PDGF/PDGFR Signaling in Cardiovascular Disease

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Abstract

As a leading cause of morbidity and mortality worldwide, Cardiovascular Disease (CVD) refers to a class of diseases occurring in heart or blood vessels. CVD includes several conditions such as myocardial infarction (heart attack) and heart stroke (heart failure). The fundamental pathological process underlying these conditions is atherosclerosis; a multi-process vascular lesion resulted from high blood pressure, hyperlipidemia and local chronic inflammatory response. Some of the lesions in later stage are vulnerable to rupture, trigger thrombosis and obstruct the blood flow of microvascular causing heart attack or stroke. Numerous stimuli and factors participate in the development of CVD including Platelet-Derived Growth Factor (PDGF). PDGF is synthesized, stored (in the alpha granules of platelets) and released by platelets upon activation. Other types of cells including smooth muscle cells, activated macrophages and endothelial cells also produce PDGF. PDGF exerts physiological functions by binding to corresponding receptors. PDGF/PDGFR signaling pathway plays a crucial role in the development of blood vessels and other organs as well as tissues. On the other hand, aberrant activation of PDGF/PDGFR signaling pathway drives the progression of cardiovascular diseases such as atherosclerosis, transplant arteriosclerosis, fibrosis, etc. However, the exact mechanism is not fully explored yet. Here we review the contemporary biomedical knowledge on the role of PDGF/PDGFR signaling and related mechanisms in promoting cardiovascular diseases.

Keywords: PDGF/PDGFR signaling; Cardiovascular disease; Atherosclerosis; Cardiac fibrosis

Introduction

Platelet-Derived Growth Factor (PDGF) was firstly identified as a serum growth factor more than 40 years ago, which stimulates the proliferation, survival, migration of fibroblasts, Smooth Muscle Cells (SMCs) and glia cells [1-3]. Four genes PDGFA, PDGFB, PDGFC and PDGFD encode PDGF polypeptide chains, which further form homo- and heterodimers PDGF-AA, -BB, -AB, -CC and -DD through disulfide bonds [4,5]. Different from PDGF-A and PDGF-B, the N-terminus of PDGF-C and PDGF-D contains a CUB (complement subcomponents Clr/Cls, urchin EGF-like protein and bone morphogenic protein 1) domain, which requires a specific protease cleave to trigger their biological activity [6,7]. PDGFs are produced and stored in platelets that are released on platelet activation. Additionally, endothelial cells, activated macrophages, smooth muscle cells and many tumor cells are reported to produce PDGFs [8].

PDGF activates PDGF receptors in a paracrine or autocrine manner. PDGF receptors are typical Receptor Tyrosine Kinase (RTK). Two types of PDGFRs have been identified, i.e. PDGFR-α and PDGFR-β. PDGF-BB binds to both the heterodimers and homodimers of the receptors. PDGF-AA only binds to PDGFR-α homodimers. PDGF-AB and -CC bind to both homodimers of the PDGFR-α and the heterodimer but PDGF-DD binds to PDGFR-β homodimers and the heterodimer. PDGFR-α is expressed in mesenchymal cells. PDGFR-β is highly expressed in Vascular SMCs (VSMC) and pericytes but endothelial cells do not express either PDGFR-α or PDGFR-β [9]. PDGFs bind to the corresponding receptors triggering a series of cellular responses under physiological or pathological conditions.

Aberrantly activated PDGF/PDGFR signaling has been demonstrated to play a pivotal role in the onset and development of organ fibrosis, tumor growth and cardiovascular diseases including atherosclerosis, transplant arteriosclerosis and pulmonary arterial hypertension. In this review, we summarize the current knowledge related to the role of PDGF/PDGF receptor signaling and mechanisms in development of cardiovascular diseases, especially atherosclerosis and cardiac fibrosis.

PDGF/PDGFR Signaling Pathway

Upon PDGF binding to corresponding receptors, the receptor dimerizes and the tyrosine residues in the intracellular domain undergo autophosphorylation. Phosphorylated PDGFR provide docking sites for various intracellular signaling proteins such as Phosphatidyl Inositol 3-kinase (PI3K), Src, Phosphatidyl Inositol 3-Kinase (PI3K), Shc, Grb2, Akt, and SHP2. Then a series of signaling pathways are activated, eliciting alterations in gene transcription, protein expression and cell behaviors including cell proliferation, growth, migration, differentiation and phenotype transition.

Activated PDGFR provides docking sites to Grb2 through its SH2 domain and complexes Sos1 through its SH3 domain. Sos1 activates RAS/Raf-1 and following MAPK cascade [10,11]. MAPK signaling pathway stimulates relevant gene transcription leading to increased cell growth, differentiation, and migration. Phosphorylated PDGFR interacts with PI3K, which has a pair of SH2 domains [12] and the activated RAS also binds to the catalytic domain of PI3K, leading to the full activation of PI3K [13]. Then activated PI3K phosphorylates AKT/PKB located on plasmic membrane and a variety of molecules such as mTOR. In addition, PDGFR mediates CAMP-Response Element Binding protein (CREB) activation regulating cellular metabolism, proliferation, migration [14]. Similarly, phosphorylated PDGFR recruits PLC-γ to the plasmic membrane through the SH2 domains and phosphorylates its Tyr 783 site [15,16], which regulate cell growth and migration. Activated PDGFR also provides docking sites for transcription factors such as Signal Transducers and Activators of Transcription (STAT), yielding their nuclear translocation and target genes expression [17].

PDGF/PDGFR signaling and atherosclerosis

Atherosclerosis is a cardiovascular disease characterized by the accumulation of lipid and fibrous elements on arterial blood vessel walls. The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries, which result in ischemia of the heart, brain or extremities followed by even infarction featured with high mortality and disability [18]. The pathogenesis of atherosclerosis is initiated by vascular endothelial dysfunction and hyperlipidemia, which are promoted by the chronic inflammatory response [19]. Reported causes for endothelial dysfunction include elevated and modified plasmic LDL, free radicals produced following smoking, hypertension, diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations, infectious microorganisms such as herpesviruses or *Chlamydia pneumoniae* and combinations of these or other factors [18,20]. The dysfunctional endothelial cells exhibit increased permeability, enhanced leukocyte adhesion and altered gene expression, all of which contribute to intimal thickening; typical atheromas ensue to different degrees [21]. The endothelial dysfunction resulted from injury leads to compensatory responses that alter the normal homeostatic properties of the endothelium. The injury also induces a cascade of events including leukocyte adhesion, monocyte migration and foam cell formation, VSMC proliferation, synthesis of extracellular matrix, phenotype transition, angiogenesis, calcification and cell death [22-24]. Meanwhile, many vasoactive molecules, cytokines and growth factors such as angiotensin, interleukins, IFN-γ, PDGF are all involved to promote the process [25-27].

Normally mammal vessels express low or undetectable PDGF and relevant receptors [28]. However, expression levels of PDGF and PDGFR are increased at lesion sites during the development of atherosclerosis [9], in macrophages, endothelial cells and VSMCs [29]. It has also been demonstrated that PDGFR level is increased in atherosclerotic plaques. PDGFR-β is mainly expressed in VSMCs while PDGFR-α is abundantly expressed in endothelial cells and macrophages. And clinical atherosclerotic samples show expression of tyrosine phosphorylation level of PDGFR-β five-fold higher than non-atherosclerotic samples [30]. In addition, PDGF-C and PDGF-D are also expressed in macrophages and VSMCs in human atherosclerotic plaques [31].

Inflammation plays a key role in the development of atherosclerosis. During the initial stage of atherosclerosis, blood vessel undergoes vascular endothelial dysfunction. Inflammatory factors are released by these endothelial cells. Concomitantly, a large number of inflammatory cells infiltrate into the subendothelial area to form a chronic inflammatory microenvironment. Subendothelial VSMCs are exposed to a large number of inflammatory factors, which stimulate the migration, proliferation and phenotypic switch of VSMCs. Then VSMCs transdifferentiate from contractile phenotype into synthetic phenotype. The latter releases a variety of inflammatory factors, which in turn stimulate macrophage foaming and accelerate the formation of atherosclerotic plaques [32]. *In vitro* and *in vivo* studies demonstrate that PDGF-C and PDGF-D stimulate the migration of monocytes by inducing the expression of Matrix Metalloproteinase (MMP)-2 and MMP-9 [33]. As a mitogen of VSMC, PDGFs also drive migration of medial VSMC into the neointima, contributing to the arrow the lumen of blood vessels [34]. Inhibition of the PDGFR tyrosine kinase by small molecule compound inhibits SMC migration and proliferation *in vitro* and decreases accumulation of α-actin-positive cells on the luminal side. PDGFR-β has also been confirmed to cause vascular inflammation. Conditionally activation of PDGFR-β signaling in VSMCs induces inflammatory reaction in the media and adventitia of aortas, which accelerates the plaque formation under either ApoE or LdlR null background [35]. In addition, blockade of PDGF/PDGFRβ pathway with neutralizing antibodies of PDGF-A inhibits atherogenesis in the Cholesterol-Fed rabbit [36]. Consistently, blockade of PDGFR-β instead of PDGFR-α using monoclonal antibodies significantly reduces atherosclerosis burden in ApoE null mice [37]. However, a study within ApoE null mice developing advanced atherosclerosis shows that blockade of the PDGF receptors delays but does not prevent accumulation of VSMCs and fibrous cap formation [38]. Hence, whether PDGF/PDGFR signaling pathway is a therapeutic target to treat atherosclerosis remains elusive and requires further investigation.

PDGF/PDGFR signaling and cardiac fibrosis

Similar to atherosclerosis, fibrosis is also a tissue-repair response to injury, characterized by increased deposition of Extracellular Matrix (ECM). Fibrosis occurs in all organs and tissues, resulting in irreversible compromised organic function. A number of cells participate in the initiation and aggravation of the process by paracrine-signaling mediated-activation and expansion of tissue mesenchymal stromal cells, i.e. fibroblasts, pericytes and myofibroblasts. Transforming Growth Factor β (TGF-β) as well as downstream signaling have been wildly considered as the predominant cause of fibrosis by stimulating the disposition of collagen and ECMs of myofibroblasts. Whereas several studies suggest PDGF/PDGFR signaling pathway as another important profibrotic factor [39], as reported in liver, dermal, renal, pulmonary and cardiac fibrosis so far.

Blocking antibodies or small molecule chemical inhibitors targeting this pathway have shown therapeutic effects on kidney, atrial, skin and lung fibrosis in different animal models [40-42]. PDGF is a potent mitogen to stimulate the proliferation of cells with myofibroblast phenotype. PDGFR-α is expressed in mesenchymal cells and highly expressed in several subtype mesenchymal progenitor cells of intestine, skin and lung. Meanwhile expression of PDGFR-α is upregulated under the stimulation of IL-1β and TGF-β. PDGFR-β is expressed in mesenchyme, particularly in VSMCs and pericytes.

Cardiac fibrosis is reported as the result of hypertension, cardiac hypertrophy and myocardial infarction, featured with disposition of ECM and collagen and the proliferation of interstitial cardiac fibroblasts. Overexpression of PDGF-C specifically in cardiomyocytes, which exhibit cardiac fibrotic phenotype and cause a series of pathological alterations including cardiac fibroblast proliferation and deposition of collagen, hypertrophy, vascular defects and the presence of Anitschkow cells in the adult myocardium [43]. Upregulation of PDGF-A in myocytes results in severe cardiac fibrosis, accompanied by up to 8-fold increased cardiac size causing the lethal death. Interestingly, overexpression of PDGF-B leads to focal and less fibrosis as well as moderate cardiac hypertrophy. The underlying explanation could be the different affinity difference between the two ligands and receptors. PDGF shows a stronger fibrotic effect in cardiac interstitial mesenchymal cells, which is mainly mediated by PDGFR-α [44]. Transgenic mice overexpressing the active core domain of PDGF-D in the heart exhibit cardiac fibrosis followed by dilated cardiomyopathy and subsequent cardiac failure [45]. Stimulation of PDGF-D in rat cardiac fibroblasts upregulates MMP-1, MMP-2 and MMP-9 protein levels as well as enhanced TGF-β pathway activation *in vitro* [46]. These findings demonstrate the potential therapeutic effect by blocking PDGF/PDGFR signaling on cardiac fibrosis. Blockade of PDGFR-α/β with neutralizing antibodies in myocardial infarction mouse models show decreased collagen deposition in the infarct. Blocking of PDGFR-β results in impaired maturation of cardiac angiogenesis. All these indicate the role of PDGF in vascular development and wound healing [47]. Thus the profibrotic effect could be utilized in the area of tissue regeneration and wound healing such as the treatment of ulcers.

Perspectives

Numerous studies have shown the clear association between PDGF/PDGFR signaling pathway and the development of cardiovascular diseases such as atherosclerosis and cardiac fibrosis. In addition, the PDGF/PDGFR signaling pathway also participates in other cardiovascular diseases, e.g. pulmonary hypertension and cardiac hypertrophy [48,49] and affects some pathological process including platelet aggregation and new blood vessel formation.

Given the importance of dysregulated PDGF/PDGFR signaling pathway in different diseases, it suggests potential therapeutic strategies by kinase inhibitors, receptor/ligand antibodies, etc. Targeting PDGF ligands is an approach to inhibit PDGF/PDGFR signaling pathway radically. Neutralizing antibodies against PDGF-BB, PDGF-CC, PDGF-DD have been tested in different animal models involving solid tumors, myocardial infarction, atherosclerosis and neointimal VSMC accumulation caused by balloon injury and all these antibodies show protective effect [50,51]. PDGFR-blocking antibodies is also an important part in the development of new therapeutic agents. Olaratumab, a recombinant human IgG1 anti-PDGFR-α monoclonal antibody, was firstly approved by FDA in the treatment of soft tissue sarcoma [52]. But it is less efficient as shown in clinical studies of glioma, prostate cancer and advanced non-small cell lung cancer. Another effective way to block the PDGF/PDGFR signaling pathway is to block the enzymatic activity of PDGFRs with small molecule tyrosine kinase inhibitors. For example, Imatinib is the first tyrosine kinase inhibitor approved for clinical treatment of Chronic Myeloid Leukemia (CML). And currently more other tyrosine kinase inhibitors are available. A recently completed CANTOS trial indicates the role of anti-inflammatory therapy in the treatment of atherosclerosis [53]. PDGF/PDGFR signaling pathway causes the vascular inflammation and accelerates the pathogenesis of organic fibrosis. Whereas relevant clinical study to explore PDGF/PDGFR signaling pathway as a therapeutic target is still lacking, which highlights further investigation.

Acknowledgement

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