PROBETEX
Experimental Pathology Resources™
靶点科技 400-004-3669

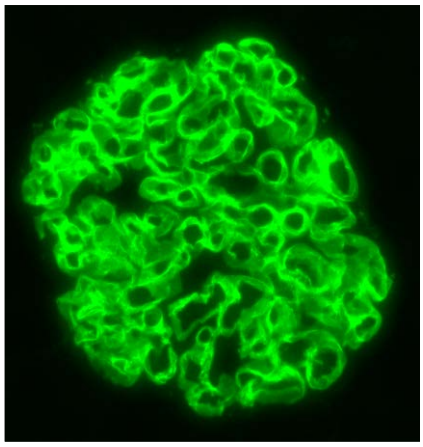
PROBETEX
Experimental Pathology Resources™

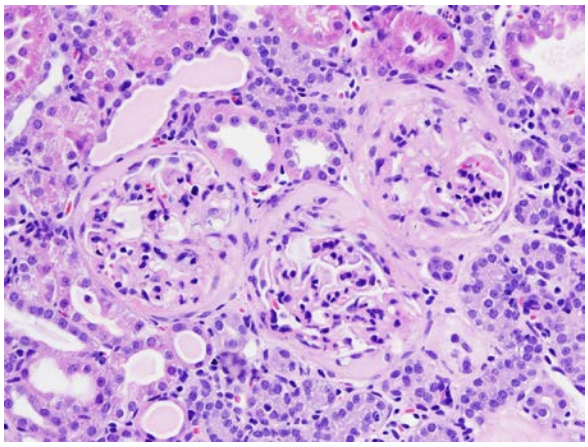
Descriptions of Classical Models of Glomerulonephritis

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 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 hypercelluarity (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.*

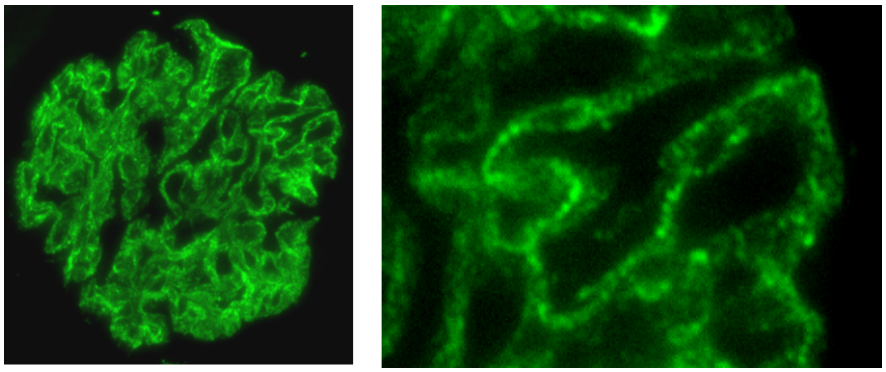




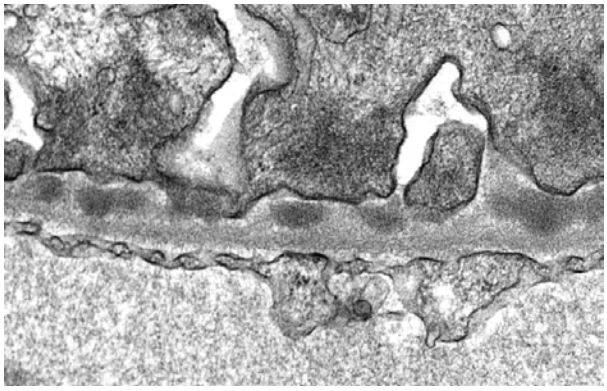
Anti-GBM disease induced by sheep antibody to whole rat glomeruli. The disease is characterized by linear deposits of sheep and rat IgG by immunofluorescence (A) and moderate mesangial hypercellularity, inflammatory infiltrates, glomerulosclerosis, and crescents in Bowman's space (H&E section).

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 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 cyclooxygnease (69), cyclin dependent kinase (70) and heparanase (71) have been successful in the amelioration of epithelial cell injury and proteinuria. *Product # PTX-002S.*



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).

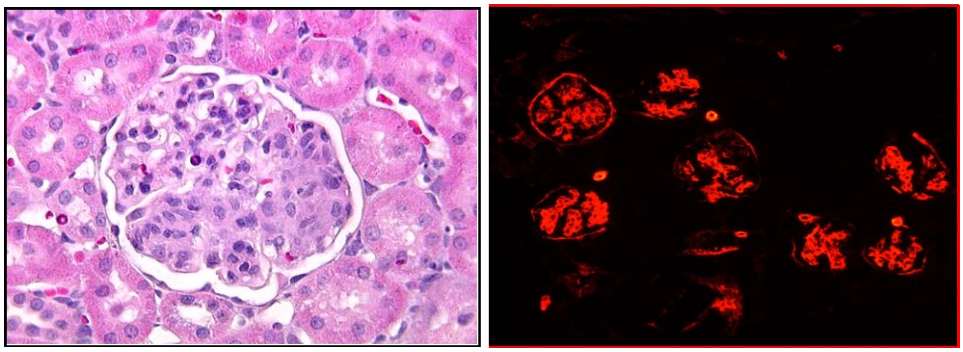


2. Mesangioproliferative glomerulonephritis:

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-β 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 α-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).

LITERATURE CITED:

1. Glassock RJ, Adler SG, Ward HJ, Cohen AH. (1996). Primary glomerular diseases. In "The Kidney"(Brenner, B.M. Ed.) 5th ed. pp. 1182-1279. W. B. Saunders Company, Philadelphia.
2. Glassock RJ, Cohen AH, Adler SG, Ward HJ. (1996). Secondary glomerular diseases. In "The Kidney"(Brenner, B.M. Ed.) 5th ed. pp. 1182-1279. W. B. Saunders Company, Philadelphia.
3. Wilson, C.B. (1996). Renal response to immunologic glomerular injury. In "The Kidney"(Brenner, B.M. Ed.) 5th ed. pp. 1253-1391. W. B. Saunders Company, Philadelphia.
4. Yamamoto T, and Wilson CB. Quantitative and qualitative studies of antibody-induced mesangial cell damage in the rat. Kidney Int 32:514-525, 1987.
5. Jefferson JA, Johnson RJ. Experimental mesangial proliferative glomerulonephritis (the anti-Thy-1.1 model). J Nephrol 12:297-307, 1999.
6. Johnson RJ, Garcia RL, Pritzl P, Alpers CE. Platelets mediate glomerular cell priliferation in immune complex nephritis induced by anti-mesangial cell antibodies in the rat. Am J Pathol 136:369-374, 1990
7. Iida, H., et al. Platelet-derived growth factor (PDGF) and PDGF receptor are induced in mesangial proliferative nephritis in the rat. Proc Natl Acad Sci USA 88:6560-6564, 1991.
8. Okuda S, Languino LR, Ruoslahti E, Border WA. Elevated expression of transforming growth factor-beta and proteoglycan production in experimental glomerulonephritis. Possible role in expansion of the mesangial extracellular matrix. J Clin Invest 86:453-62, 1990.
9. Ito Y, Goldschmeding R, Bende R, Claessen N, Chand M, Kleij L, Rabelink T, Weening J, Aten J. Kinetics of connective tissue growth factor expression during experimental proliferative glomerulonephritis. J Am Soc Nephrol 12:472-84, 2001.
10. Floege J, et al. Increased synthesis of extracellular matrix in mesangial proliferative nephritis. Kidney Int 40:477-488, 1991.
11. Johnson RJ, Raines EW, Floege J, Yoshimura A, Pritzl P, Alpers C, Ross R. Inhibition of mesangial cell proliferation and matrix expansion in glomerulonephritis in the rat by antibody to platelet-derived growth factor. J Exp Med 175:1413-1426, 1992.
12. Border WA, Okuda S, Languino LR, Sporn MB, Ruoslahti E. Suppression of experimental glomerulonephritis by antiserum against transforming growth factor beta 1. Nature 346:371-4, 1990.
13. Gilbert RE, Kelly DJ, McKay T, Chadban S, Hill PA, Cooper ME, Atkins RC, Nikolic-Paterson DJ. PDGF signal transduction inhibition ameliorates experimental mesangial proliferative glomerulonephritis. Kidney Int 59:1324-1332, 2001.
14. Ostendorf T, van Roeyen CR, Peterson JD, Kunter U, Eitner F, Hamad AJ, Chan G, Jia XC, Macaluso J, Gazit-Bornstein G, Keyt BA, Lichenstein HS, LaRochelle WJ, Floege J. A fully human monoclonal antibody (CR002) identifies PDGF-D as a novel mediator of mesangioproliferative glomerulonephritis. J Am Soc Nephrol 14:2237-47, 2003.
15. van Royen CRC, Eitner F, Martinkus S, Thieltges SR, Ostendorf T, Bokemeyer D, Luscher B, Luscher-Firzlaff JM, Floege J, Mertensw PR. Y-box protein 1mediates PDGF-B effects in mesangioproliferative glomerular disease. J Am Soc Nephrol 16:2985-2996, 2005.
16. Raffetseder U, Wernert N, Ostendorf T, van Roeyen C, Rauen T, Behrens P, Floege J, Mertens PR. Mesangial cell expression of proto-oncogene Ets-1 during progression of mesangioproliferative glomerulonephritis. Kidney Int 66:622-32, 2004.

17. Bagchus WM, Jeunink MF, Elema JD. The mesangium in anti-Thy-1 nephritis. Influx of macrophages, mesangial cell hypercellularity, and macromolecular accumulation. Am J Pathol 137:215-23, 1990.

18. Westerhuis R, van Straaten SC, van Dixhoorn MG, van Rooijen N, Verhagen NA, Dijkstra CD, de Heer E, Daha MR, Distinctive roles of neutrophils and monocytes in anti-thy-1 nephritis. Am J Pathol. 156:303-310, 2000.

19. Roos A, Sato T, Maier H, van Kooten C, Daha MR. Induction of renal cell apoptosis by antibodies and complement. Exp Nephrol 9:65-70, 2001.

20. Shimizu A, Kitamura H, Masuda Y, Ishizaki M, Sugisaki Y, Yamanaka N. Apoptosis in the repair process of experimental proliferative glomerulonephritis. Kidney Int 47:114-21, 1995.

21. Baker AJ, Mooney A, Hughes J, Lombardi D, Johnson RJ, Savill J. Mesangial cell apoptosis: the major mechanism for resolution of glomerular hypercellularity in experimental mesangial proliferative nephritis. J Clin Invest 94:2105-2116, 1994.

22. Johnson R.J., et al.. Expression of smooth muscle cell phenotype by rat mesangial cells in immune complex nephritis. Alpha-smooth muscle actin is a marker of mesangial cell proliferation. J. Clin. Invest. 87:847-858, 1991.

23. Gaertner SA, Janssen U, Ostendorf T, Koch KM, Floege J, Gwinner W. Glomerular oxidative and antioxidative systems in experimental mesangioproliferative glomerulonephritis. J Am Soc Nephrol 13:2930-7, 2002.

24. Hugo C, Shankland SJ, Bowen-Pope DF, Couser WG, Johnson RJ. Extraglomerular origin of the mesangial cell after injury. A new role of the juxtaglomerular apparatus. J Clin Invest 100:786-94, 1997.

25. Ikarashi K, Li B, Suwa M, Kawamura K, Morioka T, Yao J, Khan F, Uchiyama M, Oite T. Bone marrow cells contribute to regeneration of damaged glomerular endothelial cells. Kidney Int 67:1925-33, 2005.

26. Stahl RA, Thaiss F, Wenzel U, Helmchen U. Morphologic and functional consequences of immune-mediated mesangiolysis: development of chronic glomerular sclerosis. J Am Soc Nephrol 2:S144-148, 1992.

27. Yamamoto T, Noble NA, Miller DE, Border WA. Sustained expression of TGF-beta 1 underlies development of progressive kidney fibrosis. Kidney Int 45:916-927, 1994.

28. Couser WG. Pathogenesis of glomerular damage in glomerulonephritis. Nephrol Dial Transplant 13 Suppl 1:10-15, 1998.

29. Wiggins RC, Holzman L, Legalt DJ. Glomerular inflammation and crescent formation. In Immunologic Renal Diseases. Ed WG Couser, EG Neilson Lippincott-Raven Publishers, Philadelphia, ,pp 669-682, 2001.

30. Allison ME, Wilson CB, Gottschalk CW. Pathophysiology of experimental golomeruonephritis in rats. J Clin Invest 53: 1402-141, 1974.

31. Kerjaschki D, Neale TJ. Molecular mechanisms of glomerular injury in rat experimental membranous nephropathy (Heymann nephritis). J Am Soc Nephrol 7:2518-2526, 1996.

32. Holzman LB, Wiggins RC. Consequences of glomerular injury. Glomerular crescent formation. Sem Nephrol 11:346-53, 1991.

33. Downer G, Phan SH, Wiggins RC. Analysis of renal fibrosis in a rabbit model of crescentic nephritis. J Clin Invest 82:998-1006, 1988.

34. Feng L, Xia Y, Yoshimura T, Wilson CB. Modulation of neutrophil influx in glomerulonephritis in the rat with anti-macrophage inflammatory protein-2 (MIP-2) antibody. J Clin Invest 95:1009-1017, 1995.

35. De Vriese AS, Endlich K, Elger M, Lameire NH, Atkins RC, Lan HY, Rupin A, Kriz W, Steinhausen MW. The role of selectins in glomerular leukocyte recruitment in rat anti-glomerular basement membrane glomerulonephritis. J Am Soc Nephrol 10:2510-2517, 1999.

36. Lan HY, Nikolic-Paterson DJ, Mu W, Atkins RC. Local macrophage proliferation in the progression of glomerular and tubulointerstitial injury in rat anti-GBM glomerulonephritis. Kidney Int 48:753-760, 1995.

37. Lan HY, Nikolic-Paterson DJ, Mu W, Atkins RC. Local macrophage proliferation in the pathogenesis of glomerular crescent formation in rat anti-glomerular basement membrane (GBM) glomerulonephritis. Clin Exp Immunol 110:233-40, 1997.

38. Lan HY, Yu XQ, Yang N, Nikolic-Paterson DJ, Mu W, Pichler R, Johnson RJ, Atkins RC. De novo glomerular osteopontin expression in rat crescentic glomerulonephritis. Kidney Int 53:136-145, 1998.

39. Yu XQ, Fan JM, Nikolic-Paterson DJ, Yang N, Mu W, Pichler R, Johnson RJ, Atkins RC, Lan HY. IL-1 up-regulates osteopontin expression in experimental crescentic glomerulonephritis in the rat. Am J Pathol 154:833-841, 1999.

40. Hayashi K, Horikoshi S, Osada S, Shofuda I, Tomino Y: Macrophage-derived MT1-MMP and increased MMP-2 activity are associated with glomerular damage in crescentic glomerulonephritis J. Pathol 191: 299-305, 2000.

41. Bokemeyer D, Guglielmi KE, McGinty A, Sorokin A, Lianos EA, Dunn MJ. Activation of extracellular signal-regulated kinase in proliferative glomerulonephritis in rats. J Clin Invest 100:582-588, 1997.

42. Feng L, Loskutoff DJ, Wilson CB. Glomerular extracellular matrix accumulation in experimental anti-GBM Ab glomerulonephritis. Nephron 84:40-8, 2000.

43. Pichler R, Giachelli CM, Lombardi D, Pippin J, Gordon K, Alpers CE, Schwartz SM, Johnson RJ. Tubulointerstitial disease in glomerulonephritis. Potential role of osteopontin (uropontin). Am J Pathol 144:915-926, 1994.

44. Barnes VL, Musa J, Mitchell RJ, Barnes JL. Expression of embryonic fibronectin isoform EIIIA parallels alpha-smooth muscle actin in maturing and diseased kidney. J Histochem Cytochem 47:787-798, 1999.

45. Ogawa D, Shikata K, Matsuda M, Okada S, Usui H, Wada J. Taniguchi N. Makino H. Protective effect of a novel and selective inhibitor of inducible nitric oxide synthase on experimental crescentic glomerulonephritis in WKY rats. Nephrol Dial Transplant 17:2117-21, 2002.

46. Khan SB. Cook HT. Bhangal G. Smith J. Tam FW. Pusey CD. Antibody blockade of TNF-alpha reduces inflammation and scarring in experimental crescentic glomerulonephritis. Kidney Int 67:1812-20, 2005.

47. Saga D, Sakatsume M, Ogawa A, Tsubata Y, Kaneko Y, Kuroda T, Sato F, Ajiro J, Kondo D, Miida T, Narita I, Gejyo F. Bezafibrate suppresses rat antiglomerular basement membrane crescentic glomerulonephritis. Kidney Int 67:1821-9, 2005.

48. Levidiotis V. Freeman C. Tikellis C. Cooper ME. Power DA. Heparanase inhibition reduces proteinuria in a model of accelerated anti-glomerular basement membrane antibody disease. Nephrology. 10:167-73, 2005.

49. Leh S, Vaagnes O, Margolin SB, Iversen BM, Forslund T. Pirfenidone and candesartan ameliorate morphological damage in mild chronic anti-GBM nephritis in rats*.* Nephrol Dial Transplant 20:71-82, 2005.

50. Couser WG, Alpers CE. Membranous Nephropathy. (2001). In "Immunologic Renal Diseases" (Neilson EG, Couser WG. Eds.) 2nd ed. pp. 1029-1055. Lippincot Williams & Wilkins, Phaladelphia.

51. Heymann W, Hackel DB, Harwood S, Wilson SGF, Hunter JLP. Production of nephritic syndrome in rats by Freund'as adjuvants and rat kidney suspensions. Proc Soc Exp Biol Med 100:660-664, 1959.

52. Edgington TS, Glassock RJ, Dixon FJ. Autologous immune complex nephritis induced with renal tubular anigen. I. Identification and isolation of the pathogenetic antigen J Exp Med 127:555-5, 1968.

53. Kerjaschki D, Farquhar MG. Immunocytochemical localization of the Heymann nephritis antigen (GP330) in glomerular epithelial cells in normal Lewis rats J Exp Med 157:667-686, 1983.

54. Kanalas JJ, Makker SP. Isolation of a 330kD glycoprotein from human kidney similar to the Heymann nephritis autoantigen (gp330). J Am Soc Neph 1:792-798, 1990.

55. Yamazaki H, Ullrich R, Exner M, Saito A, Orlando RA, Kerjaschki D, Farquhar MG. All four putative ligand-binding domains in megalin contain pathogenic epitopes capable of inducing passive Heymann nephritis. J Am Soc Nephrol 9:1638-1644, 1998.

56. Cybulsky AV. Quigg RJ. Salant DJ**.** Experimental membranous nephropathy redux*.* Am J Physiol 289:F660-71, 2005*.*

57. Van Damme BJC, Fleuren GJ, Bakker WW et al. Experimental glomerulonephritis in the rat induced by antibodies directed against tubular antigens. V. Fixed glomerular antigens in the pathogenesis of heterologous immune complex glomerulonephritis. Lab Invest 38:502-, 1978.

58. Salant DJ, Belok S, Stilmant MM, et al: Determinants of glomerular localization of subepithelial immune deposits. Effects of altered antigen to antibody ratio, sterioids, vasoactive amine antagonists, and aminonucleoside of puromycin on passive Heymann nephritis in rats. Lab Invest 41:89-, 1979.

59. Salant DJ, Darby C, Couser WG. Experimental membranous glomerulonephritis in rats. Quantitative studies of glomerular immune deposit formation in isolated glomeruli and whole animals. J Clin Invest 66:71-81, 1980.

60. Adler S, Baker PJ, Pritzl P, Couser WG. Detection of terminal complement components in experimental immune glomerular injury. Kidney Int 26:830-837, 1984.

61. Schulze M, Pruchno CJ, Burns M, Baker PJ, Johnson RJ, Couser WG. Glomerular C3c localization indicates ongoing immune deposit formation and complement activation in experimental glomerulonephritis. Am J Pathol 142:179-187, 1993.

62. Kerjaschki D. Dysfunctions of cell biological mechanisms of visceral epithelial cell (podocytes) in glomerular diseases. Kidney Int 45:300-313, 1994.

63. McMillan JI, Riordan JW, Couser WG, Pollock AS, Lovett DH. Characterization of a glomerular epithelial cell metalloproteinase as matrix metalloproteinase-9 with enhanced expression in a model of membranous nephropathy. J Clin Invest 97:1094-1101, 1996.

64. Topham PS, Haydar SA, Kuphal R, Lightfoot JD, Salant DJ. Complement-mediated injury reversibly disrupts glomerular epithelial cell actin microfilaments and focal adhesions. Kidney Int 55:1763-1775, 1999.

65. Saran AM, Yuan H, Takeuchi E, McLaughlin M, Salant DJ. Complement mediates nephrin redistribution and actin dissociation in experimental membranous nephropathy. Kidney Int 64:2072-8, 2003.

66. Nakatsue T, Koike H, Han GD, Suzuki K, Miyauchi N, Yuan H, Salant DJ, Gejyo F, Shimizu F, Kawachi H. Nephrin and podocin dissociate at the onset of proteinuria in experimental membranous nephropathy. Kidney Int 67:2239-53, 2005.

67. Cybulsky AV, Takano T, Papillon J, Bijian K, Guillemette J**.** Activation of the extracellular signal-regulated kinase by complement C5b-9. Am J Physiol 289:F593-603, 2005*.*

68. Zoja C, Corna D, Rottoli D, Cattaneo D, Zanchi C, Tomasoni S, Abbate M, Remuzzi G. Effect of combining ACE inhibitor and statin in severe experimental nephropathy. Kidney Int 61:1635-45, 2002.

69. Takano T, Cybulsky AV, Cupples WA, Ajikobi DO, Papillon J, Aoudjit L. Inhibition of cyclooxygenases reduces complement-induced glomerular epithelial cell injury and proteinuria in passive Heymann nephritis. J Pharmacol Exp Therap 305:240-9, 2003.

70. Milovanceva-Popovska M, Kunter U, Ostendorf T, Petermann A, Rong S, Eitner F, Kerjaschki D, Barnett A, Floege J. R-roscovitine (CYC202) alleviates renal cell proliferation in nephritis without aggravating podocyte injury. Kidney Int 67:1362-70, 2005.

71. Levidiotis V, Freeman C, Tikellis C, Cooper ME, Power DA. Heparanase inhibition reduces proteinuria in a model of accelerated anti-glomerular basement membrane antibody disease. Nephrology 10:167-73, 2005.

Probetex, Inc.
Experimental Pathology Resources
7418 John Smith, Suite A
San Antonio, TX 78229

(210) 616-9515 FAX:(210) 616-9914
e-mail: info@probetex.com
web: http://www.Probetex.com