MINIREVIEW

The Biology of Mesangial Cells in Glomerulonephritis(43129A)

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The concept of the mesangium as a distinct entity within the glomerulus was originally proposed by Zimmermann (1) and has since received confirmation by a variety of morphologic and cell studies. By electron microscopy, it is possible to visualize a specialized cell type, the mesangial cell, which is situated between the capillaries and which has cytoplasmic projections containing processes that are in apparent contact with the basement membrane (2). The mesangial cell has a low cytoplasm to nucleus ratio and contains mitochondria, a Golgi apparatus, and endoplasmic reticulum along with a network of microtubules and intermediate filaments (2, 3). The presence of actomyosin and of tropomyosin in this network has been demonstrated by immunofluorescence using the relevant antisera (4–7). These specialized cells are embedded in an amorphous matrix which has been shown by immunocytochemical and biochemical techniques to have a composition similar to that of many extracellular matrices, consisting of the various collagens (8–13), the glycosoaminoglycans (14–19), existing principally as the proteoglycans, heparan sulfate and chondroitin sulfate, and the adhesive glycoproteins, fibronectin (6, 20–22), laminin (10, 23), and thrombospondin (24).

The geographic relationship of the mesangial cell, its projections and matrix to the glomerular basement membrane, the capillary endothelial lining and the capillary lumen, and its ability to contract suggest that it must play a critical role in the modulation of glomerular blood flow and filtration. Indeed, these pivotal functions of the mesangial cell are especially revealed during pathologic states, such as the various forms of nephritis, in which there is an increase of both mesangial cell number and mesangial matrix.

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Another important function of the mesangium is its participation in the process of plasma ultrafiltration. This process has been visualized by electron microscopic studies coupled with the use of tracers infused into the circulation. It is envisaged that the mesangium functions as a filtration barrier in two ways. First, its fenestrations, which have approximate dimensions of 376 Å × 626 Å (25), act as a molecular sieve for neutral molecules. As an example, particles of thorium dioxide, which have an average molecular length of 405 Å are restricted in their passage by this filter. Second, the structural organization of the matrix, formed largely by the anionic proteoglycans, will attract and bind positively charged macromolecules. Thus, Gallo *et al.* (26) were able to show that positively charged immune complexes were trapped more abundantly in the glomerulus than were neutral or anionic immune complexes. The participation of heparin-containing proteoglycans in mediating this effect was demonstrated by the investigations of Kanwar *et al.* (27), who showed that this effect was reduced when the kidneys were first perfused with heparinase to digest this species of matrix.

Finally, the uptake of macromolecules by the mesangium fulfills a role distinct from that of filtration. This uptake discriminates between immune complexes which possess an Fc moiety and other types of macromolecules, such as colloidal carbons. As will be discussed below, mesangial cells have been shown to possess Fc receptors, which likely account for the differential uptake. In any case, if any of these macromolecules are infused into the circulation, their uptake in the mesangium can be readily demonstrated. The determinants of this uptake are (i) the concentration of the substance in the circulation, which in turn may depend on the functional capacity of the mononuclear phagocyte system (28) and (ii) various intraglomerular hemodynamic factors (29).

Physiology of Cultured Mesangial Cells

Mesangial cells were successfully cultured by Bernik (30) and Quadracci and Striker (31) on the basis of the technique of obtaining glomeruli by differential sieving of renal cortical tissue. From these pioneering studies, there have evolved two basic methods for the culture of mesangial cells. The cells may be allowed to grow either from explants of whole glomeruli or, alternatively, from isolated glomeruli which have been digested with various enzymes to yield glomerular cores from which mesangial cells grow readily. The resultant cells have a morphology which on light microscopy shows them to be spindle shaped with many cytoplasmic projections. By electron microscopy, an oval elongated nucleus is seen along with a well-developed Golgi apparatus and rough endoplasmic reticulum. The cells appear to be analogous to vascular smooth muscle cells in possessing dense bundles of microfilaments with dense bodies, which probably represent the contractile apparatus of these cells (2, 32). By immunofluoresence, they can be shown to stain for the characteristic cytoskeletal filaments, actin, myosin, desmin, and vimentin (6, 32, 33).

In addition to this contractile mesangial cell, a second cell type has been isolated by Schreiner *et al.* (34). This cell type was originally isolated by the digestion of glomeruli and the plating of the resultant cells on petri dishes, yielding a cell which was adherent to plastic. Further analysis of this cell showed it to possess many of the characteristics of monocytes/macrophages. These cells can be shown to possess phagocytic ability, to have Fc receptors, and to present antigen. Additionally, they were shown to display the Ia antigen, suggesting that when blood monocytes, which in the rat and in mouse are Ia negative, take up residence in the mesangium, they must receive a signal which induces them to express the Ia antigen. Experiments in which rats were irradiated also provided evidence that these Ia-positive phagocytic cells in the mesangium are derived from the bone marrow (35). Further studies by Schreiner and Unanue (35) showed that not all phagocytic cells in the mesangium express the Ia antigen, although all of them could be demonstrated to express leukocyte common antigen. From these studies, it can be calculated that approximately 5% of resident cells in the mesangium have some phagocytic capacity.

The physiology of the contractile mesangial cell has been the subject of a recent comprehensive review (36). In summary, the data to date demonstrate that the contractile mesangial cell is a dynamic cell capable of many diverse functions. It is biosynthetically active, producing an array of proteins and bioactive lipids. Thus, it can be shown to synthesize renin, (37, 38), neutral proteinases (39, 40), plasminogen activator and inhibitor (41), 5′-nucleotidase (42), erythropoietin (43), a variety of growth factors (see below) and bioactive lipids, including the products of arachidonic acid metabolism and platelet activating factor. The reader is referred to the excellent review by Mene *et al.* (36) for details on these aspects of mesangial cell physiology, including the mechanisms by which mesangial cell contraction and signal transduction are regulated. The current review focuses on the interaction between the contractile mesangial cell and the immune cell, in particular the monocyte/macrophage. Emphasis has been placed on the growth factors which serve as mediators for these interactions.

The Mesangial Cell in Glomerulonephritis

The mesangial cell occupies a central position in the genesis of the cellular lesions seen in nephritis. Histologically, the lesions are characterized by an increase in the number of mesangial cells and in the amount of the surrounding mesangial matrix. The cells infiltrating the mesangium in both immune complex-mediated nephritis and in anti-glomerular basement membrane nephritis have been shown to consist predominantly of monocytes/macrophages together with smaller numbers of lymphocytes (44–46). The identity of the effector cells as monocytes/macrophages has been established by special stains, while their functional role in nephritis has been demonstrated by the treatment of experimental animal models with an antimacrophage antiserum, which has abrogated the development of proteinuria in these models of renal disease (47).

Recent experiments in several laboratories, utilizing the cultured mesangial cell as a model cell for study, have shed light on some of the mechanisms which may underlie these *in vivo* tissue reactions, especially in terms of identifying potential mediators which may subserve these reactions. Thus, information has been obtained which assists in clarifying the following issues: (i) How do immune complexes localize in the mesangial cell? What effect do these complexes have on the physiology of the mesangial cell? (ii) How do macrophage and lymphocyte products regulate mesangial cell proliferation? (iii) Does the mesangial cell in turn produce mediators which modulate immune cell function?

Mechanisms for the Uptake of Immune Complexes by the Mesangial Cell. Previous investigations have shown that when experimental animal models are infused with preformed immune complexes, these macromolecules readily localize in the mesangium of the kidney. The mechanisms underlying such uptake of immune complexes have only recently been clarified by investigations with explanted mesangial cells. As discussed earlier, there are at least two populations of mesangial cells. The most abundant mesangial cell type appears to be a contractile cell analogous to the vascular smooth muscle cell (32). Additionally, a second cell

which is Ia positive and which has the properties of a monocyte/macrophage has been identified (34). As expected, the phagocytic mesangial cell can be demonstrated to possess Fc receptors and to participate in the uptake of immune complexes. However, the numbers of such resident macrophages in the mesangium are insufficient to account for the bulk endocytosis of such complexes. More recently, the contractile mesangial cell has also been discovered to have Fc receptors. Sedor *et al.* (48), by using ^{125}I-labeled bovine γ-globulin/anti-bovine γ-globulin antigen-antibody complexes, demonstrated the presence of such receptors on Ia-negative contractile mesangial cells. By saturation binding studies with the same ligand, they showed that the mesangial Fc receptor has the characteristics of a low-affinity Fc receptor with a K_d of 640 nM and a binding site density of 1.0×10^5 sites/cell. These investigators demonstrated that occupancy of such mesangial Fc receptors led to the generation of superoxide anion. The potential of such reactive oxygen species in producing glomerular damage in nephritis is still a matter of speculation. Further investigations from the same laboratory (49), using essentially the same system, have shown that stimulation of mesangial cells by immune complexes leads not only to the generation of superoxide anion but also to the production of prostaglandin E (PGE) and thromboxane B_2 in a dose- and time-dependent manner. Simultaneously, immune complexes induced the cells to contract with 250 μg of the specific antibody inducing 45.8 ± 10.1% contraction, with an average decrease in surface area of approximately 20% as assessed by imaging microscopy. Additionally, the mechanisms of signal transduction were studied in such stimulated cells with measurements of cytosolic free calcium and phosphatidylinsositol turnover being made. Immune complexes led to a mobilization of calcium from intracellular stores as well as an influx of this cation across the plasma membrane but had no measurable effect on water-soluble inositol phosphate generation (49).

Confirmatory evidence for the presence of Fc receptors functioning in contractile mesangial cells has been provided by studies with colloidal gold particles which have been coated with bovine serum albumin followed by anti-bovine serum albumin (50). Uptake of these particles was shown to be a saturable process, inhibitable by sodium azide and cytochalasin B. By electron microscopy, the process was visualized as vesicular uptake with delivery to endosomes. Mesangial uptake of these particles was associated with stimulation of PGE_2 synthesis and production of platelet activating factor. By using subclass specific antibodies, the nature of the Fc receptor on rat mesangial cells was shown to be specific for mouse IgG-2a.

Definitive evidence for the presence of an Fc receptor in cultured mesangial cells was later furnished by Santiago *et al.* (51). They performed experiments in which mesangial cells were subjected to surface iodination followed by immunoprecipitation with either a polyclonal or monoclonal antibody prepared against murine Fcγ receptor. Both antibodies precipitated a 45-kDa iodinated protein band from cultured rat mesangial cells which co-migrated with that from murine macrophage J774 cells on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. By immunofluorescence, all mesangial cells stained positively with the polyclonal anti-Fcγ receptor antibody. Finally, a cDNA probe for the Fcγ RII-α on murine macrophages hybridized to mRNA from cultured rat mesangial cells. This mRNA was of the same size as that of the Fc receptor isolated from J774 macrophages.

The uptake of immune complexes has been shown to be modulated by various vasoactive agents. Singhal *et al.* (52) found that the uptake of gold particles coated with IgG by mesangial cells was enhanced by pretreatment of the cells with angiotensin II. Conversely, atrial natriuretic peptide and dopamine attenuated the uptake of these particles both during basal conditions and in response to stimulation by angiotensin II.

The functional capacity of the Fc receptor is also subject to regulation. Santiago *et al.* (53) reported that Fc receptor activity, Fc receptor protein, and mRNA for the Fc receptor were increased when mesangial cells were treated with either colony-stimulating factor-1 (CSF-1) or cAMP.

Regulation of Mesangial Cell Function by Products of Immune Cells. Because of the pivotal role of the monocyte/macrophage in the genesis of the lesions in glomerulonephritis, studies in many laboratories have attempted to define the role of the various macrophage products in modulating mesangial cell function. After exposure to whole macrophage supernatant, mesangial cells react in a biphasic manner (54–56). The type of response is dependent on the underlying physiologic state of the cell. In relatively slow-growing mesangial cells in culture, which approximate the typical *in vivo* state of this glomerular cell type, macrophage supernatants were shown to stimulate proliferation of these cells (54, 56). The mechanism by which this occurred was clarified by experiments in which the mesangial cells were pretreated with indomethacin (56). The stimulatory effect of the macrophage supernatants was partially abrogated, suggesting that its growth-promoting effect may be mediated in part by the release of endogenous prostaglandins. Assays for PGE in the supernatants of mesangial cell cultures supported this mechanism, as mesangial cells stimulated by macrophage products produced significantly more PGE when compared with that of control cell supernatants. Further corroboration of this mechanism was provided by the direct demonstration that exogenous PGE_2 stimu-

lates mesangial cell growth (56). Other reports show PGE_2 inhibiting proliferation.

The effect of one macrophage product, interleukin 1 (IL-1) on mesangial cell function has been the focus of intensive study. Lovett *et al.* (57) showed that purified IL-1 enhanced the proliferative rates of mesangial cells in the presence of serum but was without effect when the cells were grown in serum depleted of platelet-derived growth factor (PDGF). PDGF acted to increase the percentage of cycling cells without affecting the length of cycling times. IL-1 also has been shown to stimulate mesangial cell production of gelatinase (58), PGE (59), and oxygen radicals (60). The biochemical mechanism by which IL-1 activates the mesangial cell has been provided by further studies of Lovett *et al.* (61). In these investigations, IL-1 activated mesangial cell plasma membrane protein kinases. Plasma membranes from cycling mesangial cells were incubated with purified IL-1 and ATP in the absence of calcium and cyclic nucleotide. Macrophage IL-1 stimulated the rapid phosphorylation of several plasma membrane proteins, the most significant of which were 52–55, 46, and 20 kDa in size. Macrophage IL-1 induced specific membrane phosphorylation in concentrations as low as 1.5×10^{-12} *M*, an effect obtained with equivalent concentrations of purified mesangial cell IL-1. The 46-kDa phosphoprotein, which was the most prominent, was alkali resistant and contained phosphotyrosine when examined by phosphoamino acid analysis. The 52- to 55- and 22-kDa phosphoproteins were alkali labile and contained phosphoserine. The 46-kDa phosphoprotein was the major phosphoprotein recovered from concanavalin A-Sepharose IL-1 affinity columns. Induction of plasma membrane-associated protein kinase activity may represent one mechanism whereby IL-1 initiates mesangial cellular activation.

The stimulatory effect of IL-1 on mesangial cell growth is amplified by the action of another macrophage product. β-endorphin, a neuropeptide released by organisms during periods of stress. In studies of Ooi *et al.* (62) both β-endorphin and metenkephalin augmented the effect of IL-1 on mesangial cell proliferation in a dose-dependent fashion. Pretreatment of the cells with naloxone did not significantly reduce this amplification effect of the neuropeptides on mesangial cell growth, indicating that this effect was mediated by naloxone-insensitive receptors. These observations highlight a potential mechanism by which neuropeptides may influence immune-mediated cellular pathology.

The interaction of IL-1 with mesangial cells is further complicated by the finding that the mesangial cell itself produces IL-1. Rat mesangial cells in culture produce a substance with thymocyte-activating properties, which behaves as an endogenous pyrogen and which, on stringent biochemical analysis, has the same molecular weight, charge, specific activity, and peptide map as macrophage IL-1 (63–65). This would suggest that IL-1 can affect mesangial cell function in both a paracrine and an autocrine fashion. Continuing studies by Lovett and Larsen (66) have demonstrated the presence of mRNA for IL-1 in proliferating mesangial cells but not in nonproliferating cells. The significance of IL-1 expression in disease has been validated by observations in a model of immune complex glomerulonephritis in which nephritic kidneys were shown to contain a two-fold to three-fold increase in IL-1 mRNA compared with normals (67). Enhanced gene expression of IL-1 has also been observed in some strains of autoimmune mice (68, 69).

Another growth factor produced by macrophages is PDGF (70). PDGF has been shown to bind to mesangial cells in a specific manner and to induce the proliferation of such cells (71). This growth factor also induces the contraction of mesangial cells, as assessed by cell imaging techniques, and may exert its effect by a phospholipase C-dependent pathway (72).

Studies by Abboud *et al.* (73) show that mesangial cells produce a PDGF-like protein. This was initially demonstrated by finding that a mesangial cell product could compete with purified labeled PDGF for binding to human foreskin fibroblasts, and by showing that this PDGF-competing activity coelutes with PDGF when it is subjected to procedures which are used for the isolation of PDGF (73). Subsequently, investigators from the same laboratory have demonstrated the presence of poly(A) RNA expression of both PDGF A and B chain mRNA in human mesangial cells (71). The expression of PDGF mRNA in the mesangial cell is enhanced when they are exposed to other mitogens such as epidermal growth factor (EGF), tumor necrosis factor (TNF), and basic fibroblast growth factor (74). In fact, the mitogenic effect of EGF is partially abrogated by treatment of the cells with anti-PDGF antibody (74). These observations suggest that PDGF may be an effector molecule that plays a role in the mitogenic response of mesangial cells to many types of growth stimuli. In nephritis, PDGF may play an active role, as has been demonstrated in a model of IgA nephropathy induced by the administration of DEAE-dextran or dextran sulfate to mice. Increased expression of PDGF was correlated with the development of a pathologic picture of mesangial proliferative glomerulonephritis (75).

Preliminary observations have also been made on the effects of two other substances elaborated by the macrophage: EGF and TNF. EGF has been found to increase mesangial cell growth (76, 77) and to stimulate the production of PGE (78, 79). Its action on cell growth is modulated by the effect of transforming growth factor-β (TGF-β) (77).

TNF has been found to stimulate mesangial cell proliferation (80, 81) and to generate PGE. The acti-

vation of cyclooxygenase by TNF is a function synergistic with that of IL-1 (82, 83). TNF itself activates the IL-1 gene as well (84). Finally, TNF induces the release of procoagulant activity and oxygen radicals (85). Mesangial cells can be induced to produce TNF by various lectins and viruses (86). The significance of TNF in renal disease has been suggested by enhanced expression of this gene in various strains of autoimmune mice (68, 69).

In addition to mitogenic peptides, the macrophage also secretes substances which suppress growth. One of these is TGF-β (87). Studies from three laboratories show that this substance is capable of inhibiting the growth of mesangial cells, both under basal conditions and in response to various mitogens (77, 88, 89). Additionally, Mackay *et al.* (88) found a bifunctional effect of TGF-β which was dependent on the density of the cells plated. These investigators have demonstrated a high-affinity receptor for this peptide (K_d = 5 pM) in mesangial cells and in other glomerular cell types. The mechanism of action of TGF-β whereby it antagonizes the actions of EGF and PDGF has been examined by Jaffer *et al.* (89). They have found that this function was not mediated at the receptor level, since TGF-β did not alter the binding of either mitogen to the mesangial cell. The peptide also did not act by decreasing the synthesis of PDGF in these cells, PDGF being the autocrine effect or molecule which mediates the growth effect of these mitogens (see above). Of interest, recent preliminary observations suggest that mesangial cells are capable of producing TGF-β (90). Thus, the mesangial cell appears to have multiple internal regulatory controls by producing substances which both stimulate and inhibits its own growth. In addition to its effect on growth, TGF-β also influences matrix production by the mesangial cells. Mackay *et al.* (88) reported that this peptide increased the production of fibronectin and collagen by mesangial cells. In contrast, Border *et al.* (91) found that TGF-β increased the production of the two proteoglycans, decorin and biglycan, but had no effect on the synthesis of other matrix proteins.

Another substance liberated by activated macrophages which has been shown to suppress mesangial cell growth is 1,25-dihydroxyvitamin D_3 (92). This vitamin D metabolite inhibited the primary proliferation of mesangial cells in culture and antagonized the effect of EGF on cell growth.

Modulation of Immune Function by Mesangial Cell Products. Studies in several laboratories have shown that there is reciprocal modulation of cell function by mesangial cell products. The investigations by Lovett *et al.* (63–65), which have demonstrated the biosynthesis of IL-1 by rat mesangial cells, have been described in detail in the previous section. In addition, studies by MacCarthy *et al.* (93) found that the supernatant of mouse mesangial cells contained a factor which could induce the production of IL-1 by splenic macrophages. This was demonstrated by experiments which initially found that mesangial cell supernatant could stimulate splenic cell proliferation. The finding that this stimulating action of mesangial cell supernatant on splenic cell proliferation was dependent on the presence of macrophages in the target cell population suggested that this effect might be mediated by the release of IL-1. That this was the case was demonstrated by the presence of a co-thymocyte proliferation factor in the supernatants of cultures of macrophages incubated with mesangial cell supernatant. Further studies from the same laboratory showed that a similar mesangial cell product also induced the replication of splenic monocytes/macrophages and of blood monocytes but not of peritoneal macrophages (94). Replication of monocytes/macrophages was demonstrated both by cell enumeration and by macrophage uptake of tritiated thymidine. The replicated cells were shown to be monocytes/macrophages by the Fc receptor assay and by immunofluorescence staining of cells for the macrophage antigen, MAC-1. Purification of the factor by sequential chromatofocusing followed by gel chromatography has been accomplished, revealing the factor to have a pI of 4 and molecular mass of approximately 68,000 daltons (94). These are the characteristics of CSF-1, a substance which previously has been shown to induce monocyte/macrophage replication (95). In support of CSF-1 production by mesangial cells is the recent report that CSF-1 can be detected by radioimmunoassay in the supernatants of mouse mesangial cell cultures (96). The biosynthesis of this substance is increased by γ-interferon and inhibited by dibutryl cAMP. mRNA for CSF-1 could also be demonstrated in these cells using a specific cDNA probe. Additionally, receptors for CSF-1 were visualized in such cells using either radiolabeled CSF-1 or a probe for the mRNA of the receptor. Zoja *et al.* (84) have corroborated these observations and additionally, found that mesangial cells stimulated with IL-1 also expressed granulocyte-macrophage (GM)-CSF. Related studies (97) have shown that a product from mouse mesangial cells could induce the expression of the Ia antigen of blood monocytes (which are normally Ia negative). The process was shown to be time dependent and to be dependent on novel protein synthesis, since prior treatment of the target cell with cycloheximide abrogated the effect of the mesangial cell-derived product. This observation has implications in two areas. It provides the mechanism by which blood monocytes which take up residence in the mesangium are enabled to express the Ia antigen. It also provides the mechanism by which the mesangium can locally regulate the numbers of Ia-positive cells during nephritis. Definitive data on the synthesis of GM-CSF has been provided by the investigations by Budde *et al.* (97), who have demonstrated

a factor in the supernatant of cultured rat mesangial cells which supports the growth of the helper cell line, HT-2, which increases the growth of macrophages, and which, by serologic and biochemical analysis, has all of the characteristics of GM-CSF. Furthermore, Northern blot and *in situ* hybridization with a specific cDNA probe for murine GM-CSF showed that mesangial cells expressed GM-CSF transcripts.

In addition to IL-1, GM-CSF-1, GM-CSF, and CSF-1, recent data, reported in preliminary form, document that mesangial cells produce other immunomodulatory substances such as TGF-β (90), TNF (86), and interleukin 6 (98).

Summary

It is likely that a complex bidirectional interaction occurs between mesangial cells and the immune cells which infiltrate the mesangium during nephritis. Macrophages and other immune cells liberate a series of mediators, including substances such as IL-1, β-endorphin, TNF, and PDGF—all of which promote the growth of mesangial cells. The end result is mesangial cell proliferation and increased matrix production, both of which are seen in nephritis. The proliferating mesangial cells liberate autocoids such as IL-1 and PDGF, thereby setting up an amplifying loop. Simultaneously, suppressive factors such as TGF-β are released which antagonize the actions of these growth-promoting substances. The proliferating mesangial cells also produce immunomodulatory peptides, which will in turn act on the infiltrating macrophages to stimulate their replication and activation. Such activated macrophages continue to amplify the inflammatory lesion and also promote the phagocytosis of localized antigen-antibody complexes. The net effect of all of these interactions will depend on the dominance of substances which persist and override the roles of other molecules. Studies of the controls which regulate the production of these growth factors/immune modulators will yield insights into the fundamental mechanisms which determine the outcome in glomerulonephritis.

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1. Zimmermann KW. Uber den bau des glomerulus der saugerniere: Weitare mitteilunger. Z Mikrosk Anat Forsch **32**:176–278, 1933.
2. Latt H. Ultrastructure of the glomerulus and juxtaglomerular apparatus. In: Orloff J, Berliner RW, Eds. Handbook of Physiology: Renal Physiology. New York: Oxford University Press, Inc., pp1–29, 1973.
3. Andrews PM, Coffey AK. Cytoplasmic contractile elements in glomerular cells. Fed Proc **42**:3046–3052, 1983.
4. Becker CG. Demonstration of actomyosin in mesangial cells of the renal glomerulus. Am J Pathol **66**:97–110, 1972.
5. Becker CG, Hardy AM, Dubin T. Contractile and relaxing proteins of smooth muscle, endothelial cells and platelets. In: Didisheim P, Ed. Platelets, Thrombosis Inhibitors. New York: Schattaur Verlay, pp25–34, 1974.
6. Scheinman JI, Fish AJ, Matas AJ, Michael AF. The immunohistopathology of glomerular antigens. II. The glomerular basement membrane, actomyosin, and fibroblast surface antigens in normal, diseased and transplanted human kidneys. Am J Pathol **90**:71–84, 1978.
7. Scheinman JI, Fish AJ, Michael AF. The immunohistopathology of glomerular antigens: The glomerular basement membrane, collagen and actomyosin antigens in normal and diseased kidneys. J Clin Invest **54**:1144–1154, 1974.
8. Latta H, Cook ML. Collagen in normal rat glomeruli. J Ultrastruct Res **5**:364–373, 1961.
9. Roll FJ, Madri JA, Albert J, Furthmayr H. Codistribution of collagen types IV and AB in the basement membrane and mesangium of the kidney. J Cell Biol **85**:597–616, 1980.
10. Scheinman JI, Foidart JM, Michael AF. The immunohistology of glomerular antigens. V. The collagenous antigens of the glomerulus. Lab Invest **43**:373–381, 1980.
11. Scheinman JI, Tsai C. Monoclonal antibody to type IV collagen with selective basement membrane localization. Lab Invest **50**:101–112, 1984.
12. Martinez-Hernandez A, Gay AS, Miller EJ. Ultrastructural localization of type V collagen in the rat kidney. J Cell Biol **92**:343–349, 1982.
13. Hancock WW, Kraft N, Clarke F, Atkins RC. Production of monoclonal antibodies to fibronectin, type IV collagen and other antigens of the human glomerulus. Pathology **16**:197–206, 1984.
14. Brown DM, Michael AF, Oegema TR. Glycosaminoglycan synthesis by glomeruli in vivo and in vitro. Biochim Biophys Acta **674**:96–104, 1981.
15. Kanwar Y, Rosenzweig LJ, Jakubowski ML, Distribution of de novo synthesized sulfated glycosaminoglycans in the glomerular basement membrane and mesangial matrix. Lab Invest **49**:216–225, 1983.
16. Klein DJ, Brown DM, Oegema TR. Partial characterization of heparan and dermatan sulfate proteoglycans synthesized by normal rat glomeruli. J Biol Chem **261**:16636–16652, 1986.
17. Kanwar Y, Jakubowski ML, Rozenzweig LJ. Distribution of sulfated glycosaminoglycans in the glomerular basement membrane and mesangial matrix. Eur J Cell Biol **31**:290–296, 1983.
18. Kobayashi S, Oguri K, Yaotia E, Kobayashi K, Okayama M. Highly sulfated proteochondroitin sulfates synthesized in vitro by rat glomeruli. Biochim Biophys Acta **841**:71–80, 1985.
19. Kobayashi S, Oguri K, Kobayashi K, Okayama M. Isolation and characterization of proteoheparan sulfate synthesized in vitro by rat glomeruli. J Biol Chem **258**:12051–12057, 1983.
20. Courtoy PJ, Kanwar YS, Hynes RO, Farquhar MG. Firbonectin localization in the rat glomerulus. J Cell Biol **87**:691–696, 1980.
21. Courtoy PJ, Timpl R, Farquhar MG. Comparative distribution of laminin, type IV collagen, and fibronectin in the rat kidney cortex. J Histochem Cytochem **30**:874–880, 1982.
22. Linder E, Miettinen A, Tornroth T. Fibronectin as a marker for the glomerular mesangium in immunohistology of kidney biopsies. Lab Invest **42**:70–75, 1980.
23. Rohde H, Wick G, Timpl R. Immunochemcial characterization of the basement membrane glycoprotein laminin. Eur J Biochem **102**:195–201, 1979.
24. Wight TN, Raugi GJ, Mumby SM, Bornstein P. Light microscopic immunolocation of thrombospondin in human tissue. J Histochem Cytochem **33**:295–302, 1985.
25. Latta H, Fligiel S. Mesangial fenestrations, sieving, filtration and flow. Lab Invest **52**:591–598, 1985.

26. Gallo GR, Caulin-Glaser T, Lamm ME. Charge of circulating immune complexes as a factor in the glomerular basement membrane localization in mice. J Clin Invest **67**:1305–1313, 1981.
27. Kanwar YS, Caulin-Glaser T, Gallo GR, Lamm ME. Interaction of immune complexes with glomerular heparin sulfate-proteoglycans. Kidney Int **30**:842–851, 1986.
28. Hebert LA, Allhiser CA, Koethe SM. Some hemodynamic determinants of immune complex trapping by the kidney. Kidney Int **14**:452–465, 1978.
29. Meyer TW, Brenner BM. The contribution of glomerular hemodynamic alterations to progressive renal disease. Contemp Issues Nephrol **14**:1–16, 1986.
30. Bernik MB. Contractile activity of human glomeruli in culture. Nephron **6**:1–10, 1969.
31. Quadracci LJ, Striker GE. Growth and maintenance of glomerular cells in vitro. Proc Soc Exp Biol Med **135**:974–976, 1970.
32. Ausiello DA, Kreisberg JJ, Roy C, Karnovsky MJ. Contraction of glomerular cells of apparent mesangial origin after stimulation with angiotensin II and arginine vasopressin. J Clin Invest **65**:754–760, 1980.
33. Foidart J, Dechenne C, Dubois C, Deheneffe J, Mahieu P. Tissue culture of isolated renal glomeruli: Present and future. Adv Nephrol **10**:267–292, 1981.
34. Schreiner GF, Kiely JM, Cotran RS, Unanue ER. Characterization of resident glomerular cells in the rat expressing Ia determinants and manifesting genetically restricted interactions with lymphocytes. J Clin Invest **68**:920–931, 1981.
35. Schreiner GF, Unanue ER. Origin of the rat mesangial phagocyte and its expression of the leukocyte common antigen. Lab Invest **51**:515–523, 1984.
36. Men'e P, Simonson MS, Dunn MJ. Physiology of the mesangial cell. Physiol Rev **69**:1347–1424, 1989.
37. Dzau VJ, Kreisberg JI. Cultured glomerular mesangial cells contain renin: Influence of calcium and isoproterenol. J Cardiovasc Pharmacol **8** (suppl 10):S6–S10, 1986.
38. Chansel D, Dussaule JC, Ardaillou N, Ardaillou R. Identification and regulation of renin in human cultured mesangial cells. Am J Physiol **252**:F32–F38, 1987.
39. Davies M, Thomas GJ, Martin J, Lovett DH. The purification and characterization of a glomerular basement membrane degrading neutral proteinase from rat mesangial cells. Biochem J **251**:419–425, 1988.
40. Lovett DH, Sterzel RB, Kashgarian M, Ryan JL. Neutral proteinase activity produced in vitro by cells of the glomerular mesangium. Kidney Int **23**:342–349, 1983.
41. Lacave R, Rondeau E, Ochi S, Delarue F, Schleuning WD, Spaer JD. Characterization of a plasminogen activator and its inhibitor in human mesangial cells. Kidney Int **35**:806–811, 1989.
42. Stefanovic V, Savic V, Vlahovic P, Ardaillou N, Ardaillou R. Ecto-5′-nucleotidase of cultured rat mesangial cells. Renal Physiol **11**:85–102, 1988.
43. Kurtz A, Jelkmann W, Sinowatz F, Bauer C. Renal mesangial cells in culture in a model of erythropoietin production. Proc Natl Acad Sci USA **80**:4008–4011, 1983.
44. Hunsicker LG, Shearer TP, Plattner SB, Weisenburger D. The role of monocytes in serum sickness nephritis. J Exp Med **150**:413–425, 1979.
45. Schreiner GF, Cotran RS, Pardo V, Unanue U. 1979. A mononuclear cell component in experimental immunologic glomerulonephritis. J Exp Med **147**:369–384, 1979.
46. Monga G, Mazzucco G, di Belgiojoso GB, Busnach G. The presence and possible role of monocyte infiltration in human chronic proliferative glomerulonephritis. Am J Pathol **94**:271–275, 1979.
47. Holdworth SR, Neale TJ, Wilson CB. Abrogation of macrophage-dependent injury in experimental glomerulonephritis in the rabbit: Use of an antimacrophage serum. J Clin Invest **68**:686–698, 1981.
48. Sedor JR, Carey SW, Emancipator SN. Immune complexes bind to cultured rat glomerular mesangial cells to stimulate superoxide release. J Immunol **138**:3751–3757, 1987.
49. Knauss TC, Mene P, Ricanati SA, Kester M, Dubyak GR, Emancipator SN, Sedor JR. Immune complex activation of rat glomerular mesangial cells: Dependence on the Fc region of antibody. Am J Physiol **257**:F478–F485, 1989.
50. Neuwirth R, Singhal P, Diamond B, Hays RM, Lobmeyer L, Clay K, Schlondorff D. Evidence for immunoglobulin Fc receptor-mediated prostaglandin 2 and platelet-activating factor formation by cultured rat mesangial cells. J Clin Invest **87**:936–944, 1988.
51. Santiago A, Satriano J, DeCundido S, Holthofer H, Schreiber R, Unkeless J, Schlondorff D. A specific Fc gamma receptor on cultured rat mesangial cells. J Immunol **143**:2575–2582, 1989.
52. Singhal PC, Santiago A, Satrino J, Hays RM, Schlondorff D. Effect of vasoactive agents on uptake of immunoglobulin G complexes by mesangial cells. Am J Physiol **258**:F589–F596, 1989.
53. Santiago A, Satriano J, Mori T, Schlondorff D. Regulation of Fc receptors for IgG on cultured rat mesangial cells [Abstract]. Kidney Int **37**:430, 1990.
54. Melcion C, Lachman L, Killen PD, Morel-Maroger L, Striker GE. Mesangial cells, effect of monocyte products on proliferation and matrix synthesis. Transplant Proc **141**:559–568, 1982.
55. Ooi YM, Weiss MA, Hsu A, Ooi BS. Mechanisms of suppression of mouse mesangial cell proliferation by macrophage supernatants. J Immunol **130**:1790–1795, 1983.
56. MacCarthy EP, Hsu A, Ooi YM, Ooi BS. Modulation of mouse mesangial cell proliferation by macrophage products. Immunology **56**:695–699, 1985.
57. Lovett DH, Ryan JL, Sterzel RB. Stimulation of rat mesangial cell proliferation by macrophage interleukin 1. J Immunol **131**:2830–2836, 1983.
58. Martin J, Lovett DH, Gemsa D, Sterzel RB, Davies M. Enhancement of glomerular mesangial cell neutral proteinase secretion by macrophages: Role of interleukin 1. J Immunol **137**:525–529, 1986.
59. Lovett DH, Resch K, Gemsa D. Interleukin 1 and the glomerular mesangium II. Monokine stimulation of mesangial cell prostanoid secretion. Am J Pathol **129**:543–551, 1987.
60. Radele HH, Meier B, Topley N, Floege J, Habermehl GG, Resch K. Interleukin 1 and/or tumor necrosis factor induce oxygen radical production in mesangial cells. Kidney Int **37**:767–775, 1990.
61. Lovett DH, Martin M, Burstein S, Szamel M, Gemsa D, Resch K. Interleukin 1 and the glomerular mesangium. III. Il-1-dependent stimulation of mesangial cell protein kinase activity. Kidney Int **34**:26–35, 1988.
62. Ooi BS, MacCarthy, EP, Hsu A. Beta-endorphin amplifies the effect of interleukin-1 on mouse mesangial cell proliferation. J Lab Clin Med **110**:159–163, 1987.
63. Lovett DH, Ryan JL, Sterzel RB. A thymocyte activating factor derived from glomerular mesangial cells. J Immunol **130**:1796–1801, 1983.
64. Lovett DH, Sterzel RB, Ryan JL, Atkins E. Production of an endogenous pyrogen by glomerular mesangial cells. J Immunol **134**:670–672, 1985.
65. Lovett DH, Szamel M, Ryan JL, Sterzel RB, Gemsa D, Resch K. Interleukin 1 and the glomerular mesangium. I. Purification and characterization of a mesangial cell-derived autogrowth factor. J Immunol **136**:3700–3705, 1986.
66. Lovett DH, Larsen A. Cell cycle-dependent interleukin 1 gene expression by cultured glomerular mesangial cells. J Clin Invest **82**:115–122, 1988.

67. Weber HI, Emancipator SN, Tykocinski ML, Sedor JR. The interleukin 1 gene is expressed by rat glomerular mesangial cells and is augmented in immune complex glomerulonephritis. J Immunol **138**:3207–3212, 1987.
68. Boswell JM, Yui MA, Burt DW, Kelly VE. Increased tumor necrosis factor IL-1 beta gene expression in the kidneys of mice with lupus nephritis. J Immunol **141**:3050–3054, 1988.
69. Brennan DC, Yui MA, Wuthrich RP, Kelly VE. Tumor necrosis factor and IL-1 in New Zealand Black/White mice. Enhanced gene expression and acceleration of renal injury. J Immunol **143**:3470–3475, 1989.
70. Ross R, Raines EW, Bowen-Pope DF. The biology of platelet-derived growth factor: Review. Cell **46**:155–169, 1986.
71. Shultz PJ, DiCorleto PE, Siler BJ, Abboud HE. Mesangial cells express PDGF mRNAs and proliferate in response to PDGF. Am J Physiol **255**:F674–F684, 1988.
72. Men'e P, Abboud HE, Dubyak GR, Scarpa A, Dunn MJ. Effects of PDGF on inositol phosphates, Ca^{2+}, and contraction of mesangial cells. Am J Physiol **253**:F458–F463, 1987.
73. Abboud HE, Poptic E, DiCorleto P. Production of platelet-derived growth factor like protein by rat mesangial cells in cultures. J Clin Invest **80**:675–683, 1987.
74. Silver BJ, Jaffer FE, Abboud HE. Platelet-derived growth factor synthesis in mesangial cells: Induction by multiple peptide mitogens. Proc Natl Acad Sci USA **86**:1056–1060, 1989.
75. Gesualdo L, Abboud HE, Pinzani M, Floriano J, Lamm ME, Emancipator SE. Platelet-derived growth factor expression is increased in murine IgA nephropathy [Abstract]. Kidney Int **37**:414, 1990.
76. Jaffer F, Saunders C, Shultz P, Abbound HE. Regulation of DNA synthesis in human mesangial cells by peptide mitogens [Abstract]. Kidney Int **33**:318, 1988.
77. Yamashita W, MacCarthy EP, Hsu A, Gartside PA, Ooi BS. The effect of transforming growth factor-beta on mouse mesangial cell proliferation. Clin Exp Immunol **77**:285–288, 1989.
78. Knauss TC, Men'e P, Kester M, Abboud HE. EGF and PDGF stimulate mesangial cell prostanoid synthesis by different mechanisms [Abstract]. Kidney Int **33**:162, 1988.
79. Margolis BL, Bonventre JV, Kremer S, Kudlow J, Skorecki KL. Epidermal growth factor is synergistic with phorbol esters and vasopressin in stimulating arachidonate release and prostaglandin production renal glomerular mesangial cells. Biochem J **249**:587–592, 1988.
80. Perez J, Baud L, Ardaillou R. Tumor necrosis factor stimulates prostaglandin, cyclic AMP, and DNA synthesis by cultured rat mesangial cells [Abstract]. Kidney Int **35**:318, 1989.
81. Yamamoto T, Yuoita E, Kawasaki K, Kihara I. Tumor necrosis factor augments proliferation of rat mesangial cell [Abstract]. Kidney Int **35**:367, 1989.
82. Topley N, Floege J, Kaever V, Resch K. Interleukin-1B and tumor necrosis factor a synergistically induce PGE_2 release in human mesangial cells. Kidney Int **35**:318, 1989.
83. Barton M, Coyne DW, Morrison AR. Effects of tumor necrosis factor on PGE_2 production and cyclooxygenase activity in rat mesangial cells [Abstract]. Kidney Int **37**:205, 1990.
84. Zoja C, Bettoni S, Tini ML, Abboud HE, Remuzzi G, Rambaldi A. In vitro regulation of CSR genes by interleukin-1 and tumor necrosis factor in human mesangial cells [Abstract]. Kidney Int **37**:205, 1990.
85. Wiggins RC, Nojku N, Sedor JR. Tissue factor production by cultured rat mesangial cells. Stimulation by TNF and lipopolysaccharide. Kidney Int **37**:1281–1285, 1990.
86. Amore A, Coppo R, Emancipator SN, Roccatello D, Lamm ME, Quattrochhio G, Piccoli G. Tumor necrosis factor and interleukin-2 receptor production by cultured rat mesangial cells induced by viruses and environmental lectins [Abstract]. Kidney Int **37**:307, 1990.
87. Madtes DK, Raines EW, Sakariassen KS, Assoain RK, Sporn MB, Bell GJ, Ross R. Induction of transforming growth factor in activated human macrophages. Cell **53**:285–293, 1988.
88. Mackay K, Striker LJ, Stauffer JW, Doi T, Agoda LY, Striker GE. Transforming growth factor-beta. Murine glomerular receptor and responses of isolated glomerular cells. J Clin Invest **83**:1160–1167, 1989.
89. Jaffer F, Saunders C, Schultz P, Throckmorton D, Weinshell E, Abboud HE. Regulation of mesangial cell growth by polypeptide mitogens. Inhibitory role of transforming growth factor beta. Am J Pathol **135**:261–269, 1989.
90. Kaname S, Uchida S, Ogata E, Kurkama K. Transforming growth factor-beta gene expression in cultured rat mesangial cells [Abstract]. Kidney Int **37**:197, 1990.
91. Border WA, Okuda S, Languino LR, Ruoslahit E. Transforming growth factor-β regulates production of proteoglycans by mesangial cells. Kidney Int **37**:689–695, 1990.
92. Ooi BS, MacCarthey EP, Hong SY, Hsu A. Regulation of mouse mesangial cell proliferation by 1,25 D3 [Abstract]. Kidney Int **35**:358, 1989.
93. MacCarthy EP, Hsu A, Ooi YM, Ooi BS. Evidence for a mouse mesangial cell-derived factor that stimulates lymphocyte proliferation. J Clin Invest **76**:426–430, 1985.
94. Ooi BS, MacCarthy EP, Weiss MA, Hsu A, Ooi YM. Induction of mouse monocyte-macrophage replication by a mesangial cell-derived factor. J Lab Clin Med **110**:466–474, 1987.
95. Stanley ER, Guilbert LJ, Tushinski JR, Bartelmez SH. CSF-1: A mononuclear phagocyte lineage specific hemopoietic growth factor. J Cell Biochem **21**:151–159, 1983.
96. Mori T, Bartocci A, Satriano J, Santiago A, Schlondorff D. Mouse mesangial cells (MS) produce macrophage colony stimulation factor and express specific receptor for CSF-1. Kidney Int **37**:424, 1990.
97. Budde K, Coleman DL, Lacy J, Sterzel RB. Rat mesangial cells produce granulocyte macrophage stimulating factor. Am J Physiol **257**:F1065–F1078, 1989.
98. Benfield MR, Walker P, Nelson P, Michael AF, Kim Y. IL6 production by human mesangial cells in culture [Abstract]. Kidney Int **37**: 409, 1990.