Modulatory role of platelet-derived growth factor on cytokine-induced nerve growth factor synthesis in rat glomerular mesangial cells

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Recent evidence indicates that cytokines are potent inducers of nerve growth factor (NGF) expression in peripheral tissues and in brain. Cultured rat glomerular mesangial cells respond to interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α) by increased NGF synthesis. We found that co-stimulation of rat glomerular mesangial cells with platelet-derived growth factor (PDGF-BB) and IL-1 β /TNF- α significantly augments the IL-

1 β /TNF- α -induced NGF mRNA levels and NGF synthesis. In contrast, preincubation with PDGF-BB drastically reduces NGF gene expression and NGF protein synthesis in response to IL-1 β /TNF- α stimulation. Thus our results indicate that PDGF-BB is a potent modulator of cytokine-induced NGF expression; its precise action is critically depending on the time at which the PDGF receptor is activated.

INTRODUCTION

Nerve growth factor (NGF) is active in the development and maintenance of peripheral sympathetic and neural crest-derived sensory neurons [1]. In addition, NGF also acts in the central nervous system as a trophic agent for the cholinergic neurons of the basal forebrain and the caudate putamen [2]. Increasing evidence indicates that the NGF/NGF receptor system also modulates inflammatory and immune reactions [3,4]. For example, large amounts of NGF protein are detected at sites of inflammation and in inflammatory exudates [5]. Cytokines involved in inflammation enhance NGF production in peripheral tissues and in brain [6–8], and recent studies have revealed that functional NGF receptors are present in lymphoid tissues and on lymphocytes, and that NGF induces lymphocyte proliferation of both B and T cells [8].

We have shown previously that interleukin-1 β /tumour necrosis factor- α (IL-1 β /TNF- α) synergistically stimulate NGF synthesis in rat neocortical astrocytes [6] as well as in rat glomerular mesangial cells [9]. Glomerular mesangial cells are thought to play a crucial role in the pathogenesis of proliferative glomerular disease, a common cause of permanent glomerular damage [10–12]. These pathological changes are characterized by the proliferation of intrinsic glomerular cells, including mesangial cells, and infiltration by inflammatory cells, such as activated monocytes, macrophages and lymphocytes. These cell types invade the mesangial matrix and seem to be the major local sources of cytokines and growth-modulating factors. However, the mesangial cells themselves are able to synthesize and release different cytokines and growth factors, including IL-1 [13], IL-6 [14], TNF- α [15], platelet-derived growth factor (PDGF) [16] and transforming growth factor- β (TGF- β) [17]. Moreover, they express functional receptors for most of these agents and proliferate in response to IL-1 [13], IL-6 [14] and PDGF [16].

PDGF is expressed during the acute phase of glomerulonephritis. Its effects on proliferation, chemotaxis and collagen matrix formation suggest that PDGF may play a role in tissue repair, embryogenesis and pathophysiological states marked by excessive cell proliferation such as atherosclerosis and glomerulo-

nephritis. Together, these results suggest that a cascade comprising different cytokines and growth factors is a key component of the pathophysiology of inflammatory renal diseases. It was therefore of considerable interest to investigate how PDGF affects IL-1 β /TNF- α -induced NGF production in rat glomerular mesangial cells. Here we report that PDGF is a potent modulator of NGF synthesis in these cells.

MATERIALS AND METHODS

Cell cultures and incubation

Rat glomerular mesangial cells from male Sprague–Dawley rats (70–100 g body weight) were isolated and cultivated as described previously [18]. Single cells were cloned by limiting dilution and were grown in RPMI 1640 medium (Gibco) supplemented with 10% (v/v) fetal calf serum as described by Steiner et al. [9]. When the cells were confluent (about 10⁶ cells/plate) they were washed once with medium [serum-free Dulbecco's modified Eagle's medium (Gibco) containing 1% antibiotic solution supplemented with 0.1 mg/ml fatty acid-free BSA (Sigma) and 10 mM L-glutamine (Sigma)] and stimulated with 4 ml of medium with or without the different agents (either cytokines or growth factors) for the time periods indicated.

The supernatant was removed and stored at –50 °C until assayed for NGF protein by a sensitive immunoassay (ELISA). The cells were harvested from the dishes, pelleted and immediately frozen at –50 °C until RNA extraction was performed. The NGF mRNA content was determined by Northern blot analysis.

Enzyme immunoassay for NGF

To measure the immunoreactive NGF released into the culture medium, a two-site ELISA was used [5]. Briefly, polystyrene 96-well microtitre immunoplates (Nunc) were coated with either a polyclonal goat anti-NGF antibody or a goat preimmune serum to determine non-specific binding. The remaining non-specific

Abbreviations used: IL-1, interleukin-1; IL-6, interleukin-6; NGF, nerve growth factor; PDGF, platelet-derived growth factor; PKC, protein kinase C; TGF- β , transforming growth factor- β ; TNF- α , tumour necrosis factor- α .

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binding sites were blocked with PBS/0.05% Tween 20/1% fetal calf serum. Each plate included a complete standard curve ranging from 0 to 100 pg per 0.1 ml. Samples of 100 μ l of the cell culture medium were added to each well for 12 h at 4 °C. The plate was incubated with 6 μ g/well monoclonal antibodies against rat NGF (clone 23c4) for 3 h. Biotinylated goat anti-rat immunoglobulins were added (diluted 1:8000; Zymed) for 4 h. Specific signals were quantified using a horseradish peroxidase-conjugated streptavidin solution (diluted 1:5000; Zymed). Peroxidase activity was determined with a freshly prepared substrate solution containing 40 μ g/well *o*-phenylenediamine (Merck) and hydrogen peroxide (0.05 μ l/well) in a phosphate/citrate buffer. The reaction was stopped after 7 min with 2 M sulphuric acid. The absorbance was measured immediately at 492 nm using an ELISA reader (Dynatech MR 700).

The NGF content in the samples was determined by comparison with the NGF standard curve. Statistical analysis was performed by applying analysis of variance (ANOVA) and the statistical error was indicated as the S.E.M.

RNA extraction and blot hybridization

Total RNA was extracted from mesangial cells in guanidinium hydrochloride and isolated according to a modification of the procedure of Cheley and Anderson [19]. Total RNA contents were determined by measurements of absorbance at 260 nm. After Northern blotting, filters were hybridized to a 32 P-labelled NGF mRNA complementary to the sense message that was obtained by *in vitro* transcription of an NGF cDNA clone encoding the precursor of mouse β -NGF [20]. Autoradiograms of the filters were scanned densitometrically, and the intensities of the signals were compared with those of known amounts of co-electrophoresed NGF sense mRNA. In general, NGF mRNA contents were calculated as fg/ μ g of total RNA and expressed as percentages of controls (100%). Signals were normalized to 18 S rRNA. Statistical analysis was by ANOVA.

Immunoblot analysis of protein kinase C (PKC) isoenzymes

Mesangial cells were stimulated with PDGF-BB (30 ng/ml) for the indicated time periods. To determine the cytosolic and particulate PKC protein fractions, mesangial cells were lysed and centrifuged at 100 000 *g* as described by Huwiler et al. [21]. Then the supernatants and pellets were subjected to SDS/PAGE and blotted on to nitrocellulose paper. The filters were hybridized with monoclonal antibodies raised against PKC- α , - β and - γ isoenzymes [22] or antiserum reactive with PKC- δ , - ϵ and - ζ isoenzymes [23,24]. After washing, the filters were incubated with horseradish peroxidase-conjugated anti-mouse IgG antibodies (PKC- α , - β and - γ) or anti-rabbit IgG antibodies (PKC- δ , - ϵ and - ζ). Bands were visualized using 0.5 mg of 3,3'-diaminobenzidine and 0.03% H_2O_2 for 10 min.

RESULTS

Effect of PDGF-BB co-incubation on cytokine-induced NGF synthesis in mesangial cells

As shown in Figure 1, the simultaneous addition of the human recombinant cytokines IL- β and TNF- α (each at 1 nM) induced a time-dependent increase in NGF synthesis. Within 72 h, IL-1 β /TNF- α stimulation led to a 23-fold increase in NGF protein compared with unstimulated controls. Incubation of cultured mesangial cells with PDGF-BB alone (30 ng/ml) also triggered a significant stimulation of NGF release (2.5-fold within 72 h). On the other hand, co-stimulation of mesangial cells with all three mediator substances [PDGF-BB (30 ng/ml), IL-1 β (1 nM) and

Figure 1 Time-dependent stimulation of NGF protein expression by cytokines

Mesangial cells were incubated in the presence of IL-1 β /TNF- α (1 nM each), PDGF-BB (30 ng/ml) or a combination of all three substances as shown. After the indicated incubation period, medium was removed and NGF protein was measured as described in the Materials and methods section. Data are means $\pm$ S.E.M. of four independent experiments. Statistical analysis was by ANOVA. The difference between IL-1 β /TNF- α -treated samples and unstimulated controls became highly significant ($P < 0.001$) after 24 h. Significant differences between IL-1 β /TNF- α -treated samples and IL-1 β /TNF- α + PDGF-BB-treated samples are indicated in the Figure: †† $P < 0.001$.

Table 1 Effect of PDGF-BB on IL-1 β - and TNF- α -induced NGF expression

Mesangial cells were incubated for 24 h in the presence of IL-1 β (1 nM), TNF- α (1 nM), PDGF-BB (30 ng/ml) or various combinations of these substances as indicated. The medium was then removed and NGF protein was measured as described in the Materials and methods section. Data are means $\pm$ S.E.M. of four independent experiments. Statistical analysis was performed by ANOVA (* $P < 0.05$, ** $P < 0.001$ compared with unstimulated controls; †† $P < 0.001$ compared with IL-1 β /TNF- α -treated samples).

Addition	NGF protein (pg/ml)
Control	2 $\pm$ 1††
PDGF-BB	136 $\pm$ 21**††
IL-1 β	62 $\pm$ 9*††
TNF- α	40 $\pm$ 5*††
IL-1 β + PDGF-BB	122 $\pm$ 12**††
TNF- α + PDGF-BB	140 $\pm$ 12**††
IL-1 β /TNF- α	353 $\pm$ 12**
IL-1 β /TNF- α + PDGF-BB	365 $\pm$ 29**

TNF- α (1 nM)] resulted in a 33-fold increase, suggesting that these substances have a greater than additive effect on NGF release (Figure 1). Unstimulated controls produced only low amounts of NGF protein. This basal level amounted to 25.8 $\pm$ 3.5 pg of NGF/ml of cell culture medium after 72 h and was observed in all experiments.

Next we tested whether PDGF-BB is also able to interact synergistically with IL-1 β or TNF- α alone. As shown in Table 1, IL-1 β and TNF- α increased NGF production only marginally. After a 24 h co-incubation with IL-1 β (1 nM)/PDGF-BB (30 ng/ml) or TNF- α (1 nM)/PDGF-BB (30 ng/ml) the NGF protein levels were comparable with levels observed after a 24 h treatment with PDGF-BB (30 ng/ml) alone (Table 1). The NGF protein levels resulting from these three treatment groups were

Table 2 Effect of PDGF-AA on cytokine-induced NGF expression

Mesangial cells were incubated for 48 h with PDGF-AA (30 ng/ml) or IL-1 β /TNF- α (1 nM each), or a combination of all three substances as indicated. The medium was then removed and NGF protein was measured as described in the Materials and methods section. Data are means of four independent experiments. Statistical analysis was by ANOVA (** P < 0.001 compared with unstimulated controls; †† P < 0.001 compared with IL-1 β /TNF- α -treated samples).

Addition	NGF protein (pg/ml)
Control	19 ± 4††
PDGF-AA	22 ± 11††
IL-1 β /TNF- α	440 ± 20**
IL-1 β /TNF- α + PDGF-AA	452 ± 39**

Figure 2 Time-dependent stimulation of NGF mRNA expression by cytokines

Mesangial cells were incubated for various time periods with PDGF-BB (30 ng/ml) or IL-1 β /TNF- α (1 nM each) in the presence or absence of PDGF-BB. (a) Time course of NGF mRNA levels in mesangial cells, stimulated as indicated. Total cellular RNA was extracted and analysed by quantitative Northern blotting as described in the Materials and methods section. Data are means $\pm$ S.E.M. (n = 4) (* P < 0.05 and ** P < 0.001 compared with unstimulated controls; †† P < 0.001 compared with IL-1 β /TNF- α -treated samples). (b) Autoradiogram of a representative experiment of Northern blot analysis of NGF mRNA (1.3 kb). Mesangial cells were incubated for 24 h with vehicle (lane 1), with PDGF-BB (30 ng/ml) (lane 2), with IL-1 β /TNF- α (1 nM each) (lane 3) or with a combination of PDGF-BB and IL-1 β /TNF- α (lane 4). A sample of 10 μ g of total RNA was loaded on to each lane.

significantly different (P < 0.001) from controls as well as from the group treated with IL-1 β /TNF- α (each 1 nM).

We also tested PDGF-AA, another isoform of PDGF, but were not able to see any effect of PDGF-AA on cytokine-induced NGF expression (Table 2). This is not unexpected, as mesangial cells have been shown to express only the β - but not the α -receptor for PDGF and hence do not bind PDGF-AA [25].

To determine whether the cytokine-induced stimulation of

Table 3 Effect of PDGF-BB preincubation on cytokine-induced NGF expression

Mesangial cells were preincubated for 9 h with PDGF-BB (30 ng/ml) or vehicle. After this time period IL-1 β /TNF- α (both 1 nM) were added for the following 24 h. After a total 33 h incubation period, medium was removed and NGF protein was measured as described in the Materials and methods section. Data are means $\pm$ S.E.M. of four independent experiments, each determined at least in triplicate. Total cellular RNA was extracted and analysed by quantitative Northern blotting as described in the Materials and methods section. Data are means $\pm$ S.E.M. of four independent experiments. Statistical analysis was by ANOVA (** P < 0.001 compared with unstimulated controls; †† P < 0.001 compared with IL-1 β /TNF- α stimulation).

Addition	NGF protein (pg/ml)	NGF mRNA/18 S (% of control)
Control	12 ± 13††	100 ± 11††
PDGF-BB	34 ± 18††	102 ± 29††
IL-1 β /TNF- α	389 ± 43**	1638 ± 202**
IL-1 β /TNF- α + PDGF-BB	333 ± 14**	211 ± 100**††

NGF release was due to increased NGF synthesis, the NGF mRNA levels in controls and cytokine-stimulated mesangial cells were quantified at various time points by Northern blot analysis (Figure 2). NGF mRNA levels in mesangial cells stimulated with IL-1 β /TNF- α began to increase after 8 h, reaching a maximum after 36 h (5.6-fold increase compared with unstimulated controls) and remained elevated for more than 48 h. As shown in Figure 2(a), PDGF-BB significantly enhanced IL-1 β /TNF- α -induced NGF mRNA levels; a maximal effect was obtained within 24 h. These findings suggest that PDGF-BB-mediated up-regulation of NGF protein is most likely due to enhanced NGF gene expression. A representative autoradiogram of cytokine-induced NGF mRNA levels after 24 h is shown in Figure 2(b). Whereas PDGF-BB alone (lane 2) elicited only a minimal effect compared with unstimulated controls (lane 1), an enhancement by PDGF-BB of the stimulation caused by cytokines alone (lane 3) is clearly visible (lane 4).

Effect of PDGF-BB preincubation on cytokine-induced NGF synthesis in mesangial cells

To determine whether PDGF-BB modulates the responsiveness of rat glomerular mesangial cells to cytokines, mesangial cells were pretreated with PDGF-BB (30 ng/ml) before stimulation with IL-1 β /TNF- α . As shown in Table 3, the marked induction of NGF mRNA triggered by IL-1 β and TNF- α within 24 h was drastically reduced by PDGF-BB preincubation. In contrast with the mRNA, NGF protein was only slightly affected at 24 h (Table 3) and decreased with a much slower time course. As shown in Table 4, PDGF-BB preincubation suppressed cytokine-induced NGF protein secretion to basal levels within 72 h. The effect was highly significant (P < 0.001) by 48 h.

PDGF-BB treatment of mesangial cells does not down-regulate PKC isoenzymes

To evaluate possible mechanisms of the PDGF-BB effects seen in co- and pre-incubation experiments, we examined the action of PDGF-BB on PKC isoenzymes in mesangial cells. It has been shown that PDGF-BB modulates the expression of IL-1 and TNF receptors [26–29]. Furthermore, it has been reported that PDGF-BB causes a translocation of PKC isoenzymes α and β from the cytosol into the nucleus in vascular smooth muscle cells [30]. However, no data are available on the effects of long-term PDGF treatment on PKC isoenzymes.

Table 4 Effect of PDGF-BB preincubation on cytokine-induced NGF protein synthesis

Mesangial cells were preincubated for 9 h with PDGF-BB (30 ng/ml) followed by various incubation periods with IL-1 β /TNF- α (both 1 nM) as indicated. The medium was then removed and NGF protein was measured as described in the Materials and methods section and is expressed in pg/ml. Unstimulated controls produced 12 $\pm$ 8 pg of NGF/ml. Data are means $\pm$ S.E.M. of four independent experiments. Statistical analysis was performed by ANOVA ($\dagger\dagger P < 0.001$ compared with the corresponding IL-1 β /TNF- α stimulation).

Time (h)	NGF (pg/ml)	
	IL-1 β /TNF- α	IL-1 β /TNF- α + PDGF-BB
24	3892 $\pm$ 43	330 $\pm$ 14
48	294 $\pm$ 27	61.2 $\pm$ 8.5 $\dagger\dagger$
72	251 $\pm$ 26	22.1 $\pm$ 16.0 $\dagger\dagger$

Figure 3 Effect of PDGF-BB on PKC isoenzyme levels in rat glomerular mesangial cells

Immunoblot analysis of PKC isoenzymes was performed as indicated in the Materials and methods section. The Figure represents the results from a single study; the entire experiment was repeated twice with the same results. Mesangial cells were incubated for various time periods with PDGF-BB (30 ng/ml): control (lane 1); 30 s (lane 2); 1 min (lane 3); 2 min (lane 4); 5 min (lane 5); 20 min (lane 6); 1 h (lane 7); 24 h (lane 8).

Mesangial cells have been reported to express four PKC isoenzymes [23,24]. As shown in Figure 3, PDGF-BB does not affect PKC isoenzyme levels in rat glomerular mesangial cells up to 24 h of incubation. These results rule out the possibility that a down-regulation of PKC is responsible for the observed effects on NGF levels in experiments where mesangial cells were co- and pre-incubated with PDGF-BB.

Effect of TGF- β on cytokine-induced NGF synthesis in mesangial cells

We also investigated the effect of TGF- β on cytokine-induced NGF production. As shown in Table 5, the addition of TGF- β 1 (1 ng/ml) or TGF- β 2 (1 ng/ml) to unstimulated mesangial cells caused no noticeable increase in NGF protein levels. However, the addition of TGF- β 1 (1 ng/ml) or TGF- β 2 (1 ng/ml) to mesangial cells already stimulated with IL-1 β /TNF- α (each

Table 5 Effects of TGF- β 1 and TGF- β 2 on cytokine-induced NGF protein synthesis

Mesangial cells were incubated for 24 h with TGF- β 1 (1 ng/ml), TGF- β 2 (1 ng/ml), IL-1 β /TNF- α (each 1 nM), or a combination of three substances as indicated. The medium was then removed and NGF protein was measured as described in the Materials and methods section. Data are means $\pm$ S.E.M. of four independent experiments. Statistical analysis was performed by ANOVA ($\dagger\dagger P < 0.001$ compared with unstimulated controls; $\dagger P < 0.05$, $\dagger\dagger P < 0.001$ compared with IL-1 β /TNF- α stimulation).

Addition	NGF (pg/ml)
Control	2 $\pm$ 2 $\dagger\dagger$
TGF- β 1	4 $\pm$ 12 $\dagger\dagger$
TGF- β 2	7 $\pm$ 8 $\dagger\dagger$
IL-1 β /TNF- α	340 $\pm$ 87 $\dagger\dagger$
IL-1 β /TNF- α + TGF- β 1	470 $\pm$ 25 $\dagger\dagger$
IL-1 β /TNF- α + TGF- β 2	504 $\pm$ 22 $\dagger\dagger$

1 nM) up-regulated IL-1 β /TNF- α -elicited NGF protein synthesis significantly ($P < 0.05$) (Table 5).

DISCUSSION

We report here for the first time that PDGF-BB is a potent modulator of cytokine-induced NGF synthesis in rat glomerular mesangial cells. We show that PDGF-BB has differential effects on IL-1 β /TNF- α -induced NGF synthesis depending on the time of PDGF-BB treatment.

Rat glomerular mesangial cells, which play a pivotal role in immunological and inflammatory reactions, were previously reported to synthesize and release NGF upon stimulation with the cytokines IL-1 β and TNF- α [9] in culture. Although the signal transduction mechanisms leading to this response are not well understood, a cytokine-mediated phospholipase A₂ activation appears to be involved, since dexamethasone and mepacrine, two potent phospholipase A₂ inhibitors, abolished cytokine-induced NGF synthesis [9].

Our experiments indicate that, depending on the time of PDGF-BB addition to cultured mesangial cells, exactly opposite effects on IL-1 β /TNF- α -induced NGF synthesis can be elicited. Simultaneous addition of the cytokines and PDGF-BB leads to a significant up-regulation of IL-1 β /TNF- α -induced NGF production, whereas preincubation with PDGF-BB virtually abolishes the NGF synthesis seen after the addition of IL-1 β /TNF- α . NGF protein levels change several hours after NGF mRNA levels, due to the temporal sequence of transcription and translation.

The effect of PDGF when added at the same time as TNF- α and IL-1 β may be a complex one, resulting from the superposition of two separate actions of PDGF. Presumably the initial effect of PDGF is to enhance NGF secretion, but then after 9 h of PDGF incubation an inhibitory action of PDGF becomes apparent equivalent to that seen in Tables 3 and 4. Incubation of mesangial cells with PDGF-BB alone or with a combination of PDGF-BB and IL-1 β or PDGF-BB and TNF- α has only minimal effects on NGF synthesis and release. However, PDGF-BB preincubation drastically interferes with cytokine-induced NGF mRNA steady-state levels, by effects either on transcription rate or on mRNA stability. Our experiments provide evidence for the ability of PDGF-BB to change significantly the specific response of mesangial cells to cytokines. Whether this modulatory effect of PDGF-BB reflects a decrease in the number or affinity of cell surface cytokine receptors or altered intracellular transduction mechanisms remains to be elucidated. One candidate for the

mediation of the action of PDGF is PKC. It has been shown that PDGF-BB causes a translocation of PKC isoenzymes α and β from the cytosol into the nucleus in vascular smooth muscle cells [30]. In contrast, we did not see any effect of PDGF-BB treatment on PKC isoenzymes in glomerular mesangial cells, as evaluated by immunoblot analysis of cytosol and particulate fractions. However, this does not exclude the possibility that a distinct PKC isoenzyme shows a change in activity only in a certain compartment of mesangial cells. In this context, it is worth noting that PKC has been reported to modulate IL-1 receptor as well as TNF receptor expression. But again the data are quite controversial, as PKC has been found to up-regulate as well as to down-regulate IL-1 β and TNF- α receptors, depending on the cell type examined [26–29].

Interestingly, preincubation of cultured fibroblasts with PDGF has been reported to result in an up-regulation of cell surface IL-1 receptors that could be blocked by inhibitors of transcription [31]. These findings provide evidence that, at least in fibroblasts, responsiveness to IL-1 may be modulated by growth factors at the level of IL-1 receptor gene expression.

It has been shown that mouse, rat and human glomerular mesangial cells in culture release PDGF which stimulates DNA synthesis in an autocrine manner [11,16,25]. Findings that PDGF receptor expression is up-regulated in kidney rejection and that PDGF production is enhanced in active glomerulonephritis [16,32–35] imply an important role for PDGF in immune responses in the kidney. Furthermore, antibodies to PDGF inhibit mesangial cell proliferation and matrix expansion seen in rats with mesangial proliferative nephritis induced by an antibody to the Thy-1 antigen that is expressed on mesangial cells [36].

We have observed that NGF protein levels increased after combined treatment with TGF- β 1 or TGF- β 2 and IL-1 β /TNF- α compared with cells stimulated with IL-1 β /TNF- α alone, which could point to a modulation by TGF- β of cytokine-induced NGF levels.

Evidence has been provided previously that the low-affinity NGF receptor (p75) is essential for renal development in rodents. In one study, the inhibition of p75 NGF receptor expression by use of anti-sense oligonucleotides led to the disruption of kidney morphogenesis [37]. The expression of the p75 NGF receptor protein is chronologically and spatially restricted in human glomerulogenesis and the pattern in late stage glomeruli is similar to that of PDGF receptor. Whereas the NGF receptor is partially down-regulated in normal mature glomeruli, it is up-regulated in a variety of glomerulopathies [38]. The re-expression of NGF and PDGF receptors during glomerular disease points to a degree of developmental recapitulation in the injured glomerular mesangium.

Taken together, these results provide evidence for the involvement of cytokines (IL-1 β , TNF- α) and growth factors (PDGF-BB, TGF- β) in the regulation of NGF synthesis in rat glomerular mesangial cells. In turn, NGF may modulate local immune responses within the glomeruli, contributing to the pathogenesis of acute glomerular injury and nephritis. Further studies are in progress to elucidate the exact mechanisms responsible for PDGF modulation of NGF expression in mesangial cells.

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