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Mini review

The PDGF system and its antagonists in liver fibrosis

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ABSTRACT

Platelet derived growth factor (PDGF) signaling plays an important role in activated hepatic stellate cells and portal fibroblast proliferation, chemotaxis, migration and cell survival. PDGF receptors and ligands are upregulated in experimental liver fibrotic models as well as in human liver fibrotic diseases. Blocking of PDGF signaling ameliorates experimental liver fibrogenesis. The plurality of molecular and cellular activities of PDGF and its involvement in initiation, progression and resolution of hepatic fibrogenesis offers an infinite number of therapeutic possibilities. These include the application of therapeutic antibodies (e.g. AbyD3263, MOR8457) which specifically sequester individual PDGF isoforms or the inhibition of PDGF isoforms by synthetic aptamers. In particular, the isolation of innovative slow off-rate modified aptamers (e.g., SOMAmer SL1 and SL5) that carry functional groups absent in natural nucleic acids by the Systematic Evolution of Ligands by EXponential (SELEX) enrichment technique offers the possibility to design high affinity aptamers that target PDGF isoforms for clinical purposes. Dominant-negative soluble PDGF receptors are also effective in attenuation of hepatic stellate cell proliferation and hepatic fibrogenesis. Moreover, some multikinase inhibitors targeting PDGF signaling have been intensively tested during the last decade and are on the way into advanced preclinical studies and clinical trials. This narrative review aims to gauge the recent progression of research into PDGF systems and liver fibrosis.

1. Introduction

Platelet-derived growth factor (PDGF) belongs to the family of growth factors consisting of four secreted extracellular ligands encoded by four different genes. They are assembled into disulfide-bonded dimers *via* homo- or heterodimerization [1]. PDGF-A and -B may form both homodimers and heterodimers (PDGF-AA, -AB, -BB) but PDGF-C and -D exist only as homodimers (PDGF-CC and -DD). The different PDGF members show a high sequence identity with vascular endothelial growth factors (VEGF) and are therefore often referred to as the PDGF/VEGF family in mammals and invertebrates. All members share the highly conserved and specific PDGF/VEGF homology domain necessary for receptor binding and activation. The PDGF ligands exert their biological effects through the two structurally related tyrosine kinase receptors PDGFR-α and PDGFR-β. Important ligand/receptor interactions *in vivo* are PDGF-AA and PDGF-CC that induce PDGFR-α dimerization, PDGF-BB and PDGF-DD which induce PDGFR-β dimerization. Other interactions between PDGF ligands and receptors have been demonstrated in cell culture experiments, but *in vivo* evidence is currently still lacking [2].

2. Biological functions of PDGF

The common biological functions of the PDGF signaling pathway include regulation of cellular proliferation and survival, angiogenesis, cell migration, membrane ruffles, cytoskeletal rearrangements with the reorganization of the actin filament system and stimulation of synthesis of the major components of the connective tissue matrix, such as collagen, glycosaminoglycans, and proteoglycans [3]. Due to its potent stimulation of growth and chemotaxis in humans and experimental animals, PDGF promotes tissue remodeling and healing of injuries in soft tissue.

3. Liver fibrogenesis a wound healing response

Wound healing in mammalian organs is coordinated with three overlapping but distinct phases through initiation of an

Abbreviations: α-SMA, α-smooth muscle actin; α_2M, α-2-macroglobulin; BDL, bile duct ligation; Con A, concanavalin A; DMN, dimethylnitrosamine; ECM, extracellular matrix; FSAP, factor VII-activating protease; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell(s); IL, interleukin; MFB, myofibroblast(s); MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; PDGFR-α/β, PDGF receptor type α or β; PF, portal fibroblasts; PTEN, phosphatase and tensin homolog; SPARC, secreted protein acidic and rich in cysteine; TIMP, tissue inhibitor of metalloproteinases; tPA, tissue plasminogen activator; UUO, unilateral ureteral obstruction; VEGF, vascular endothelial growth factor.

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inflammatory response followed by extracellular matrix (ECM) deposition and granulation tissue formation and concluded by tissue remodeling and maturation to complete the healing process [4]. To achieve optimal wound healing each of these steps requires tight regulation. The myofibroblasts (MFB), derived from differentiation of resident activated fibroblasts or recruited fibrocytes, proliferate and rapidly synthesize ECM to maintain tissue integrity while the damaged tissue is being repaired and they further express α-smooth muscle actin (α-SMA). If however the ECM synthesis in MFB is not kept in balance, the excessive matrix deposition can lead to fibrosis, scarring, loss of tissue structure, and organ function.

Hepatic fibrosis is a reversible wound-healing response characterized by the accumulation of ECM following liver injury. If the insult is acute or self-limited these changes are transient and liver architecture is restored to its normal composition, but if the injury sustains, chronic inflammation and accumulation of ECM will persist and lead to progressive substitution of liver parenchyma by scar tissue. This process culminates into cirrhosis, the end consequence of progressive fibrosis, which can lead to a poor outcome and high mortality.

The underlying cellular mechanisms involved in hepatic fibrogenesis principally involve the activation of hepatic stellate cells (HSC) and portal fibroblasts (PF), the principal fibrogenic cell types in liver [5,6]. Following injury by any of the causes, HSC and PF undergo activation responses, wherein quiescent cells transit into proliferative MFB that have the potential to produce ECM proteins. Hepatocytes and Kupffer cells are involved in the initiation and perpetuation of HSC and PF activation through the release of a variety of compounds that exert paracrine stimulation of HSC and PF, including reactive oxygen species, cytokines, chemokines and growth factors. Activated HSC respond to these paracrine signals through proliferation, chemotaxis, contractility, release of cytokines and chemokines, loss of retinoids and deposition of ECM molecules [6]. PDGF plays a major role in several of these phenotypic responses, especially in stellate cell proliferation and chemotaxis.

3.1. PDGF is a potent HSC and PF mitogen

Among other polypeptide growth factors potentially involved in chronic wound healing responses, PDGF is the most potent mitogen for cultured HSC. PDGF-B and -D are the most effective in stimulating HSC and PF proliferation and intracellular signaling [7–9], correlation with a predominant expression of PDGFR-β compared to PDGFR-α in activated HSC [10,11]. Increased PDGF expression of cells expressing PDGFR has been demonstrated following both acute and chronic liver tissue damage in experimental and human diseases [12–15], thereby confirming the active role of this growth factor in liver repair and fibrosis. In addition, PDGF is pro-fibrogenic in conditions where inflammation is less evident, such as experimental cholestatic liver injury [16,17,8]. In this setting, PDGF synthesis and release is sustained by proliferating bile duct cells. In liver tissue obtained from patients with chronic liver diseases, expression of PDGF and its receptor subunits appears strictly correlated with the extent of necroinflammation and fibrosis [13].

3.2. Receptor binding of PDGF isoforms

PDGF ligands bind to the protein tyrosine kinase receptors, α- and β-PDGF receptors (Fig. 1). These two receptor isoforms dimerize upon binding to the PDGF dimer leading to three possible receptor combinations, namely -αα, -ββ and -αβ. The extracellular region of the receptor consists of five immunoglobulin-like domains while the intracellular part is a tyrosine kinase domain. PDGF-AA binds only to PDGFR-αα, while PDGF-BB is the only PDGF that can bind all three receptor combinations with high affinity [18]. PDGF-CC specifically interacts with PDGFR-αα and -αβ, but not with -ββ, and thereby resembles PDGF-AB [19,20]. PDGF-DD

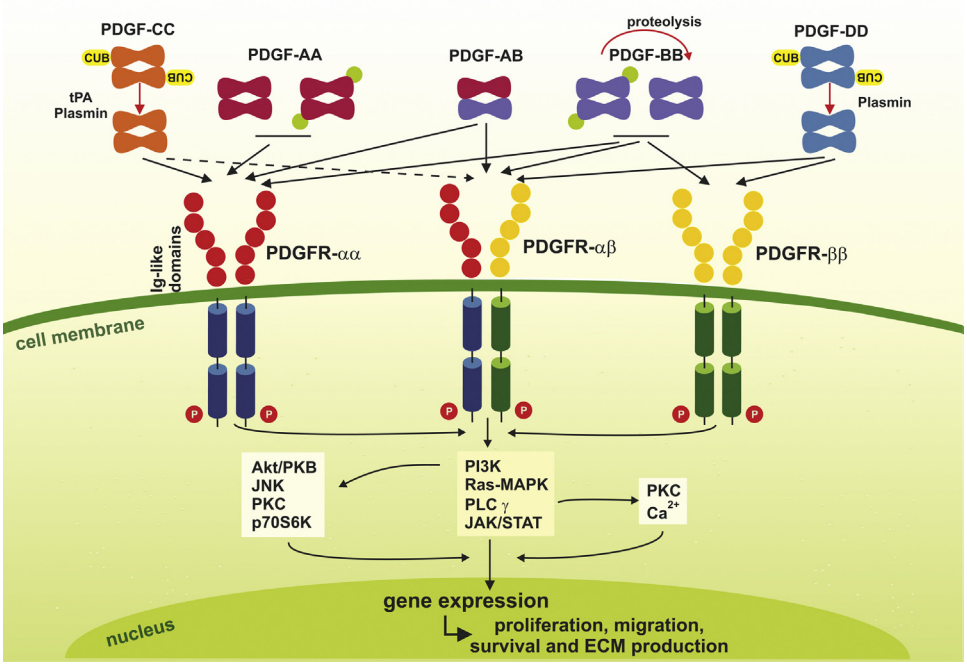

Fig. 1. Simplified scheme of the PDGF system. PDGF-A and -B are secreted as active homo- or heterodimers. Two forms of PDGF-A are produced by alternative splicing of the PDGF-A transcript. PDGF-B possesses a C-terminal basic retention motif that binds to ECM components and can be removed by proteases. PDGF-C and -D are secreted as inactive precursor homodimers which need extracellular cleavage of the CUB domain for receptor binding and activation. Plasmin can activate both PDGF-C and -D, while tissue plasminogen activator (tPA) is specific for PDGF-C. PDGF binding to PDGFR results in autophosphorylation and activation of different signaling pathways like JAK/STAT-, PI3K-, PLC-γ- or MAPK pathways, resulting in cell proliferation, migration, survival and ECM production.