Commentary

Reshaping the Interstitium by Platelet-Derived Growth Factor

Implications for Progressive Renal Disease

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Reshaping life! People who can say that have never understood a thing about life—they have never felt its
breath, its heartbeat—however much they have seen
or done. They look on it as a lump of raw material that
needs to be processed by them, to be ennobled by their
touch. But life is never a material, a substance to be
molded. If you want to know, life is the principle of
self-renewal, it is constantly renewing and remaking
and changing and transfiguring itself, it is infinitely
beyond your or my obtuse theories about it.

— From Doctor Zhivago by Boris Pasternak.
Translated by Max Hayward and Manya

Reshaping life in tissues damaged by and recover-
ing from diverse insults requires the involvement of
growth-promoting substances.1–3 By sustaining cell
growth and proliferation, these substances infuse a
certain vitality that allows tissues to renew and re-
make themselves in the aftermath of architectural
alterations and cell loss incurred by necrosis and
apoptosis. Elaboration of growth-promoting sub-
stances may thus be viewed as a response to injury,
one that facilitates the repair of injured tissues and
enables their return to their uninjured state.

Synthesized and released inordinately or inappro-
priately, however, growth-promoting substances
may change and transfigure tissues. By driving cell
proliferation and synthesis of extracellular matrix
components without the appropriate biological man-
date, growth-promoting substances may incite dis-
ease rather than serve as a response to it. Indeed,
for an increasing number of diseases, such as car-
cinogenesis,4 atherosclerosis,5 parenchymal fibro-
sis,6–8 and acute lung injury,9 growth-promoting
substances are incriminated in the transformation of
tissues observed in these states.

The observations of Tang and collaborators10
point to another disease process, tubulointerstitial
injury, in which growth-promoting substances may
be involved. These investigators demonstrate that
the administration of platelet-derived growth factor
(PDGF)-BB, in contrast to PDGF-AA, impressively
stimulates proliferation of interstitial fibroblasts and
synthesis of interstitial collagen. These observations
are important from a multiplicity of considerations.
First, by identifying the interstitial fibroblast as a cell
receptive to the mitogenic actions of PDGF, they
complement studies demonstrating mesangial cell
proliferation after the administration of PDGF pro-
tein11 or the introduction of the PDGF gene in the
kidney,12 and second, by demonstrating increased
synthesis of interstitial collagen III along with fibro-
blast proliferation, the findings of Tang et al10 sup-
port the growing recognition of PDGF as a valid
mediator of progressive renal injury.6,13,14

The view that PDGF is involved in progressive
renal injury is based on studies demonstrating up-
regulation of PDGF and its receptor in experimental
glomerulopathies6,13,15,16 and human renal dis-
ease.6,17,18 in conjunction with reduction in renal in-
jury afforded by maneuvers that attenuate the effects
of PDGF.19,20 Findings in the anti-Thy model of glo-

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merulonephritis are particularly germane.6 The Thy-1.1 antigen resides on mesangial cells, and the administration of an antibody to this antigen lyses mesangial cells through complement-dependent and nitric oxide-dependent mechanisms.6,21 Such cell loss is attended by proliferation of surviving mesangial cells and elaboration of the extracellular matrix.6,21 Eventually, the mesangium is restored, the excess matrix is removed, and the glomerulus emerges with hardly a discernible structural or functional blemish.6,13,21 In this model, there is marked up-regulation in PDGF B-chain mRNA and protein and in PDGF receptor β-subunit mRNA and protein in the mesangium along with mesangial cell proliferation.6,13,15,16 The administration of heparin, an agent with multiple effects on cell growth including the binding of PDGF, inhibits cell proliferation and reduces expansion of the mesangial matrix in conjunction with down-regulation of PDGF receptor β-subunit.19 Complementary, and more persuasive, evidence for a role for PDGF in this disease model comes from studies in which the administration of a neutralizing anti-PDGF antibody reduces proliferation of mesangial cells and expansion of the extracellular matrix.20

The observations of Tang et al10 thus demonstrate an effect of PDGF on the interstitial fibroblast and matrix that mimics the mesangial response observed in diseased states characterized by up-regulation of PDGF. Their observations also underscore the remarkable alliance that exists between enhanced renal growth and attendant renal injury, the latter exhibited, in part, by expansion of the extracellular matrix.22,23 These intertwining phenomena of growth and injury are assigned a prominent role in current concepts of progressive renal injury.22,23 Heightened cellular growth often appears as a harbinger of renal injury in a number of disease models whether such models are induced by hemodynamic, metabolic, dietary, or immunological manipulations.22,23 Although multiple processes could account for such linkage,24,25 the findings of Tang et al10 demonstrate that the alliance of these processes may reside in a certain commonality of origin such as a growth factor with mitogenic and fibrogenic properties.

Tang et al10 also demonstrate that these proliferating fibroblasts expressed α-smooth muscle actin, which, interestingly, is expressed in abundance by mesangial cells in the anti-Thy model of glomerulonephritis.26 This protein represents the form of actin that allows smooth muscle cell to contract.27,28 Fibroblasts in granulation tissue expressing α-smooth muscle actin are termed myofibroblasts.27,28 Myofibroblasts decline in number as wounds heal and, conversely, are prominent in states in which exuberant scar formation occurs. Presumably by facilitating contraction of tissue, myofibroblasts in large numbers could contribute to the disfigurement of tissues observed in scarred areas.27,28 Thus the presence of myofibroblasts in the PDGF-stimulated interstitium carries the concern that scarring of the interstitium may result.

It is with regard to expansion and scarring of the interstitium that the observations of Tang et al10 are the most telling. In virtually all forms of progressive renal disease, the interstitium and tubules are inescapably altered; mononuclear cells and fibrotic tissue infiltrate and expand the interstitial space at the expense of the tubular compartment.29 These tubulointerstitial changes were once viewed as a curious side show to main events enacted in glomeruli but are now highlighted, in preference to glomerular histological changes, as the dominant predictor of progressive renal disease.29 A large number of clinical studies demonstrate that, regardless of the nature of the underlying renal disease, impaired renal function more closely correlates with histological changes in the tubular and interstitial compartments in the kidney rather than with histological changes in the glomerular compartment.30–33 This prognostic value for tubulointerstitial changes holds true when such analyses are conducted for composite scores for tubulointerstitial disease30–32 or for specific features of tubulointerstitial disease, namely, interstitial fibrosis31 or interstitial mononuclear cells.32,33 PDGF may promote tubulointerstitial disease through multiple pathways. PDGF-driven fibrogenesis may expand the interstitium and, by separating the tubular epithelium from their nutrient-bearing capillaries, impair tubular reabsorptive and secretory processes.31 Decreased sodium reabsorption activates tubuloglomerular feedback and thus diminishes glomerular blood flow and glomerular filtration rate.31 PDGF may also directly reduce renal blood flow and glomerular filtration rate because of its vasoconstrictive effect.13 PDGF-incited fibrogenesis may encroach upon, and decrease, the number of intertubular capillaries31 and, by impairing the postglomerular circulation, increase glomerular hydrostatic pressure and glomerular size, alterations incriminated as determinants of progressive renal injury.34,35 PDGF is chemotactic and thus may provide a stimulus for mononuclear cells to infiltrate the interstitium.6,13,14 PDGF may also contribute to characteristics observed in interstitial fibroblasts harvested from diseased kidneys; these fibroblasts, in contrast to those from normal kidneys, demonstrate hyperproliferative responses, synthesize different types and greater quantities of
collagen, and can condition media to induce hyper-proliferation of dermal fibroblasts. Thus, fibroblasts from diseased kidneys are invested with properties that promote ongoing fibrogenesis. It is intriguing whether PDGF may contribute to these changes. Finally, in certain diseased states, kidney cells such as mesangial cells become hyperresponsive to the proliferative effects of PDGF; if a similar phenomenon were to occur in interstitial fibroblasts, amplification of the interstitial effects of PDGF would result. Relevant to this possibility is the observation that the number of PDGF receptors is increased on fibroblasts in the vicinity of macrophages (a source of PDGF) in the tubulointerstitial infiltrate in patients with chronic rejection. Interestingly, in a rat model of chronic rejection, up-regulation of glomerular PDGF accompanies glomerular injury. Through a number of mechanisms, PDGF, present in increased amounts in the interstitium, may exert effects on renal tubules, glomeruli, tubules, blood vessels, and the interstitium, which sustain progressive derangement in renal structure and function. The functional effects of PDGF, as administered in the study by Tang et al., namely, glomerular filtration rate, rates of urinary protein excretion, and tubular function would thus be of interest.

PDGF may be produced from multiple sites in the diseased kidney and, from such origins, make its way to the interstitium. In primary glomerulopathies, PDGF, released from cells indigenous to or infiltrating the glomerulus, may seep into the glomerular mesangial area. As the glomerular mesangium is in contiguity with the interstitium, glomerular PDGF may thus percolate into the interstitium. Glomerular-derived PDGF may also be delivered to tubules as PDGF traverses a leaky glomerular filtration barrier and thence into the urinary space. Macrophages are rich sources of PDGF, and these cells may migrate into the interstitium as a consequence of the recruitment of blood monocytes by glomerular inflammation. So summoned, monocytes infiltrate the perivascular sheath of the hilar arterioles, the periglomerular area, and eventually ramify throughout the interstitium. PDGF may also originate from the tubular epithelium and the endothelium of the interstitial capillaries. Finally, an increasing number of stimuli, for example, angiotensin II, thrombin, transforming growth factor (TGF-β), and endothelin, foster the synthesis or release of PDGF. Thus, in the diseased kidney, PDGF originating from multiple sites may converge upon the interstitium and set in train the effects described above. The challenging question now faced is the extent to which the amounts of PDGF that evince biological effects in the study of Tang et al. approximates to the amounts of PDGF that may be found in the diseased kidney.

Tang et al. observed that proliferation of fibroblasts was closely followed by apoptosis, the latter appearing as early as 3 days into the course of administration of PDGF-BB, increasing by day 7 and normalizing by day 21. Although the origin of these apoptotic cells is not certain, the presence of α-smooth muscle actin raises the possibility that these cells were myofibroblasts. It is noteworthy that in these studies apoptosis occurred during the continued administration of PDGF, a growth factor widely regarded as a survival signal for cells and one that, in other circumstances, rescues cells from apoptosis. Indeed, apoptosis can be induced by the removal of growth factors such as PDGF. Death by apoptosis is exalted in the current literature in a way that no other form of death, or even life, has ever been. This veneration of death—this apotheosis of apoptosis—arises from the widespread appreciation of the remarkable features of this phenomenon. First, in facilitating the reparation of tissues after injury and in shaping organs and tissues during morphogenesis, apoptosis serves the interests of tissues and organs and not those of the haplessly dying cell; apoptosis thus answers to a greater and higher cause. Second, in its responsivity to cues from neighboring cells that elicit or forestall it, the apoptotic death sentence reflects the judicial involvement of surrounding cells. Third, in its predictability in onset in certain settings, especially during embryogenesis and organogenesis, apoptosis speaks to the ineluctability of cellular rhythms as vitality is lost in the denouement of some inherent cellular genetic program. Finally, in the precise and controlled way in which cells are extirpated, apoptosis enables the removal of cellular debris without a vicinal, and potentially adverse, inflammatory response. To this phenomenon, Tang et al. contributes an interesting instance wherein apoptosis occurs even during the administration of an anti-apoptotic, life-giving growth factor, PDGF. In their studies, the decisive factor that determined the death of myofibroblasts, whether such death represented the inevitable culmination of a terminally differentiated cell, now effete and no longer capable of fulfilling its raison d'être, or whether such death resulted from attempts on the part of the surrounding interstitium to regulate its resident population, is clearly unknown. However, this visitation of death upon cells exposed to a potent survival factor is undoubtedly remarkable.
The possible involvement of TGF-β in mediating the interstitial effects of PDGF merits comment. TGF-β can induce apoptosis in various cells including fibroblasts,55 is a powerful stimulus to the synthesis of extracellular matrix,7 and consistently elicits the transformation of fibroblasts into myofibroblasts.56 Thus, many of the described effects in this study can be induced by TGF-β. Moreover, a compelling aggregate of data incriminates TGF-β1 in the pathogenesis of glomerular injury induced in the anti-Thy-1 model7,21,57–59 and in progressive renal injury induced by repeated doses of anti-Thy-1.60 TGF-β induces and is itself induced by PDGF.14 PDGF facilitates the synthesis and secretion of TGF-β1 by proximal tubular epithelial cells in response to pathological stimuli such as increased concentrations of glucose.61 As recently emphasized, evidence for the involvement of one growth factor in a given setting does not negate the involvement of another13,14; for example, in the model of glomerulonephritis induced by Habu snake venom, the appearance of mesangial cell proliferation and mesangial matrix expansion reflects, in all likelihood, the profiles of expression of PDGF and TGF-β.62 More detailed studies of the role of TGF-β in PDGF-induced tubulointerstitial disease would be of interest.

Whether the kidney, compared with other organs, is particularly or uniquely vulnerable to the described effects of PDGF also merits attention. PDGF, as administered in this study, may exert organ- or tissuespecific effects. The delivery of PDGF to, or the activity of PDGF within, the kidney may differ from other tissues. The efficacy with which α2-macroglobulin, the major binding protein for PDGF13,14 and thus a pivotal regulator of the availability of PDGF to exert its actions, binds PDGF may differ in various tissues. Just as important is the relative responsiveness of the fibroblast in various organs to the actions of PDGF. There is increasing recognition of the heterogeneity that exists in fibroblasts. Kidney fibroblasts, for example, display a different proliferative response to cytokines and a different repertoire of collagen production when compared with skin fibroblasts.63 Indeed, even within the kidney, fibroblasts are quite heterogeneous; papillary fibroblasts proliferate in response to PDGF released from the inner medullary collecting duct whereas cortical fibroblasts do not.43 Thus, the study of Tang et al10 raises questions about the comparative effects of PDGF on fibroblasts in other organs besides the kidney and, even within the kidney, the relative effects of PDGF on fibroblasts that reside in the cortex, medulla, and papilla.

In summary, in their examination of the in vivo effects of PDGF on the renal interstitium, Tang et al10 provide findings that are timely, persuasive, and relevant to current attempts at understanding mechanisms of progressive renal injury. Their findings provide a secure vantage point from which additional investigation into the role of PDGF in progressive tubulointerstitial disease may proceed. Moreover, by exploring the effect of PDGF administered in vivo on cell growth, extracellular matrix synthesis and apoptosis, biological themes of fundamental importance, this study possesses an appeal and relevance that range way beyond the parochial concerns of the kidney.

References

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