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PDGF-C and PDGF-D in ocular diseases

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ABSTRACT

PDGFs and their receptors are critical regulators of numerous tissues and organs, including the eye. Extensive studies have shown that PDGFs and their receptors play critical roles in many ocular neovascular diseases, such as neovascular age-related macular degeneration, retinopathy of prematurity, and proliferative vitreoretinopathy. In addition, PDGFs and PDGFRs are also important players in ocular diseases involving the degeneration of retinal neuronal and vascular cells, such as glaucoma and retinitis pigmentosa. Due to their critical roles in the pathogenesis of many blinding ocular diseases, the PDGFs and PDGFRs have been considered as important target molecules for the treatment of eye diseases. PDGF-C and PDGF-D are relatively new members of the PDGF family and are potent angiogenic and survival factors. Recent studies have demonstrated their important roles in different types of eye diseases. Thus, modulating PDGF-C and PDGF-D activities may have therapeutic values for the treatment of ocular neovascular and degenerative diseases. This review mainly summarizes the recent advances on PDGF-C and PDGF-D biology in relationship to some major ocular diseases.

Introduction

The Platelet-derived growth factor (PDGF) family includes PDGF-A, PDGF-B, PDGF-C and PDGF-D. PDGF-A and PDGF-B were discovered in the 1970s (Betsholtz et al., 1986; Doolittle et al., 1983; Heldin et al., 1986; Johnsson et al., 1982; Kohler and Lipton, 1974; Westermark and Wasteson, 1976) from platelets as peptides that can increase the proliferation of smooth muscle cells (Seifert et al., 1984). PDGF-C and PDGF-D, however, are the relatively new PDGF family members identified in 2000 and 2001 respectively (Andrae et al., 2008; Bergsten et al., 2001; LaRochelle et al., 2001; Li et al., 2000).

The PDGF family members are potent mitogens secreted by different types of cells, including vascular endothelial cells, vascular smooth muscle cells, pericytes, fibroblasts, mesenchymal cells, epithelial cells, astrocytes, and macrophages. Together, the PDGFs make four homodimers, PDGF-AA, PDGF-BB, PDGF-CC and PDGF-DD, and a single heterodimeric polypeptide PDGF-AB. The PDGFs use the platelet derived growth factor receptors (PDGFRs) to exert their diverse functions under physiological or pathological conditions (Kazlauskas, 2017; Li and Eriksson, 2003; Reigstad et al., 2005). There are two homodimers of the PDGFRs, PDGFR-αα and PDGFR-ββ, and one heterodimeric form PDGFR-αβ. All PDGF family members and their receptors are expressed in the central nervous system (Hamada et al., 2002), including the retina in the eye, an extended part of the CNS. Particularly, PDGF-C and PDGF-D are abundantly expressed in the retina and retinal pigment epithelial (RPE) cells (Ray et al., 2005).

Extensive studies have shown that the PDGFs and their receptors play critical roles in many ocular neovascular diseases, such as proliferative vitreoretinopathy (PVR), retinopathy of prematurity (ROP), and neovascular age-related macular degeneration (NV-AMD) (Witmer et al., 2003), which are associated with dysfunctions of multiple components, such as blood vessels, inflammatory cells and RPE cells. Moreover, the PDGFs and PDGFRs are also important players in ocular pathologies involving the degeneration of retinal ganglion cells and photoreceptors, such as in glaucoma and retinitis pigmentosa (RP) (Berger et al., 2010). Due to their critical roles in the pathogenesis of many ocular diseases, the PDGFs and PDGFRs have been considered as important target molecules for the treatment of eye diseases.

Roles of PDGF-C and PDGF-D in proliferative vitreoretinopathy

PVR is a blinding disease resulted from rhegmatogenous retinal detachment following retinal reattachment surgery (Pastor et al.,

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2016) (Fig. 1). PVR is characterized by the outgrowth of the inner and outer membranes of the retina. This leads to the formation of fibrovascular membranes, which ultimately causes retinal scaring and traction (Pennock et al., 2014). PVR can arise before surgery, but is more common after surgical procedures (Claes and Lafeta, 2014). It has been estimated that PVR occurs in about 5–10% of all retinal detachment cases (Pastor et al., 2016).

Current therapeutic interventions for PVR include surgeries such as scleral buckling, membrane peeling, pars plana vitrectomy, and pneumatic retinopexy. However, all these procedures impair visual acuity significantly due to damage to the retinae (Coffee et al., 2014; Sadaka and Giuliari, 2012). Other therapeutic options include anti-inflammatory drugs (Cheema et al., 2007), anti-proliferative reagents (Charteris et al., 2004), and antineoplastic drugs (Hou et al., 2015). However, these drugs are not able to impede the progression of the disease effectively.

Numerous studies have shown that the pathogenesis of PVR is orchestrated by multiple aspects, such as growth factors (Charteris, 1998; Wubben et al., 2016), cytokines (Harada et al., 2006; Limb et al., 1991), extracellular matrix proteins (Feist et al., 2014) and various cellular interactions (Pennock et al., 2011). Importantly, clinical studies have demonstrated the presence of PDGFs in human vitreous samples of PVR patients (Akiyama et al., 2006; Andrews et al., 1999; Lei et al., 2007, 2011; Lei and Kazlauskas, 2014; Mori et al., 2002; Pastor et al., 2016; Si et al., 2013). Moreover, activated PDGF receptors have been found on the epiretinal membranes of PVR patients (Cui et al., 2009). Noteworthy, one of the most abundant vitreal growth factors detected in both experimental PVR models and PVR patients is PDGF-C (Lei et al., 2007). Indeed, both PDGF-C and PDGF-D have been shown to promote the proliferation and migration of RPE cells (Li et al., 2007) (Fig. 1). Moreover, studies using animal model have shown that PDGF-C promotes ECM production and remodeling via PDGFR-α (Wiradjaja et al., 2013). In addition, in PVR, a critical pathology is the transformation of RPE cells into fibroblast-like cells via epithelial-mesenchymal transition (EMT) (Bastiaans et al., 2013).

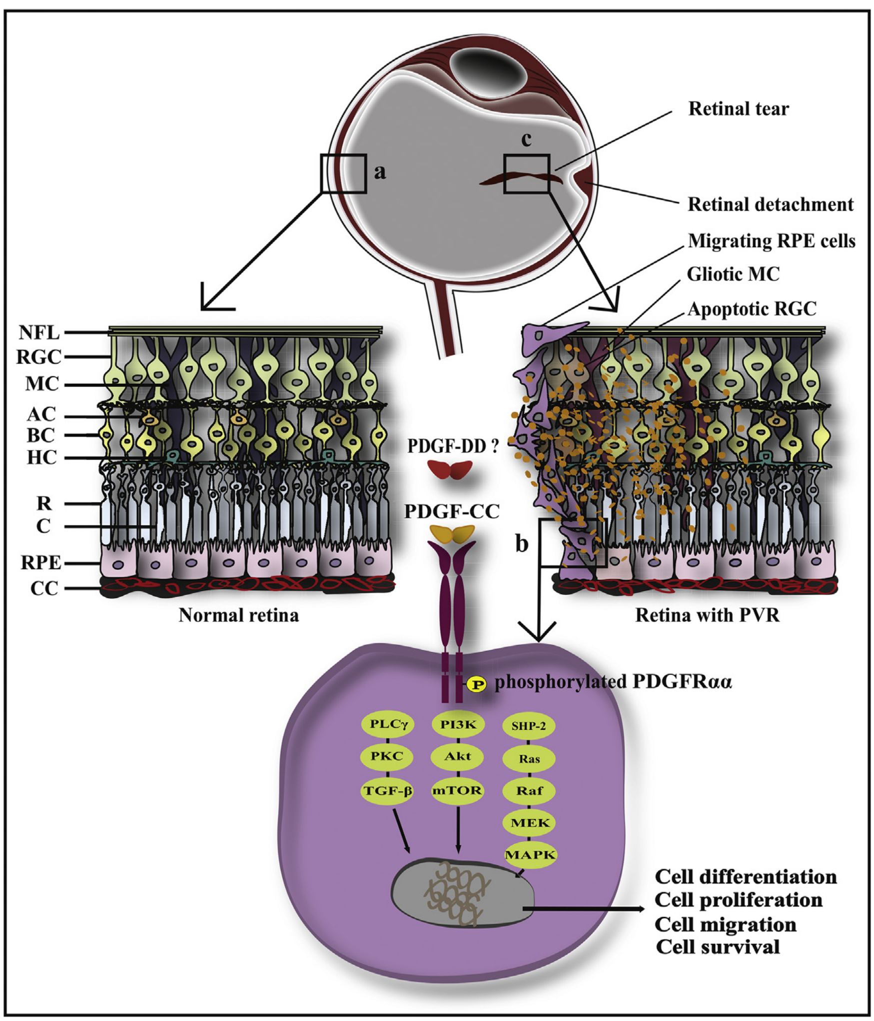

Fig. 1. PDGF-C signaling in proliferative vitreoretinopathy (PVR).
The human retina is highly laminated. Inset box a shows that in a cross section view, the retina is embraced with superior nerve fibre layer, retinal ganglion cells, radial Müller cells, amacrine cells, bipolar cells, horizontal cells, rod cells, cone cells, retinal pigment epithelial cells, and choriocapillaris. Repeating retinal detachment steers the retinal tear and compromises the retinal integrity, which subsequently triggers the production of various growth factors and proteases to initiate the wound healing process with damaged gliotic MCs, apoptotic RGCs, invading RPE cells and other retinal cells. Inset box b shows that elevated levels of PDGF-C activate PDGF receptor alpha signaling, which promotes transcriptional changes to enforce cell differentiation, proliferation, migration, survival, epithelial mesenchymal transition and extracellular remodeling. Inset box c shows that in a cross section view of the retina with PVR, the otherwise stationary RPE cells are highly differentiated and migrate towards the nerve fibre layer. The presence and potential role of PDGF-D in PVR remain to be investigated. NFL: nerve fibre layer, RGC: retinal ganglion cell, AC: amacrine cell, MC: Müller cell, BC: bipolar cell, HC: horizontal cells, R: rod cell, C: cone cell, RPE: retinal pigment epithelial cell, CC: choriocapillary.