MINIREVIEW

Biology of the Mesangial Cell in Glomerulonephritis–Role of Cytokines[1] (44054)

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Abstract. **The mesangial cell occupies a central position in the genesis of the pertubations occurring during the pathogenesis of glomerulonephritis. *In vitro* studies have shown that this cell is a metabolically active cell producing a variety of cytokines which act as autocoids; such cytokines are also liberated by the monocytes/macrophages which infiltrate the glomerulus in nephritis. This review summarizes the evidence for the participation of these cytokines in animal models of nephritis and in human renal disease, focusing on the roles of basic fibroblast growth factor, platelet-derived growth factor, transforming growth factor–β, colony-stimulating factor–1, tumor necrosis factor, interleukin-1, and interleukin-6.** [P.S.E.B.M. 1996, Vol 213]

One of the hallmarks of glomerulonephritis is the proliferation of the mesangial cell accompanied usually by an increase of mesangial matrix. The mesangial cell is an actively metabolic cell which synthesizes an array of substances, including various cytokines which act as autocoids, stimulating the cell to proliferate and to produce various proteins (reviewed in Ref. 1). Such cytokines are also liberated by the monocytes/macrophages which infiltrate the glomerulus during the onset of nephritis. The interactions between these cytokines and the mesangial cell have been found to result in many of the pertubations discerned during the evolution of immune-mediated renal disease. This update summarizes the evidence for the participation of some of these cytokines in the pathogenesis of glomerulonephritis. The cytokines which have been shown in animal models and in human disease to have a significant role in the genesis of immune-mediated renal disease include (i) basic fibroblast growth factor (bFGF); (ii) platelet-derived growth factor (PDGF); (iii) transforming growth factor–β (TGFβ); (iv) colony-stimulating factor–1 (CSF-1); (v) tumor necrosis factor (TNF); (vi) interleukin-1 (IL-1); (vii) interleukin-6 (IL-6).

Basic Fibroblast Growth Factor

bFGF is a 18-kDa cationic protein (2), which has been shown to be expressed by glomerular mesangial cells (3) and by podocytes and glomerular epithelial cells (4). *In vitro* studies have shown that this cytokine acts on two of these cell types to induce proliferation (3, 4). The participation of this cytokine in the genesis of renal disease has been shown by a number of recent investigations (3, 5–8). In studies examining the function of this protein in the evolution of glomerulone-

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phritis (3, 5), investigators studied a rat model of glomerulonephritis induced by the administration of anti-Thy 1.1 antibody. In this model there is complement-dependent mesangiolysis which peaks at Day 1 followed by mesangial cell proliferation occurring 3–5 days after disease induction. Glomerular bFGF was found initially to decrease markedly, a finding consistent with the release of bFGF after complement-mediated mesangiolysis. During the subsequent mesangial proliferative phase, glomerular bFGF protein and mRNA increased above normal concentrations. The ability of bFGF to induce mesangial cell proliferation in this model of renal disease was further demonstrated by experiments in which animals were given a subnephritogenic dose of anti-Thy 1.1 antibody followed 24 hr later with an intravenous injection of bFGF. In these animals, there was an approximately 5-fold increase in glomerular cell proliferation. Normal unmanipulated rats given the same dose of bFGF did not exhibit this glomerular cell proliferation, suggesting that bFGF was mitogenic for injured mesangial cells. Interestingly, in contrast to the effect of PDGF on mesangial cell matrix protein synthesis in this model, bFGF had no discernible effect on the production of such proteins.

In addition to its role in the induction of mesangial cell proliferation, bFGF has also been implicated in recent studies as a possible mediator of glomerulosclerosis (6, 7). In one study, Sprague-Dawley rats were given daily injections of bFGF for 13 weeks. The animals so treated developed albuminuria and increases in serum creatinine, indicating the development of chronic renal failure. Histologically, the renal lesions were those of classic focal glomerulosclerosis. The evolution of these lesions was traced by sequential observations which revealed the following. Podocyte lesions were common in the early stages. Mitotic figures in podocytes, with a considerable number of multinucleated podocyte profiles were seen in the treated animals. Since an increase in cell number was not evident, the investigators concluded that bFGF stimulated the podocytes to enter the cell cycle and to undergo nuclear division. However, since the podocyte is a highly differentiated cell, it was unable to complete cell division, resulting in bi- or multinucleated cells; in yet other cells, cell division failed, leading to complete degeneration. Most podocytes in these bFGF-treated animals exhibited extensive degenerative changes, including marked pseudocyst formation, cell body attenuation, extensive foot process effacement, and detachment from the glomerular basement membrane. A sequel of podocyte detachment was the formation of tuft adhesions to Bowman's capsule, a nidus established by the attachment of parietal cells to a naked GBM area. Expansion of these tuft adhesions occurred by the growth and encroachment of more parietal cells onto adjacent capillary loops, resulting in solid synechiae with collapsed capillaries, giving rise ultimately to focal sclerosis. The distribution of such adhesions on the inner surface of Bowman's capsule appeared to be random, including all locations between the vascular and urinary pole. Of interest, the lesions were more pronounced in males than females, suggesting a modulatory effect of sex hormones.

Another study examined the role of bFGF in the induction of glomerular sclerosis using a different animal model (7), namely, passive Heymann's nephritis (PHN) in which the rats were given an antiserum to crude tubular antigen (called Fx1A). Rats were then divided into two groups, one group of which received daily boluses (from Days 3 to 8 after the antiserum injection) of bFGF and the other, equivalent volumes of the vehicle. On Day 8, bFGF-injected rats developed more pronounced proteinuria than controls; by Day 120, these rats developed renal failure as evidenced by a rise of serum creatinine paralleled by sclerosis of a significant number of glomeruli. Histological examination of glomeruli of bFGF-treated animals showed mitotic figures, pseudocyst formation, foot process retraction, focal detachment from the glomerular basement membrane, and desmin expression. bFGF administration did not alter antibody or complement deposition or glomerular leukocyte influx, excluding the participation of these mechanisms as being responsible for the changes seen. In addition, it was shown that bFGF could induce proteinuria and podocyte damage in rats injected with only 10% of the regular antiserum dose. The investigators postulated that there was upregulation of bFGF receptor expression induced by the antiserum used to induce Heymann's nephritis, resulting in augmented podocyte damage by bFGF which led to increased glomerular permeability and accelerated glomerulosclerosis. It was concluded that release of bFGF from glomerular sources, including podocytes themselves, could represent an important mechanism by which podocyte damage was enhanced or self-sustained.

Finally, the potential pathogenic effect of bFGF in the development of HIV nephropathy has been implicated in a transgenic model in which mice developed lesions similar to those found in patients affected by the virus (8). In this HIV transgenic model, the mice developed tubular epithelial cell proliferation and injury. In areas of microcystic proliferation, immunoreactive bFGF co-localized with the extracellular matrix. Kidneys from the transgenic mice also showed increased bFGF low-affinity binding sites, particularly in the interstitium. *In vitro,* transgenic renal epithelial cells proliferated (spontaneously) more rapidly, in marked contrast to nontransgenic renal cells where such findings could only be mimicked by exogenous bFGF. The results of the study suggested to the au-

thors that bFGF might play an important role in the pathogenesis of HIV-associated nephropathy.

Platelet-Derived Growth Factor

In vitro studies have previously shown that PDGF, a mitogen for cells of mesenchymal origin is produced by mesangial cells and binds to them, stimulating them to proliferate (9, 10). The role of this growth factor in the genesis of nephritis has been explored in various animal models and in human biopsies. Yoshimura *et al.* (11) used an *in situ* hybridization method to determine if there was increased expression of PDGF B-chain mRNA in the kidneys of animals developing mesangial proliferative glomerulonephritis induced by the infusion of anti-Thy 1.1 antibody. In normal rats, the majority of glomeruli were negative for this protein whereas almost two-thirds of all glomeruli of nephritic animals exhibited segmental or diffuse staining for PDGF B-chain mRNA. The increase in PDGF B-chain mRNA was localized to areas of hypercellularity and was associated with an increase in cells positive for B-chains by immunostaining with a specific monoclonal antibody. Complement depletion, which prevented the mesangial cell proliferation also abrogated the increase in cells expressing the PDGF B-chain mRNA and protein. Extending observations in this model, Floege *et al.* (5) infused PDGF into either unmanipulated rats or rats given a subnephritogenic dose of anti-Thy 1.1 and showed that the cytokine increased glomerular cell proliferation 32-fold in the anti-Thy 1.1 rats and 11-fold in normal rats. The cells proliferating were demonstrated by double staining to be mostly mesangial cells. In addition (by contrast with rats infused with bFGF), the glomeruli exhibited matrix expansion with increased deposition of type IV collagen, laminin, and fibronectin protein, as well as upregulated laminin and collagen IV mRNA expression. The data indicate that PDGF is an *in vivo* mitogen for mesangial cells; they also demonstrate that previous subclinical injury can enhance this mesangial cell response. Definitive evidence for the role of PDGF in this model of nephritis was provided by experiments in which the animals were treated with an antibody to PDGF (or nonimmune IgG in control animals) after induction of the disease with anti-Thy 1.1 (12). Inhibition of the effect of PDGF resulted in a significant reduction in mesangial cell proliferation and prevented the increased deposition of extracellular matrix proteins associated with this disease.

Gesualdo *et al.* (13) examined the expression of PDGF in two animal models of IgA nephropathy induced by immunization with either cationic dextran or anionic dextran. Immunization with the cationic antigen produced glomerular disease characterized by predominantly mesangial matrix expansion while immunization with anionic dextran produced a glomerular lesion characterized by mesangial cell proliferation. In both models, increased expression of PDGF B-chain mRNA was found by solution hybridization assay of whole mouse kidneys; PDGF A-chain mRNA could not be demonstrated in these kidneys. By immunochemical methods, PDGF was localized primarily in the mesangial areas of glomeruli and to a lesser extent in the interstitium. The increased PDGF expression correlated with the degree of hypercellularity and with the clinical features of the disease.

The role of this molecule in the renal disease of the autoimmune lpr mice was studied by Liu and Ooi (14), who examined the response of the mesangial cells of 5-week-old mice to this cytokine (young mice were used so that their mesangial cells would not have been subjected to the effects of cytokines liberated by infiltrating cells). It was found that the cells of such mice were more responsive to the mitogenic effect of PDGF, proliferating more readily when compared with the growth rates of their congenic nonautoimmune controls. It was postulated that this autoimmune mouse strain had a tendency to develop mesangial proliferative lesions since its cells were more susceptible to the effect of this mitogen.

Studies have also been done examining the expression of PDGF in kidneys of patients suffering from a variety of renal disorders, ranging from minimal change disease to mesangial proliferative glomerulonephritis (15). Increase expression of the cytokine was found to parallel the severity of the proliferative glomerular changes.

Another approach to demonstrating the role of PDGF in renal disease was to examine the expression of the receptor for this cytokine. Using the model of anti-Thy 1.1 nephritis, Lida *et al.* (16) investigated for the expression of this receptor during the induction of nephritis and found that the PDGF-receptor β subunit mRNA and protein were increased in glomeruli exhibiting mesangial proliferative glomerulonephritis. In contrast to the expression of PDGF, which appeared to involve only a subpopulation of mesangial cells, the majority of mesangial cells expressed the receptor. Both complement depletion and platelet depletion significantly reduced the mesangial cell proliferation and expression of PDGF and the PDGF receptor. Using an antibody to the β subunit of the PDGF receptor, Alpers *et al.* (17) demonstrated the expression of this receptor by mesangial cells and by parietal epithelial cells of human and primate kidneys. In addition, there was also widespread expression of this protein by cortical and medullary peritubular interstitial cells. These findings provide the basis for activation of these structures by PDGF. Gesualdo (18) studied the expression of PDGF-α and β receptors in 10 normal and 40 pathologic kidneys by both immunohistochemical and by *in situ* hybridization techniques. In normal kidneys,

both PDGF-α and β receptors were expressed at both the glomerular and interstitial level, the latter receptor being expressed more intensely than the former. PDGF-β receptor gene and protein expression were upregulated in proliferative nephritides, both at the glomerular and interstitial level, with correlation with the grade of histologic lesions. By comparison, the expression of both receptors in nonproliferative nephritides was comparable to those found in normal kidneys. Diseased kidneys exhibited only a slight increase of PDGF-α receptor expression, principally at the interstitial level.

Finally, the role of PDGF in the eventuation of glomerulosclerosis in the renal ablation model of renal disease has been documented by studies (19) investigating the sequence of cellular events which precede glomerulosclerosis. Approximately 5 days after ablation, mesangial cell proliferation was observed (coincident with glomerular platelet influx). Glomerular PDGF B-chain and PDGF receptor gene and protein expression increased during glomerular cell proliferation. Proteinuria, glomerular sclerotic changes and leukocytic infiltration (consisting mostly of monocytes/macrophages) followed cell proliferation. The authors postulated the following sequence of events: (i) proliferation of intrinsic glomerular cells precedes glomerulosclerosis; (ii) proliferation may be initiated by degranulating platelets and sustained by PDGF released by intrinsic glomerular cells; (iii) glomerular monocyte/macrophage infiltration occurs after infiltration and may contribute to the glomerular sclerotic changes.

Transforming Growth Factor–β

In vitro studies have shown that mesangial cells produce this cytokine, possess receptors for it and are modulated by its effects on their rates of growth and matrix protein synthesis (20–22). The function of this protein in the anti-thymocyte serum (ATS) model of mesangial glomerulonephritis was assessed by Okuda *et al.* (23). Glomeruli cultured from these nephritic animals showed an increase in proteoglycan (consisting mostly of biglycan and decorin) and fibronectin synthesis that began on Day 4, peaked on Day 7, and returned to normal by Day 28. This synthetic activity of the glomeruli was paralleled by increased expression of TGFβ activity of the glomeruli as well as by histologic manifestations showing increase in mesangial matrix. Definitive evidence for the role of TGFβ as a molecular mediator in this model of renal disease was provided by further experiments by Border *et al.* (24) who administered an antibody to TGFβ at the time of induction of the glomerular disease. When this was done, there was suppression of glomerular production of matrix proteins with dramatic attenuation of the histologic manifestations of the disease. Another approach towards demonstrating a similar effect was achieved by the concurrent administration of a natural inhibitor of TGFβ, namely decorin (25). Decorin is a proteoglycan which has been shown by Yamaguchi *et al.* (26) to be induced by TGFβ and to function as an inhibitor of the biologic activity of the cytokine. When decorin was given to the animals which received ATS, there was a marked reduction in the production of glomerular matrix proteins with parallel improvement in the histologic manifestations of the renal disease.

The implication of TGFβ in another model of nephritis, namely, anti-glomerular basement-membrane (anti-GBM) nephritis, was shown by Coimbra *et al.* (27), who were able to demonstrate the production of TGFβ by nephritic cortices and by nephritic glomeruli during the evolution of the disease; this was paralleled by increases in cortical and glomerular TGFβ mRNA and by increases in glomerular collagen deposition.

The function of TGFβ has also been examined in the lpr mouse model of autoimmune nephritis (14). Mesangial cells of these mice were found to be relatively insensitive to the inhibitory actions of this cytokine on cell growth, accentuating the tendency to proliferate when acted on by stimulatory cytokines such as PDGF.

The involvement of this cytokine in human disease has been demonstrated by investigations examining for the expression of the protein and its mRNA in renal tissue by immunostaining and by *in situ* hybridization (28, 29). The studies revealed that normal kidneys exhibited weak expression for TGFβ protein and its mRNA. In disorders where extracellular matrix deposition was not a significant feature, the expression of the cytokine was not different from that of normal tissue. By comparison, in diseases with marked extracellular matrix accumulation, there was enhanced expression of TGFβ in the glomeruli and in the interstitium (28, 29).

In addition to its function as a mediator in stimulating mesangial matrix increase in the various forms of nephritis, TGFβ has also been shown to play a crucial role in the pathogenesis of sclerosis of the kidney. Yamamoto *et al.* (30) studied a model of glomerulosclerosis produced by two injections of ATS. In this model, animals exhibited glomerulosclerosis and tubular interstitial fibrosis by the eighteenth week with marked collagen types I and III deposition; the histological changes were also accompanied by persistent proteinuria and azotemia. These clinicopathologic manifestations were paralleled by increases in the expression of TGFβ protein and TGFβ mRNA throughout the course of the disease together with infiltration of the tubulointerstitium with mononuclear cells strongly expressing TGFβ. The markers of TGFβ activity, a special isoform of fibronectin, tenascin, biglycan, and plasminogen activator inhibitor–1 were

also elevated in the kidney undergoing fibrosis. Direct demonstration of the role of TGFβ in the induction of renal sclerosis has been obtained by the *in vivo* transfection of the gene for this protein into the rat kidney (31). Unilateral transfection of rat kidneys with either the PDGF gene or the TGFβ gene was performed. TGFβ gene transfection produced a kidney with extensive extracellular matrix expansion and only moderate mesangial cell proliferation, whereas PDGF gene transfection produced a striking increase in cellularity with some extracellular matrix expansion.

In addition to its action in promoting the synthesis of extracellular matrix components, TGFβ has two other actions which converge on the same goal. One of them is its ability to influence the activity of enzymes that degrade matrix proteins, namely, the protease enzymes. The protein plasmin is one of the key enzymes involved in such degradative processes. Its production is regulated by the balance between plasminogen activator (PA) and its inhibitor, plasminogen activator inhibitor (PAI). TGFβ was shown to promote the glomerular synthesis of PAI and to abolish the activator of PA when added to cultured normal glomeruli (31). Glomeruli cultured from nephritic animals also exhibited a decrease in PA activity and an increase in PAI synthesis with increased deposition of the inhibitor into the matrix. PAI bound to the matrix is believed to protect the matrix from degradation. Glomeruli isolated from animals administered with anti-TGFβ showed a marked reduction of PAI deposition in the matrix.

Another function of TGFβ is its ability to influence the synthesis of the various integrins. TGFβ could be shown to promote the synthesis of the α1-β1 and α5-β1 integrins by normal glomeruli (32). During the course of anti-thymocyte serum induced nephritis, the expression in glomeruli of α1, α5, and β1 subunits was shown to parallel both mesangial content of the ligands for the α1-β1 and α5-β1 integrins, laminin, collagen, and fibronectin, and TGFβ protein, increasing on Day 7 and decreasing towards normal by Day 28 (32). These studies suggest that TGFβ induced increases in integrin expression on glomerular cells contribute to the accumulation of pathologic matrix by providing increased numbers of receptors for binding of matrix components to the glomerular cell surface and for the deposition of these components into the extracellular matrix (32).

Colony-Stimulating Factor–1

Mesangial cells have been shown by in-vitro studies to produce this macrophage activating cytokine (33, 34). Its function in the pathophysiology of immune renal disease has been examined in the lpr autoimmune strain of mice which develop an analogue of lupus nephritis. Yui *et al.* (35) showed that lpr mice have increased levels of circulating CSF-1 as early as 1 week of age; the levels decreased between 2 to 4 months and then steadily increased beginning at 4 months of age. CSF-1 transcripts were also shown to be elevated in the kidneys of these mice, suggesting a renal source of the CSF-1 (35). However, when mesangial cells of these mice were examined for their capacity to produce this cytokine, the amounts of functional CSF-1 produced by these cells were found to be reduced (compared with amounts produced by nonautoimmune strains) (36, 37). Of interest, transcripts of CSF-1 produced by the cells of the lpr mice were found to be increased, suggesting an abnormality in the post-transcriptional biosynthetic pathway for the protein (37). Further studies were done by Bloom *et al.* (38), who showed that CSF-1 mRNA was detected at an early age of these autoimmune mice and increased with the severity of the disease. They also identified two populations of macrophages from the kidneys of these mice, a preproteinuric macrophage, which required CSF-1 for survival and proliferation, and a proteinuric macrophage, which was more mature and was CSF-1 independent. They speculated that CSF-1 was chemoattractant for the influx of macrophages into the kidney and also induced the proliferation and differentiation of these cells within the glomeruli, these cellular processes eventually leading to renal injury. An alternative explanation has been proposed for the reduced CSF-1 produced by the autoimmune mesangial cells (37). It has been suggested that since CSF-1 activates macrophages to phagocytic activity and since macrophages have been shown to have a scavenging function within the glomerulus in nephritis (39), a deficiency of CSF-1 may lead to deficient activation of this macrophage function with resultant persistence of immune complexes within the glomerulus.

Tumor Necrosis Factor

Tumor necrosis factor has pleomorphic actions on the mesangial cell, stimulating it to produce prostaglandins, superoxide, procoagulant and a variety of phlogistic substances (reviewed in Ref. 40). Its participation in glomerulonephritis was suggested by studies which showed increased expression of this molecule in the kidneys of animals exhibiting nephrotoxic nephritis, serum sickness nephritis and autoimmune nephritis (41–45). Glomeruli cultured from such animals were shown to produce increased levels of this substance compared to control animals (41–45). The macrophage population was identified as a cellular source for the production of this cytokine in nephrotoxic nephritis since macrophage depletion in these animals blocked augmentation of glomerular TNF production (44). One mechanism shown to result in the production of TNF by phagocytes was the interaction of these cells with

glomerular basement membrane containing immune complexes (46). A more direct demonstration of the role of TNF was shown by studies in which animals injected with subnephritogenic doses of anti-GBM antibody were pretreated with TNF; the cytokine synergistically increased proteinuria and accumulation of neutrophils in these animals (41). More definitive evidence for the role of TNF has been provided by experiments injecting animals with anti-TNF or the soluble receptor for TNF after which anti-GBM nephritis was induced by the infusion of anti-GBM antibody (47, 48). Pretreatment of animals with either anti-TNF or the soluble receptor for TNF resulted in an amelioration of nephritis in terms of a reduction of the amount of albuminuria, prevalence of glomerular thrombi, and intensity of neutrophil infiltrate.

Interleukin-1

The mesangial cell has been shown to produce IL-1 and to be responsive to its actions (49–51). Increased expression of this cytokine has been found in the kidneys of animals developing experimentally induced nephritis and autoimmune nephritis (42, 43, 52). The nephritogenic potential of this substance was shown by experiments in which IL-1 pretreatment of the animals injected with subnephritogenic doses of anti-GBM synergistically increased proteinuria. Another demonstration for the function of this protein in glomerulonephritis was revealed by experiments in which animals developing anti-GBM nephritis were treated with an IL-1 receptor antagonist (53). The study showed that the receptor antagonist was able to reduce the expression of ICAM-1 and the associated PMN and monocyte infiltration, leading to an amelioration of clinical and histologic nephritis in these animals. Confirmation of these results has been provided by investigations in which animals developing anti-GBM have been pretreated with either the antibody to IL-1 or the soluble receptor of IL-1 (47, 48). Under these circumstances, there was a significant reduction of proteinuria, occurrence of capillary thrombi, and infiltration with neutrophils (47, 48).

Interleukin-6

This interleukin has been shown to be an autocoid, being secreted by mesangial cells and acting on these cells to cause them to proliferate (54). A striking demonstration of the function of this substance in the pathophysiology of renal disease was revealed by studies in transgenic IL-6 mice; such animals exhibited severe mesangial cell proliferation and matrix increase (55). The involvement of this cytokine in human glomerulonephritis was demonstrated by studies which showed that mesangial cells of biopsies of patients suffering from mesangial cell proliferative glomerulonephritis produced this substance (as visualized by immunohistochemical techniques) while cells of kidneys affected by nonproliferative disorders did not (54). Additionally, urinary IL-6 levels of such patients were elevated, in comparison with the concentrations found in nonproliferative glomerulonephritis (54). Further evidence for the role of IL-6 in human renal disease was adduced from measurements of urine concentrations of the cytokine in patients with IgA nephropathy and with lupus nephritis (56, 57). In both instances, elevated levels of IL-6 correlated with disease activity and with progression of disease.

It is germane to point out that while most experiments have shown a pro-inflammatory role for IL-6, there are two studies that have demonstrated the reverse: an *in vitro* study has shown that IL-6 inhibited mesangial cell proliferation (58); and an *in vivo* investigation in which animals developing nephrotoxic nephritis were treated with IL-6 revealed an anti-inflammatory effect of the cytokine. Animals treated with IL-6 exhibited significantly less proteinuria and fewer capillary thrombi compared with untreated controls (59).

In summary, data have accumulated from a number of studies to delineate important roles for a variety of cytokines in the pathogenesis of glomerulonephritis. Future studies will likely demonstrate the involvement of even more of these substances. Eventually, it will be possible to devise effective treatment strategies based on counteracting the actions of these potent cell modulators.

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