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PDGF-D and Renal Disease: Yet Another One of Those Growth Factors?

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Life in the platelet-derived growth factor (PDGF) world used to be simple for the last twenty years. The system consisted of two PDGF chains, PDGF-A and -B, that are secreted as homodimers or heterodimers and bind to dimeric PDGF receptors composed of α- and/or β-chains. Whereas PDGF-A binds to the α-chain only, PDGF-B is a ligand for all receptor types (1). Recently, EST database homology searching identified two novel PDGF isoforms, designated PDGF-C and -D, that are released as homodimers, PDGF–CC and –DD (2–4). These two new isoforms differ from the classical PDGFs because they form homodimers only and are produced as latent factors. Proteolytic cleavage of a CUB-domain from each chain is then required for activation (5). The proteases involved in this process *in vivo* remain to be identified. To add to the complexity, some experimental data suggest that latent PDGF-CC or –DD homodimers, after removal of only one CUB-domain, become antagonists, whereas agonistic activity only results if both CUB-domains are removed (5). Following this proteolytic processing, the core domain of PDGF-CC appears to be largely a ligand for the PDGF $\alpha\alpha$-receptor, whereas PDGF-DD binds predominantly to the PDGF $\beta\beta$-receptor (5).

All four PDGF isoforms and both receptor chains are expressed in the kidney, albeit in distinct spatial arrangements (1,6,7). Why then is PDGF-D of any particular interest for nephrologists? Over the last years, considerable evidence has been gathered to implicate PDGF-B in the pathogenesis of renal disease (1): it is essential for glomerular, particularly mesangial, development, it is overexpressed in many glomerular diseases, and it is centrally involved in mesangioproliferative changes *in vivo*. Various therapeutic approaches that inhibit PDGF-B bioactivity, *e.g.*, using neutralizing antibodies, antagonistic DNA-aptamers (8), gene transfer of soluble PDGF β-receptor (9), or PDGF β-receptor blockers (10), have substantiated the notion that PDGF-B is a potentially very important novel target in glomerular disease. Given that PDGF-D, like PDGF-B, signals through the PDGF β-receptor, overlapping biologic activity is to be expected. Indeed, hepatic overexpression of PDGF-D has been demonstrated by Hudkins *et al.* (11) to induce mesangioproliferative changes in mice, and we (12) have recently reported that specific antagonism of PDGF-D in mesangioproliferative nephritis markedly reduces the pathologic mesangial cell proliferation. Of particular interest in this latter study was the observation that PDGF-D, unlike PDGF-B, apparently also acts as an endocrine growth factor because plasma levels increased about 1000-fold in nephritis (12).

In contrast to glomerular diseases, much less is known of the biologic actions of PDGF in the renal tubulointerstitium. Whereas the α-receptor is expressed constitutively in interstitial cells (1), the β-receptor is only present in injured interstitium (13,14). Upregulation of both receptor chains in fibrotic renal interstitium was confirmed in the study by Taneda *et al.* (15), which is published in the present issue of *JASN*. More importantly, this study also assessed the expression of PDGF-D. Like PDGF-B, expression of PDGF-D rapidly increased in renal interstitial cells after unilateral ureteral obstruction, whereas PDGF-A and –C remained unchanged in fibrotic areas. Areas of PDGF-D overexpression closely overlapped with regions of β-receptor upregulation, providing the basis for increased biologic activity. Taneda *et al.* (15) then confirmed these mouse data in human renal biopsies of patients with chronic obstructive nephropathy. This study thereby provides a first hint at the possibility that interference with PDGF-D may not only be an attractive goal in glomerular disease but also in either the primary or the much more common secondary renal tubulointerstitial damage process. Specific intervention studies will have to verify this assumption.

Can we use PDGF-B data to extrapolate to the potential role of PDGF-D in the tubulointerstitium analogous to the glomerular data described above? No specific PDGF-B inhibition study has been published in models with primary or secondary tubulointerstitial damage. Probably the best evidence for a role of PDGF-B and β-receptor in renal interstitial disease is derived from the study of Tang *et al.* (16) in which pharmacologic doses of recombinant PDGF-BB, but not PDGF-AA, induced tubulointerstitial myofibroblast transformation and fibrosis. This study therefore supports the notion that signaling through the PDGF β-receptor, be it PDGF-B or –D induced, is of relevance in renal interstitial disease.

If PDGF-D and –B are so similar in terms of biologic activities in the kidney, it is at first glance puzzling that specific inhibition of either isoform can dramatically affect renal disease even in instances where both are overexpressed,

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such as in mesangioproliferative nephritis (8,12). Three explanations may account for these observations: (*1*) overexpression of PDGF-B and –D is temporarily separated, a possibility not supported by studies in glomerular or tubulointerstitial disease (12,15); (*2*) oxerexpression of PDGF-B and –D are spatially separated, which may be the case to some degree in the tubulointerstitium (15) but not the glomerulus (12); and (*3*) PDGF-B and –D interact with each other, which has not yet been shown.

To answer the title question: no, PDGF-D is not yet another one of those growth factors, but it is rapidly on its way to becoming just as established as PDGF-B as a central mediator of renal disease and thus a highly interesting therapeutic target. Finally, the study of Taneda *et al.* (15) is also an excellent example of why even now, or maybe especially nowadays, when we have high throughput screening, large scale DNA-arrays, and proteomics, we still need high-quality pathology assessments like this one to document what these new players are good (or bad) for.

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See related article, "Obstructive Uropathy in Mice and Humans: Potential Role for PDGF-D in the Progression of Tubulointerstital Injury," on pages 2544–2555.