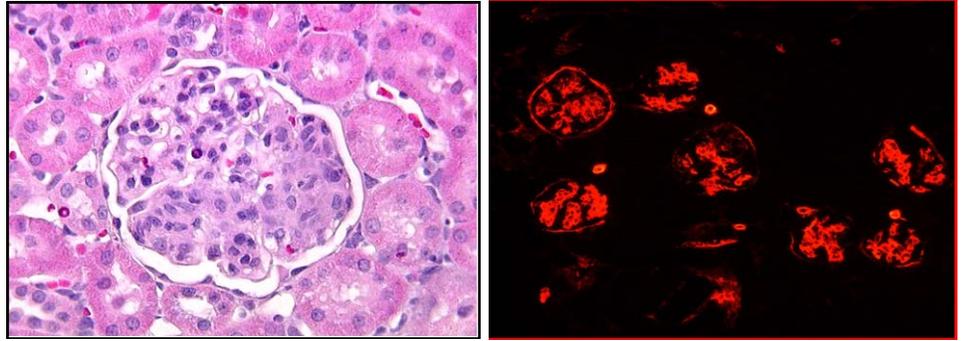
## 2. Mesangioproliferative glomerulonephritis:

Mesangial proliferation is a very common feature of many human glomerular diseases including IgA nephropathy, resolving post-infectious glomerulonephritis and a number of secondary glomerular diseases such as lupus nephritis, Schonlein-Henoch purpura, rheumatoid arthritis, liver cirrhosis, Alport's syndrome, and diabetic nephropathy (1,2). The disease is characterized by varying degrees of mesangial hypercellularity and mesangial matrix expansion. In progressive cases these cellular changes may lead to glomerular capillary narrowing, sclerosis and capsular adhesions as a result of injury by a variety of immunologic, toxic, metabolic, mechanical, and inflammatory mediators (1-3). Although several experimental models have been developed, the most widely used model for the study of mesangial proliferation has been the anti-thymocyte (anti-Thy-1) model (4,5). Antibody to thymocytes (ATS) is reactive to a surface Thy-1 antigen present on rat mesangial cells (4,5). Administration of ATS induces a complement-dependent mesangiolysis followed by a rapid mesangial proliferative glomerulonephritis that peaks within 5 days after injection, and then resolves over time (4,5).

ATS (anti-Thy-1) is a very well characterized rat model of human mesangioproliferative glomerulonephritis and has been exceptionally useful in examining mechanisms of mesangial cell injury, mediators of proliferation, and extracellular matrix synthesis (5-10). Eloquent studies identified roles for PDGF, TGF- $\beta$  and FGF in the pathogenesis of proliferation and matrix synthesis during disease progression (11-16). Moreover, the model has been used for the investigation of inflammatory response to glomerular injury (17,18). Mesangial cell apoptosis also occurs early and late in the disease and the model has been used to study programmed cell death in kidney disease (19-21). Other uses for the model are the examination mesangial

cell response to injury and expression of  $\alpha$ -smooth muscle actin (22), oxidative stress (23) origin of glomerular cells (24,25) and the progression of glomerulosclerosis or interstitial fibrosis (26,27), which may be elicited by multiple injections of the antisera a few days apart (26,27) The utility of this model to examine early cellular mechanisms in response to cell injury, recovery or advancement to fibrosis is apparent. Also the repeated injection of anti-Thy-1 and development of fibrosis may be analogous to persistent mesangial

injury and progressive renal disease in humans. *Product # PTX-003S.*



Mesangioproliferative glomerulonephritis in a rat kidney 5 days after injection of sheep anti-thymocyte (Thy-1) serum. Glomerular mesangial hypercellularity and focal proliferative nodules are characteristic of the disease by H&E (A). Mesangial cell activation is demonstrated by acquisition of alpha-smooth muscle actin by immunofluorescence (B).

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