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Focus on Molecules: Platelet-derived Growth Factor C, PDGF-C

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1. Structure/Activation

There are 5 members of the PDGF family (PDGF-A, B, -AB, -C and -D) (Fredriksson et al., 2004; Reigstad et al., 2005). PDGF-C was the second to last to be discovered when 3 independent groups cloned the *PDGF-c* gene in 2000 (Accession number: NM_016205) (Reigstad et al., 2005). It consists of 6 exons that code for a 345 amino acid protein. Exon 1 has a long untranslated region and encodes the signal peptide whose putative site for signal-peptidase cleavage is located between amino acids 22 and 23 (Fig 1). Exon 2 and 3 encode the 110 amino acid CUB domain (residues 50-160), which is followed by a hinge region of 70 amino acids (residues 161-230) that is encoded by exon 4 (Fig 1). Exon 5 and 6 code for the 115 amino acid growth factor domain (residues 231-345) (Fig 1), which has 27-35% identity with corresponding regions of PDGF and VEGF family members. There are three putative N-linked glycosylation sites located at positions 25, 55, and 254. Because of the presence of 8 appropriately positioned cysteine residues, the growth factor domain of PDGF-C is predicted (the crystal structure for PDGF-C has not been solved) to form a cysteine knot.

Together with PDGF-D, PDGF-C differs from the other PDGF family members in that they are secreted in a latent form. Proteolytic cleavage of the N-terminal CUB domain liberates the growth factor domain such that it is able to bind and activate PDGFRs. “CUB” is an acronym for Ctr/Clr, urchin endothelial growth factor-like protein and bone morphogenic protein 1. These domains are found in a wide variety of proteins, and are believed to mediate protein-protein and protein-carbohydrate interactions. In the context of PDGF-C, the CUB domain appears to prevent PDGF-C from activating the PDGFR. In the context of the VEGF family, CUB domains promote interaction of ligands and receptors. Neuropilins 1 and 2 are CUB-domain containing transmembrane proteins that facilitate that binding of VEGF₁₆₅ with their signaling receptors. While there are some reports that CUB domains are biologically active, the prevailing thought is that they function to both localize the secreted PDGF-C and repress its activity.

There are two proteases capable of activating PDGF-C: plasmin and tissue plasminogen activator (tPA). Plasmin was originally identified as a PDGF-C processing protease in an in vitro screen of purified proteases. More recently, we learned that plasmin was the major PDGF-

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C processing activity in the vitreous of patients with retinal diseases such as proliferative vitreoretinopathy (PVR) (Lei et al., 2007a). In contrast, tPA was the predominant PDGF-C processing activity present in the conditioned medium of tissue culture cells. A side-by-side comparison of the two proteases indicated that plasmin was vastly more potent than tPA (Lei et al., 2007a). This finding, together with the fact that tPA can activate plasminogen (by proteolytically processing plasminogen), suggests that in settings where both proteases are present, plasmin will be the primary PDGF-C processing protease, whereas tPA may indirectly contribute by activating plasmin.

2. Function

PDGF-CC has important functions both in embryonic development and in adult tissues (Fredriksson et al., 2004; Reigstad et al., 2005). *Pdgfc*^{-/-} mice die in the perinatal period owing to feeding and respiratory difficulties associated with a complete cleft of the secondary palate. In the adult PDGF-C appears to contribute to wound healing since PDGF-C stimulated fibroblast proliferation, epithelial migration, extensive vascularization and neutrophil infiltration.

There is direct and indirect evidence that PDGF-C contributes to angiogenesis. The indirect data include reports that PDGF-C was present in actively angiogenic tissues such as placenta, some embryonic tissues, and tumors. In the context of a cornea pocket assay PDGF-C induced angiogenesis, although not as potently as VEGF (vascular endothelial growth factor) or bFGF (basic fibroblast growth factor). Finally, administration of PDGF-C promoted post-ischemic revascularization of the heart and limb. The mechanism appeared to involve the recruitment and maturation of both endothelial and pericyte precursors.

PDGF-C regulates biological processes via PDGF receptors. Each half of the PDGF-C dimer binds to a PDGF receptor (PDGFR) subunit resulting in receptor dimerization. This boosts the activity of the tyrosine kinase domain (contained within the intracellular portion of the PDGFR) and thereby initiates intracellular signaling events that trigger cellular responses such as proliferation, migration, contraction and survival. Thus PDGF-C activates intracellular signaling events that engage a host of cellular responses that are essential for numerous biological processes that are required for the development and health of mammals.

3. Disease involvement

PDGF-C contributes to tumor formation and fibrotic diseases (Fredriksson et al., 2004; Reigstad et al., 2005). For instance, cells derived from Ewing tumors overexpress PDGF-C, and their tumorigenicity can be reduced by expressing a dominant negative form of PDGF-C. Similarly, overexpressing PDGF-C in NIH 3T3 cells enables these cells to form tumors in mice. Overexpression of PDGF-C does not always lead to tumor formation. Forced expression of PDGF-C in the heart lead to cardiac hypertrophy, whereas overexpressing PDGF-C in the liver induced fibrosis (as well as hepatocellular carcinomas). Furthermore, bleomycin-induced lung injury is associated with increased expression of PDGF-C. While PDGF-C's capacity to drive proliferation and protect from apoptosis are likely to underlie the tumorigenic and hyperplastic phenomena, induction of matrix metalloproteinases and their inhibitors (TIMPs) are likely avenues by which PDGF-C promotes fibrosis.

A mystery surrounding PDGF-C is why it does not transform more cells types. Mesenchymal (such a fibroblasts) and epithelial (such as retinal pigment epithelial) cells express all 3 components needed to establish an autocrine loop: PDGF-C, proteases that process PDGF-C and PDGFRs (Lei et al., 2007a). Furthermore, these cells are routinely cultured in the presence of serum that contains plasmin, a potent PDGF-C processing protease. While the answer may simply be that there is not enough PDGF-C to deregulate these cells, there may be additional

mechanisms regulating the activity of PDGF-C and/or the signaling events emanating from the PDGFR.

4. Future studies

PDGF-C is capable of driving many of the cellular and biological processes that are central to a host of ocular diseases. For instance, PDGF-C may promote proliferation, migration and contraction of cells during the genesis of PVR. Similarly, the capacity of PDGF-C to induce fibrosis implicates it in the formation of the epiretinal membranes that form in PVR, proliferative diabetic retinopathy (PDR) and retinopathy of prematurity (ROP). Finally, PDGF-C may participate in the angiogenic component of PDR, ROP and the wet phase of age related macular degeneration. Our recent findings that the vitreous of patients with a variety of retinal diseases have high levels of PDGF-C and proteases capable of processing PDGF-C (Lei et al., 2007a; Lei et al., 2007b) provide evidence for the potential involvement of this PDGF family member in ocular diseases. Additional studies investigating the role of PDGF-C in ocular diseases will be catalyzed by an increased appreciation of what types of cellular and biological processes PDGF-C regulates, and the availability of reagents to detect both the latent and active forms of PDGF-C.

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Fig 1. The domains of PDGF-C

Secreted PDGF consists of a signal peptide (that is subsequently cleaved; narrow arrow), a CUB domain (open rectangle), a hinge (segment between the CUB and growth factor domains) and a growth factor domain (filled triangle). The large arrow indicates the position at which PDGF-C is proteolytically processed; the amino acid sequence denotes the cleavage site. The gray circles indicate putative glycosylation sites.