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PDGFs and their receptors in vascular stem/progenitor cells: Functions and therapeutic potential in retinal vasculopathy

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ABSTRACT

Vascular stem/progenitor cells (VSCs) include endothelial progenitor cells, smooth muscle progenitor cells, pericytes, and mesenchymal stem cells. VSCs can produce functional and mature vascular cells required to build blood vessels. VSCs therefore play critical roles in vascular repair and regeneration, particularly, in various retinal vasculopathies, in which vascular defects are a devastating pathology. The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are important regulators of numerous physiological events and diseases, and they play key roles in regulating the formation and function of blood vessels. A better understanding of the effects of PDGFs/PDGFRs on VSCs and a thorough elucidation of their therapeutic potential in the treatment of retinal vasculopathies are critical for both basic and translational research and may lead to better therapies for human vascular diseases.

1. Introduction

Blood vessels, formed mainly through vasculogenesis and angiogenesis (Carmeliet, 2005), are vital for blood supply and the functions and structural properties of organs and tissues. Blood vessels are mainly composed of two cell types: endothelial cells (ECs) and mural cells (MCs). There are two types of MCs: vascular smooth muscle cells (SMCs) and pericytes. ECs line the vascular lumen to provide a barrier between circulating blood and tissues, whereas MCs are located peripherally and coat the EC tube. SMCs are associated with large blood vessels, such as arteries, arterioles, and veins. The contractile ability of SMCs is responsible for the regulation of blood flow and blood pressure. Pericytes are found in capillaries, small venules, and newly formed blood vessels. Pericytes stabilize the vessels and regulate blood flow too. The proper maintenance and reciprocal interaction between ECs and MCs are required for the normal formation, stabilization, and function of the vasculature (Armulik et al., 2005). It has been long thought that the formation of new blood vessels in adults only requires mature vascular cells (Parker Kerrigan et al., 2017). However, two decades ago, the discovery of $CD34^{+}VEGFR2^{+}$ endothelial progenitor cells (EPCs) in peripheral blood that are capable of generating new blood vessels changed the paradigm of vascular biology (Asahara et al., 1997). Since then, numerous studies have reported that cells residing in the vascular wall, bone marrow, circulation, or other extravascular tissues can differentiate into various types of mature vascular cells needed to build blood vessels. These cells have been named vascular stem/progenitor cells (VSCs) (Zhang and Xu, 2014).

The platelet-derived growth factors (PDGFs) are critical players in a variety of physiological and pathological processes (Ishii et al., 2017). In particular, PDGFs play important roles in blood vessel formation and retinal vasculopathies (Sadiq et al., 2016). Major retinal vasculopathies include diabetic retinopathy (DR), retinopathy of prematurity (ROP), the wet form of age-related macular degeneration (wAMD) and retinitis pigmentosa (RP), which are the major causes of vision loss or blindness. In this review, we summarize the functions of PDGFs/PDGFRs in the regulation of VSCs, and further discuss their therapeutic potentials in retinal vasculopathies in relationship to VSCs.

2. PDGFs and their receptors

The PDGFs belong to the cystine knot protein superfamily. They are encoded by four different genes *PDGF-A*, *PDGF-B*, *PDGF-C*, and *PDGF-D*, and exist as homodimers interconnected by disulfide bonds (PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD) or as heterodimers (PDGF-AB) (Boor et al., 2014). Initially identified in 1970s as serum proteins that stimulate fibroblast and SMC growth and migration, PDGF-AA, -BB, and -AB have been studied intensively and are considered as classical PDGFs (Heldin and Westermark,

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1999). PDGF-CC and PDGF-DD, however, were discovered as new members of the PDGF family nearly twenty years after the finding of PDGF-AA and PDGF-BB (Bergsten et al., 2001; Li et al., 2000). Unlike the classical PDGFs, PDGF-CC and PDGF-DD are secreted as inactive precursors, and cleavage of the N-terminal CUB domain is necessary for their activation. This can be accomplished by proteases such as plasmin, tissue plasminogen activator and urokinase plasminogen activator (Demoulin and Essaghir, 2014).

PDGF ligands exert their biological effects through binding to homo- or heterodimers of the two PDGFR proteins, PDGFR-α and PDGFR-β, with different affinities. PDGFR-αα binds to all PDGF dimers with an exception of PDGF-DD, whereas PDGFR-ββ associates with PDGF-BB and PDGF-DD. PDGFR-αβ has been reported to be activated by all PDGFs except PDGF-AA. However, the affinities of PDGF-CC and PDGF-DD to PDGFR-αβ are much lower than those of PDGF-AB and PDGF-BB (Cao, 2013). Dimerization of receptors is a key process to promote the autophosphorylation of intracellular kinases, which further activates downstream signaling pathways through specific domains such as SH2, PDZ, and PTB (Andrae et al., 2008). This in turn results in the activation of various downstream signaling cascades, such as PI3K, PLC-γ, JAK and MAPK, thus regulating numerous biological events (Demoulin and Essaghir, 2014).

3. Vascular stem/progenitor cells (VSCs)

The integrity and functions of blood vessels may be impaired by various stresses or pathologies, thereby requiring the capacity of blood vessels to repair and regenerate after damage. Accumulating evidence suggests that there exist different types of vascular stem/progenitor cells, which can give rise to differentiated vascular cells (Psaltis and Simari, 2015). There are mainly four types of VSCs, namely vascular endothelial progenitor cells (EPCs), smooth muscle progenitor cells (SMPCs), mesenchymal stem cells (MSCs), and pericytes. EPCs are the first isolated adult vascular progenitor cells that are found to be able to differentiate into ECs (Asahara et al., 1997). The presence of human SMPCs in peripheral blood that can give rise to SMCs was first reported in 2002 (Simper et al., 2002). MSCs have the potential to differentiate into both ECs (Oswald et al., 2004) and SMCs (Kashiwakura et al., 2003). In addition, MSCs co-cultured with EPCs can enhance the differentiation of MSCs to pericyte-like cells (Loibl et al., 2014). Pericytes have been reported to behave like MSCs that can generate different types of cells, such as chondrocytes, osteocytes, adipocytes, skeletal muscles and neurons (Armulik et al., 2011). Pericytes have been shown to be capable of differentiating into coronary artery SMCs in response to the activation of Notch pathway (Volz et al., 2015). However, a recent study using a lineage-tracing method to mark $Tbx18^{+}$ cells as pericytes reveals different results. It shows that these cells maintained their own identity and did not behave like progenitors for other lineages in several mouse disease models (Guimaraes-Camboa et al., 2017). This notion challenges the view that pericytes are mutipotent cells. In this section, we mainly summarize current findings on the origins of VSCs and discuss the criteria to characterize VSCs. The effects of PDGFs/PDGFRs on VSCs are also discussed.

3.1. The origins of VSCs: many sources but low abundance

3.1.1. Sources of EPCs

Bone marrow (Murayama and Asahara, 2002) and peripheral blood (Asahara et al., 1997) are considered as the major sources for EPCs. In addition, EPCs can also be found in vascular walls (Zengin et al., 2006), liver, small intestine (Aicher et al., 2007) and perinatal tissues, such as umbilical cord blood (Ingram et al., 2004) and placenta (Fig. 1) (Rapp et al., 2012). Circulating EPCs have been considered as the most important source of cells for vessel regeneration because their isolation is relatively easy. Moreover, numerous studies have shown that the number of circulating EPCs may serve as a biomarker since the numbers have been shown to be correlated with many pathological conditions, such as tumor and peripheral artery diseases (Bitterli et al., 2016; Ge et al., 2015). On the other hand, the results of some other studies question the importance of circulating EPCs. Firstly, it has been shown that the ability of circulating EPCs to differentiate into ECs and to engraft into vessels after injury is less than that of resident EPCs (Hagensen et al., 2010; Kawasaki et al., 2015; Rapp et al., 2012). Secondly, it is reported that the contribution of circulating EPCs to neovasculature is more likely mediated by a paracrine effect, such as secretion of angiogenic factors (Baker et al., 2013), or by releasing microparticles or microvesicles (Deregibus et al., 2007; Wang et al., 2013). Thirdly, it has been shown that the number of circulating EPCs is very limited as they comprise less than 0.01% of mononuclear cells in peripheral blood (Gross and Herbrig, 2004). Although it has been shown that cord blood contains more EPCs, their absolute number is still small (up to 0.64% of all mononuclear blood cells), which may hinder their therapeutic implication in cell therapy (Case et al., 2007). Attempts to increase the number of human EPCs via different *in vitro* expansion methods may offer potential ways to obtain sufficient EPCs needed. A comparison of these methods is listed in Table 1.

3.1.2. Origins of SMPCs

In adults, SMPCs can be found in the bone marrow, circulating blood, vascular wall, and extravascular matrix (Orlandi and Bennett, 2010). Other reservoirs for SMPCs include the skin (Steinbach and Husain, 2016), adipose tissue (Ma et al., 2017), and umbilical cord blood (Fig. 1) (Le Ricousse-Roussanne et al., 2004). The importance of circulating SMPCs have been shown in both preclinical and clinical studies. For example, SMPCs are found to play an important role in preclinical models of arteriosclerosis (Sun et al., 2016). In patients with different pathologies, the number of functions of SMPCs are often compromised. For example, in patients with diabetes or coronary artery disease, the numbers of SMPCs are lower than those of healthy population (Sugiyama et al., 2006; van Ark et al., 2012). In patients with Moyamoya disease, SMPCs exhibit altered gene expression profiles during the progression of the disease (Kang et al., 2014). Many studies have investigated how to increase the number and functions of SMPCs and several regulating molecules have been identified, such as TGF-β (Wang et al., 2012a) and HB-EGF (Wang et al., 2016b). Still, due to the relatively scarce amount of SMPCs *in vivo*, knowledge on SMPCs are still poor and more studies are need to better characterized them.

3.1.3. Sources of MSCs

MSCs are one of the most intensively studied stem cells for regenerative medicine. MSCs display great potential for cell therapy in both preclinical models and clinical trials. Compared with other types of stem/progenitor cells, MSCs have unique advantages. Firstly, they are relatively ease to harvest and have a fair availability. Secondly, they have an immunosuppressive effect and can secret many beneficial factors, such as cytokines and exosomes (Kim and Park, 2017; Lou et al., 2017). Owing to their ability to differentiate into ECs and SMCs, MSCs are considered to be a promising source of cells for vascular regeneration. The niches for MSC include bone marrow, vascular wall, heart, adipose tissue, skeletal muscle, liver, umbilical cord blood and placenta (Fig. 1) (Hashemian et al., 2015). Notably, adipose tissue can yield around 500-fold more MSCs than bone marrow, representing an important source of MSCs (Fraser et al., 2006).

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