At first glance, inflammation in general and growth factors in particular represent an extremely complex, if not chaotic, ensemble and clinicians are often confused by an ever-growing list of factors and a wealth of data on their biological activities. Given the redundancy of many growth factor actions and the myriad of their mutual interactions, it has come as somewhat of a surprise that specific antagonism of single cytokines is not only possible but also highly effective in clinical situations. The best example so far is the impressive effect of tumor necrosis factor-α (TNF-α) blockade in patients with rheumatoid arthritis or inflammatory bowel disease.

Over the last years considerable evidence has been gathered to implicate platelet-derived growth factor (PDGF) in the pathogenesis of renal disease [reviewed in 1]. In the molecule, two chains, PDGF-A and PDGF-B, form the biologically active homo- or heterodimers (very recently, novel PDGF-C and PDGF-D chains have been cloned but nothing is known on their renal actions). In the glomerulus, the PDGF-B chain, either as part of PDGF-BB or PDGF-AB, is the most active molecule. PDGF-B is produced within the glomerulus, released by infiltrating cells, overexpressed in many glomerular diseases, and in vitro potently increases proliferation and matrix synthesis in mesangial cells. In vivo, administration of PDGF-BB or the glomerular transfection with PDGF-B cDNA results in mesangioproliferative changes without other renal pathology. The most convincing evidence for a crucial and nonredundant role of PDGF-B in mesangial biology is derived from mice genetically deficient in PDGF-B or its receptor, which after birth quickly die of renal abnormalities. The notable abnormality is in the glomeruli, which contain normal glomerular endothelial and epithelial cells and a normal basement membrane, but completely lack a mesangium.

Given the above, antagonism of PDGF-B in glomerular disease has become the focus of several studies. Experiments with a neutralizing antibody against PDGF confirmed that it can acutely decrease mesangial cell proliferation and matrix accumulation in the anti-Thy 1.1 mesangioproliferative nephritis in rats [2]. A more potent PDGF antagonist, a specific DNA-aptamer, was also highly effective in reducing mesangial proliferation and matrix accumulation in this model [3]. More important, a few days of treatment with this latter antagonist during the mesangioproliferative phase of a chronic anti-Thy 1.1 model completely prevented the subsequent development of renal failure and glomerular as well as tubulointerstitial scarring [4]. This study by Ostendorf et al thereby provided the first evidence of the long-held belief that specific reduction of mesangial cell proliferation in vivo is indeed a meaningful therapeutic approach to mesangioproliferative disease [4].

The major disadvantages of the abc PDGF-B antagonists are the need for parenteral application, the cost of producing them, and, in the case of neutralizing antibodies, their immunogenicity. Given the slowly progressive nature of most human mesangioproliferative diseases, prolonged treatment is usually necessary and would be greatly facilitated if PDGF-B antagonists were easy to produce and could be taken orally. Unfortunately, to date, only a few oral anti-PDGF agents are available. Trapidil, originally marketed as an antiplatelet agent, also inhibits the binding of PDGF to its receptor [5] and results in a moderate reduction of glomerular cell proliferation in the anti-Thy 1.1 nephritis model [6]. Whether this is the result of its antiplatelet or anti-PDGF activity presently remains unknown. More recently, tyrosine kinase blockers have been developed, which more or less specifically impair the ability of the PDGF receptor to signal through its intracellular tyrosine kinase domain. Again, using the anti-Thy 1.1 model, an inhibitor (KI 6896) that can be taken orally and prevents autophosphorylation of both the PDGF receptor β-chain and the basic fibroblast growth factor (bFGF) receptor, has been shown to reduce glomerular cell proliferation but not matrix accumulation in vivo [7]. This study now has been extended by Gilbert et al, who, in this issue of Kidney International [8], report their experience with a tyrosine kinase inhibitor (STI 571, formerly referred to as Novartis compound CGP 57148) that blocks the PDGF receptor, the nonreceptor tyrosine kinase Abl, as well as the c-kit receptor, the latter of which is expressed, for example, on hematopoetic stem cells [9]. Gilbert et al
provide convincing evidence that STI 571, administered intraperitoneally from day 1 to 6 after induction of anti-Thy 1.1 nephritis, can lead to a highly significant reduction of mesangial cell activation and proliferation as well as glomerular accumulation of extracellular matrix [8].

In addition to its role in mesangioproliferative disease, PDGF-B might also represent a therapeutic target in renal interstitial damage [1]. However, in the only study available to date, intraperitoneal treatment with a PDGF receptor kinase blocker (AG 1295) in the ureteral ligation model in rats only produced a mild attenuation of renal interstitial fibrosis [10]. Whether this implies that PDGF-B is of low importance in renal fibrosis or whether the findings relate to low efficacy of AG 1295 in vivo remains to be determined.

Will PDGF-B antagonism work in human glomerular disease? To date, all in vivo data have been generated in rat models, mostly in mesangioproliferative anti-Thy 1.1 nephritis. Clearly, data in other models of glomerular disease are necessary before the value of PDGF-antagonism in humans can be judged more definitively. Will prolonged PDGF-B antagonism be safe? Unlike its prominent role in embryogenesis, in particular in renal development (see above), PDGF-B apparently is not required for normal adult life. For example, mice transgenic for a circulating PDGF antagonist (the extracellular domain of the PDGF \( \beta \)-receptor), which was produced starting in late embryogenesis and adulthood only, showed no phenotypic abnormalities [11]. Furthermore, experimental renal studies [8], as well as phase I and II studies with PDGF-B antagonists that can be taken orally by tumor patients, have shown little toxicity [9]. Therefore, anti-PDGF-B therapy continues to represent an excellent candidate for our future therapeutic repertoire to combat glomerular disease in humans.

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