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Review Article

Platelet derived growth factor inhibitors: A potential therapeutic approach for ocular neovascularization

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Abstract

Retinochoroidal vascular diseases are the leading causes of blindness in the developed world. They include diabetic retinopathy (DR), retinal vein occlusion, retinopathy of prematurity, age-related macular degeneration (AMD), and pathological myopia, among many others. Several different therapies are currently under consideration for the aforementioned disorders. In the following section, agents targeting platelet-derived growth factor (PDGF) are discussed as a potential therapeutic option for retinochoroidal vascular diseases. PDGF plays an important role in the angiogenesis cascade that is activated in retinochoroidal vascular diseases. The mechanism of action, side effects, efficacy, and the potential synergistic role of these agents in combination with other treatment options is discussed. The future of treatment of retinochoroidal vascular diseases, particularly AMD, has become more exciting due to agents such as PDGF antagonists.

Keywords: Platelet derived growth factor, Retinal vascular disease, Age related macular degeneration, Diabetic retinopathy, PDGF

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Introduction

Platelet-derived growth factor (PDGF) was first isolated from platelet extracts in the early 1970s and classified as a mitogen for fibroblasts and cells of mesenchymal origin.[1] The α granules of platelets are known to be a major storage site for PDGF; however, recent studies have also shown presence of PDGF in several other cell types. Mice studies have highlighted the essential role of PDGF in the early development of the embryo, with a deficiency resulting in defective formation of the lungs, vessels, placenta, brain, and skeleton. In these organs, cell types such as mesangial cells, pericytes, fibroblasts, and glial cells were shown to be dependent on PDGF.[2]

The PDGF family consists of four ligands: A, B, C and D. They function as homodimers with the exception of ligand ''AB'', which acts as a heterodimer.[3] All four PDGF ligands bind two structurally related tyrosine kinase cell surface receptors, α and β,[4] which relay the message internally and initiate signal induction via Ras and phosphatidylinositol-II pathways. These pathways are essential for PDGF-induced cell migration and mitogenesis, respectively.[5] PDGF-AA, -AB, -BB and -CC activate the PDGF receptor-α (PDGFRα) while PDGF-BB and -DD bind to PDGFRβ (Fig. 1). PDGF-A is expressed by neurons and astrocytes[6] and, together with PDGFRα, is responsible for recruitment and subsequent development of astrocyte precursors in the retina.[6,7] PDGF-C plays a critical role in neuronal survival and prevention from

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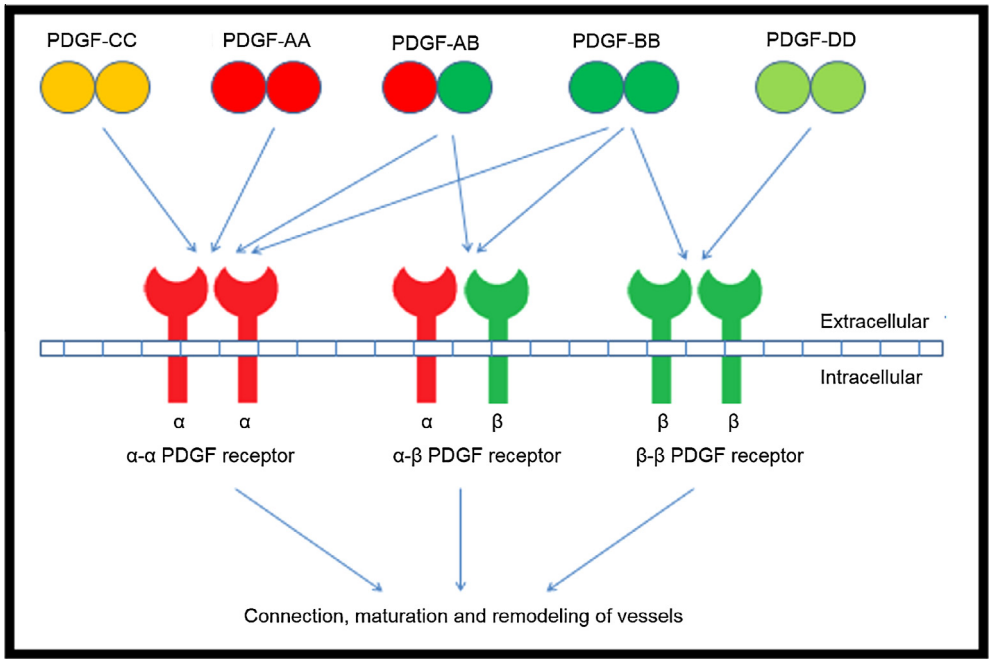

Figure 1. Flowchart demonstrating the PDGF ligand–receptor interaction.

apoptosis via regulation of expression of the glycogen synthase kinase 3β.[8] In animal models, eyes treated with PDGF showed decreased retinal pigment epithelial and photoreceptor degeneration.[9] Pericytes express PDGFRβ, allowing PDGF-BB and PDGFRβ to play an important role in the maintenance of retinal vasculature.[10,11]

PDGF over-activity has also been linked with several systemic conditions including autocrine stimulation of various cells in tumors, atherosclerosis, and fibrotic conditions such as lung, liver, and kidney fibrosis.[12] In fact, PDGF antagonists are currently being evaluated for the treatment of pulmonary hypertension [13] and several different tumors.[14–16]

Methodology

A systematic search of literature was conducted on PubMed, Scopus, and Google Scholar with no limitation on language or year of publication. Words searched included PDGF, Platelet Derived Growth Factor, PDGF AND antagonist, PDGF AND retinal diseases, PDGF AND AMD, PDGF AND DME, PDGF AND retinal vascular diseases.

PDGF and retinochoroidal vascular diseases

A common feature of most retinochoroidal diseases is some degree of vascular insult that leads to ischemia. Such injury consequently leads to release of a wide range of factors that alter the course of the disease process. It was first postulated in 1948 that an angiogenic factor was responsible for retinal neovascularization (NV).[17] Since then, several other key factors have been identified for their critical role in the disease process. Hypoxia inducible factor-1 (HIF-1) was identified as a transcription factor that mediates increased expression of several genes associated with NV. These genes lead to the increased transcription of several key factors that are eventually responsible for new vessel formation; these include vascular endothelial growth factor (VEGF), PDGF, stromal derived growth factor-1 (SDF-1), and placental growth factor (PIGF).

Angiogenesis is considered to consist of five basic steps (Fig. 2) that include degradation of basement membranes, migration of endothelial cells, tube formation by endothelial cells, new basement membrane formation and finally, encirclement by pericytes for stabilization. In-vitro studies have demonstrated the role of PDGF in the angiogenesis process.[18] It has been shown to promote migration and proliferation of endothelial cells along with an increase in the recruitment of pericytes. These findings, therefore, suggest that PDGF plays a key role in the angiogenesis cascade.

High glucose levels have been shown in-vitro to lead to increased expression of PDGF-β, and therefore, an increase in its binding to PDGF-BB.[19] This glucose-related increased

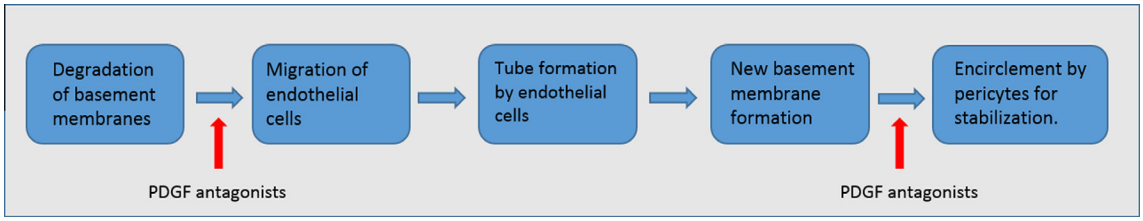

Figure 2. Flowchart depicting the various steps involved in the pathway of angiogenesis.