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Platelet-Derived Growth Factor (PDGF) and PDGF-Receptor Gene Expression are Upregulated in Mesangial Proliferative Nephritis: An Effect Mediated by Complement and Platelets

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Mesangial cell proliferation is a major histologic finding in many types of glomerulonephritis, including IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis and some variants of focal glomerulosclerosis. We have demonstrated an important role for platelets in the mediation of glomerular cell proliferation in a model of mesangial proliferative GN (MesPGN) induced with antibody directed against the Thy 1 antigen expressed on the membrane of mesangial cells.[1] Yamamoto and Wilson[2] have reported that this proliferative lesion is mediated by complement. To evaluate the pathogenetic significance of platelet-derived growth factor (PDGF) and PDGF-receptor (R) in platelet and complement mediated glomerular cell proliferation, we examined the gene expression of PDGF and PDGF-R in glomeruli in anti-Thy 1 antibody-induced GN (anti-Thy 1 GN), a well characterized model of MesPGN in the rat.

Anti-Thy 1 GN was induced in rats with a single intravenous injection of anti-thymocyte serum (ATS). The unmanipulated rats with anti-Thy 1 GN were sacrificed under ether anesthesia at 1, 3 and 5 days. The complement-depleted and platelet-depleted rats were sacrificed 3 days after induction of anti-Thy 1 GN. For each group of rats, kidney biopsies were taken for histologic studies and then the glomeruli were isolated. For each biopsy, cellularity was expressed as the total number of nuclei for glomerular cross-section in tissue sections stained with periodic acid Schiff (PAS). Proliferation was expressed as the number of cells per glomerular cross section that stained by immunoperoxidase for proliferating cell nuclear antigen (PCNA).[1] The isolated glomeruli were lysed and total RNA was extracted and purified according to the method of Chomczynski and Sacchi.[3] The total glomerular RNA was denatured, electrophoresed and transferred to a nylon membrane. The membrane was prehybridized and hybridized with ^{32}P-labeled cDNA for PDGF (A- and B-chains) and PDGF-R (α and β subunits). After washing and drying the membrane, autoradiography was performed.

Rats with anti-Thy 1 GN developed acute mesangiolysis that was maximal at 24 h (i.e., day 1). This was followed by a significant increase in the total number of glomerular cells as well as the number of proliferating (i.e., PCNA+) glomerular cells at 3 and 5 days. Complement or platelet depleted rats had significantly fewer numbers of total and proliferating cells in glomeruli compared to unmanipulated rats with anti-Thy 1 GN at day 3. Mesangiolysis was completely prevented by complement depletion, but was unaffected by platelet depletion.

The PDGF A-chain mRNA was weakly expressed in glomeruli in rats at 3 and 5 days after induction of anti-Thy 1 GN, although it was undetectable in normal rats, rats with GN at day 1 and complement or platelet depleted rats with GN at day 3. In contrast, the PDGF B-chain mRNA was expressed at low levels in normal rats, rats with GN at day 1 and complement or platelet depleted rats with GN at day 3. The expression of PDGF B-chain mRNA was markedly increased in rats with anti-Thy 1 GN at 3 and 5 days. The PDGF-R α-subunit mRNA was not detected in glomeruli in normal rats and rats with anti-Thy 1 GN. In contrast to the findings for PDGF-R α-subunit mRNA, PDGF-R β-subunit mRNA was expressed in normal rat glomeruli. The expression of PDGF-R β-subunit mRNA was markedly increased

at 3 and 5 days. The levels of PDGF-R β-subunit transcript in complement and platelet depleted rats were significantly lower than in unmanipulated rats with GN at day 3 and were equivalent to that observed in normal rats.

In conclusion, the present study documents that gene expression of PDGF and PDGF-R subunit is upregulated in glomeruli in rats with MesPGN coincident with glomerular cell proliferation. The depletion of complement or platelets, which mediate cell proliferation, prevents the increase in PDGF and PDGF-R β-subunit mRNA in glomeruli in anti-Thy 1 GN. It is suggested that the upregulation of PDGF and PDGF-R expression may play an important role in the pathogenesis of cell proliferation in MesPGN.

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