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PDGF-C and PDGF-D signaling in vascular diseases and animal models

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ABSTRACT

Members of the platelet-derived growth factor (PDGF) family are well known to be involved in different pathological conditions. The cellular and molecular mechanisms induced by the PDGF signaling have been well studied. Nevertheless, there is much more to discover about their functions and some important questions to be answered. This review summarizes the known roles of two of the PDGFs, PDGF-C and PDGF-D, in vascular diseases. There are clear implications for these growth factors in several vascular diseases, such as atherosclerosis and stroke. The PDGF receptors are broadly expressed in the cardiovascular system in cells such as fibroblasts, smooth muscle cells and pericytes. Altered expression of the receptors and the ligands have been found in various cardiovascular diseases and current studies have shown important implications of PDGF-C and PDGF-D signaling in fibrosis, neovascularization, atherosclerosis and restenosis.

1. Introduction

Cardiovascular disease accounts for a large proportion of deaths, and the disease's development depends on a pathological change in a large number of factors. Infiltrated leukocytes and activated vascular cells such as endothelial cells, smooth muscle cells (SMC) and fibroblasts secrete different growth factors, cytokines and other inflammatory factors that facilitates a local low grade inflammation resulting in tissue remodeling. Among these factors, the platelet-derived growth factors (PDGF) play an important role involving multiple mechanisms responsible for vascular pathologies such as atherosclerosis, restenosis, aortic aneurysm and pulmonary arterial hypertension, resulting in ischemia, myocardial infarction and stroke as example.

The PDGF family is probably one of the best studied growth factor systems. The PDGF family consists of four members; the classical PDGF-A and PDGF-B, but also the novel PDGF-C and PDGF-D. The classical PDGFs are well studied, however, even though it was more than 15 years ago, since the novel PDGF-C and PDGF-D were discovered, they have not yet been studied in detail in the context of vascular and cardiovascular disease. The two were discovered in 2000 (Li et al., 2000) and 2001 (Bergsten et al., 2001; LaRochelle et al., 2001). This review will focus on and summarize the literature of PDGF-C and PDGF-D, and their receptors PDGFR-α and PDGFR-β, in the field of vascular physiology and pathology, including angiogenesis and vascular disease.

2. PDGF structure and signaling

The structure and signaling of the PDGF family has been described and reviewed elsewhere in detail, therefore it is only summarized in brief in this review. Members of the PDGF family binds to and signals through the PDGF receptors (Fig. 1). They are tyrosine kinase receptors, which are expressed in two different forms, PDGFR-α and PDGFR-β, that encode a transmembrane protein with an extracellular ligand-binding domain and an intracellular tyrosine kinase domain (Heldin and Westermark, 1999; Kazlauskas, 2017; Westermark et al., 1989, 1990). These two receptor isoforms dimerize upon ligand binding, which leads to one of the three possible receptor combination -αα, -αβ and -ββ. The dimerization results in receptor autophosphorylation on tyrosine residues in the intracellular domain (Heldin and Westermark, 1999; Kelly et al., 1991; Westermark et al., 1989, 1990). Autophosphorylation further activates the receptor kinase and docking sites for downstream signaling molecules and modulation of different pathways (Kazlauskas and Cooper, 1989; Reigstad et al., 2005; Westermark et al., 1989, 1990).

PDGF-AA can bind the PDGFR-αα and PDGF-BB binds all forms, (i.e., PDGFR-αα, PDGFR-αβ and PDGFR-ββ) (Andrae et al., 2008;

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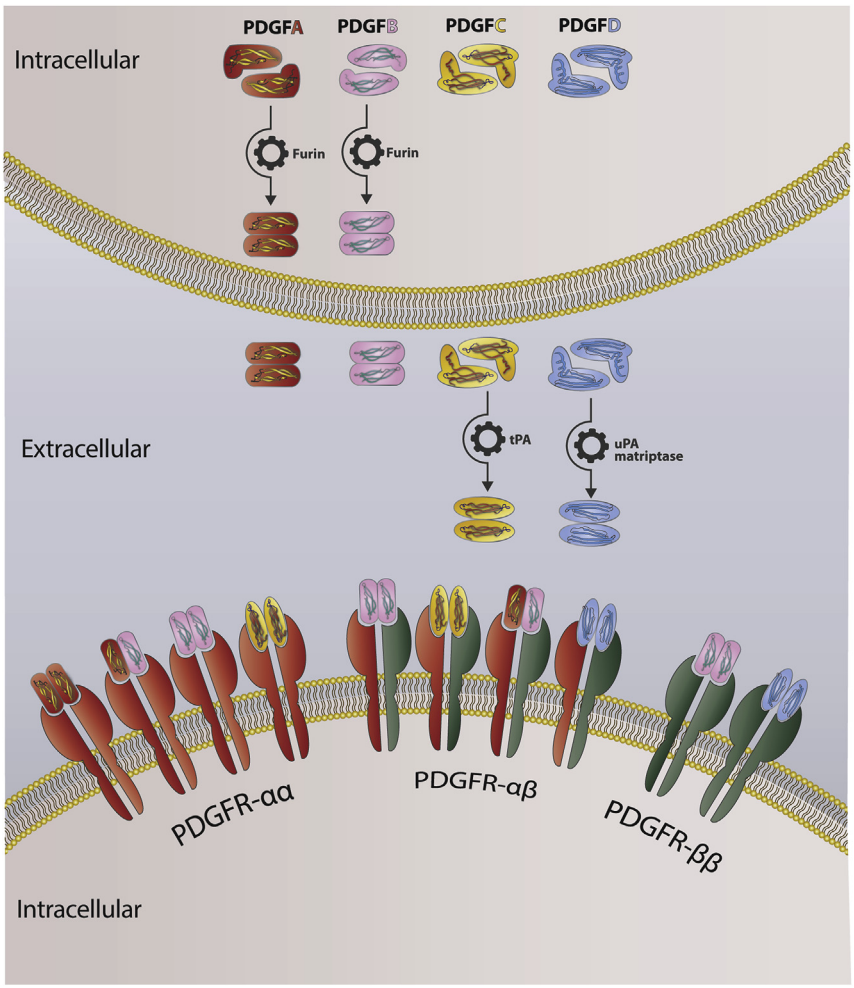

Fig. 1. Simplified schematic overview demonstrating PDGF processing, secretion and receptor binding from both *in vitro* and *in vivo* studies. Furin is mainly responsible for the intracellular cleavage of propeptides in PDGF-A and PDGF-B that can bind to the extracellular matrix or diffuse if the c-terminal retention motif is cleaved. PDGF-C and PDGF-D are secreted in inactive forms and are activated by tPA and uPA or matriptase, respectively.

Heldin and Westermark, 1999; Raines, 2004; Seifert et al., 1989). The heterodimer PDGF-AB can bind PDGFR-αα and PDGFR-αβ.

As for PDGF-A and PDGF-B, PDGF-C and PDGF-D also exert their biological functions by binding to these receptors (Andrae et al., 2008; Fredriksson et al., 2004; Heldin and Westermark, 1999). PDGF-CC preferentially binds to and signals through PDGFR-α homodimers (Li and Eriksson, 2003; Li et al., 2000), while PDGF-DD mainly binds to PDGFR-β homodimers (Bergsten et al., 2001; LaRochelle et al., 2001). The signaling effects of PDGF-A and PDGF-B have been extensively investigated, and since PDGF-C and D also bind these receptors, one could predict similar effects.

Due to their highly conserved cysteine knot motif, PDGF-C and PDGF-D belong to the PDGF/vascular endothelial growth factor (PDGF/VEGF) family and reside in humans on chromosome 4 and 11, respectively (Uutela et al., 2001). In addition to having the common structure of classic PDGFs (i.e. PDGF-A and PDGF-B), PDGF-C and PDGF-D both have an additional unique N-terminal CUB domain (Complement subcomponents c1r/c1s, Urchin epidermal growth factor (EGF)-like protein and Bone morphogenic protein 1), which binds to the extracellular matrix to prevent diffusion (Andrae et al., 2008; Bergsten et al., 2001; Bork and Beckmann, 1993; LaRochelle et al., 2001; Li et al., 2000). The CUB domain blocks the receptor binding of the C-terminal growth factor domain and needs to be cleaved extracellularly to make the growth factor domain active and induce receptor signaling (Bergsten et al., 2001; LaRochelle et al., 2001; Li et al., 2000). The hinge regions of PDGF-C and PDGF-D are between the CUB domain and the growth factor domain and contain cleavage sites for proteolytic removal of the CUB domain before receptor binding. PDGF-C and PDGF-D occur as homodimers (PDGF-CC and PDGF-DD), which are secreted in their full-length form before proteolytic activation. The extracellular cleavage is performed by serine proteases. Plasmin and tissue plasminogen activator (tPA) cleave PDGF-C (Fredriksson et al., 2004, 2005; Gilbertson et al., 2001; Li et al., 2000), while plasmin, urokinase plasminogen activator (uPA) and matriptase were found to cleave PDGF-D (Ehnman et al., 2009; Reigstad et al., 2005; Ustach et al., 2010; Ustach and Kim, 2005).

Riehle and colleagues used tPA knockout mice crossed with transgenic mice overexpressing PDGF-C and showed that cleaved PDGF-C levels remained high (Riehle et al., 2014), indicating that other proteases might also be involved in cleavage of PDGF-C. A study also showed that using matriptase to remove the CUB domain increases the binding of PDGF-DD to extracellular matrix, whereas the cleavage of the growth factor domain reduces the association of PDGF-D and extracellular matrix and can act as dominant-negative ligand that prevents PDGF-B mediated PDGFR-β activation (Huang and Kim, 2015). Interestingly, recent findings show that PDGFR signaling can be modified by neuropilin-1, which binds PDGF-D and

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