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PDGF receptors in tumor stroma: Biological effects and associations with prognosis and response to treatment

Arne Östman

Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Platelet-derived growth factor (PDGF) ligands and their receptors (PDGFRα and PDGFRβ) regulate mesenchymal cells, such as fibroblasts and pericytes. These cells are important constituents of tumor stroma where they impact on tumor growth, metastasis and drug response.
Studies in model systems have demonstrated ability of the PDGF system to regulate the tumor-stimulatory effects of fibroblasts, as well as their ability to promote cancer cell migration and invasion. Animal studies imply PDGFR-signaling as a regulator of tumor drug uptake.
Emerging correlative analyses of different tumor collections are identifying clinically relevant variations in stromal PDGFR status, and associations between PDGFR status in tumor stroma and survival. These associations could either relate to effects of stromal PDGFR signaling on the natural course of the disease or response to treatment.
The availability of clinically approved PDGFR-inhibitory drugs suggest interesting possibilities for novel clinical studies, performed on selected patient sub-groups, which further exploits tumor stroma-derived PDGFR signaling.

1. Introduction

The family of platelet-derived growth factor (PDGF) ligands and their cognate tyrosine kinase PDGF alpha- and beta-receptors (PDGFRα and PDGFRβ) are important regulators of mesenchymal cells such as fibroblasts, pericytes and smooth muscle cells [3,26].

The core of this review is a summary of studies in experimental systems which collectively imply this growth factor system as regulator of multiple aspects of tumor biology (Section 3). Additionally, a set of correlative analyses of PDGFR status in clinical samples, and the association with prognosis and response to treatment are presented (Section 4). Available and clinically approved drugs targeting PDGFRs are also discussed (Section 5). As a background a brief introduction is provided on the molecular biology of PDGF/PDGFRs and the role of this growth factor system during development (Section 2).

2. Molecular and developmental biology of the PDGF system

2.1. Molecular biology of the PDGF system

The PDGF system is composed of five homo- or heterodimeric ligands (PDGF-AA, -AB, -BB, -CC, -DD) and the two receptor tyrosine kinases PDGFRα and PDGFRβ, which can either homo- or hetero-dimerize [3] (Fig. 1).

Biochemical analyses and phenotype studies in genetically modified mice indicate that PDGF-AA and PDGF-CC predominantly act via PDGFRα, whereas PDGF-BB primarily mediates PDGFβR responses during development [3]. PDGF-DD is considered to be a PDGFRβ-specific ligand, even though its physiological role is less characterized.

PDGF ligands are proteolytically processed before binding to PDGFRs. PDGF-AA and PDGF-BB are activated in the trans-Golgi network by proprotein convertases [55,56]. PDGF-CC and PDGF-DD are processed by extracellular proteases after secretion [11,14,15,65,66]. PDGF activity is thus not only controlled at the gene expression level, but also by bioavailability.

Ligand binding to PDGFRs leads to PDGFR phosphorylation and activation [21]. Phosphorylation of PDGFRs induces recruitment of a large set of signaling molecules to specific phosphor-tyrosine residues, that together initiate a balanced cellular response composed of a combination of positive and regulatory pathways. Details of PDGF-receptor signaling have been covered in other reviews [21,26].

2.2. PDGF signaling in development

PDGF signaling is involved in many processes in embryonic development. Analyses of the phenotypes of knock-out mice have uncovered a set of developmental processes that are controlled by PDGFRs [3,6].

E-mail address: Arne.Ostman@ki.se.

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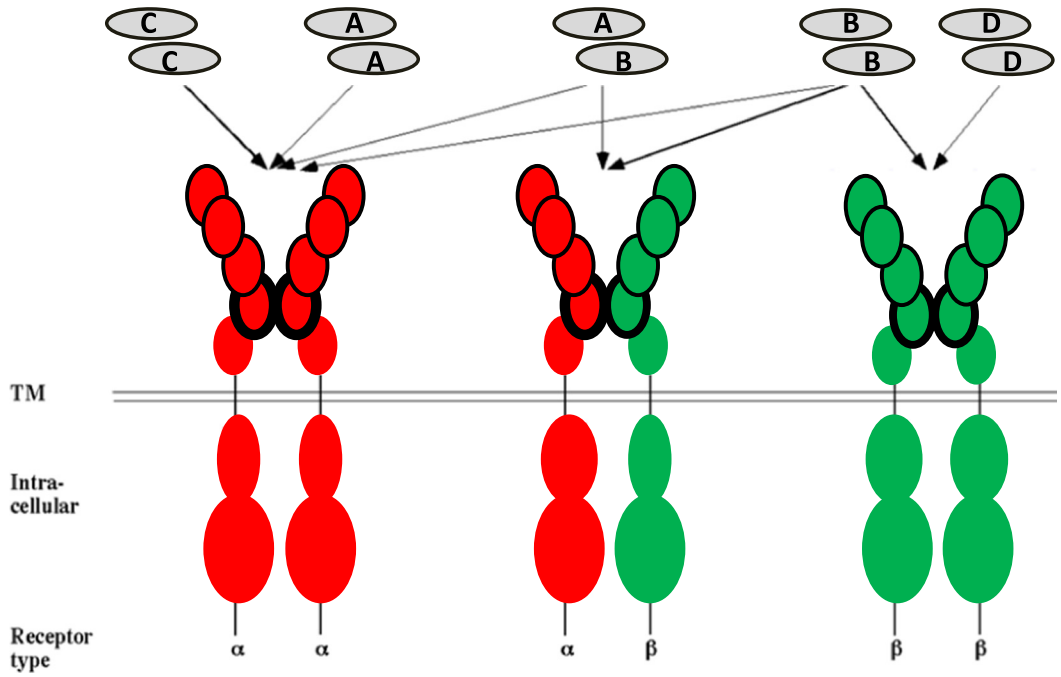

Fig. 1. Schematic illustration of the five PDGF isoforms, the structural organization of the PDGF receptors and ligand-receptor interactions. Thin contour of Ig-domain 1–3 indicates involvement in ligand-binding [35]. The thick contoured 4th Ig-domain has been implied in receptor-receptor interactions [38]. Schematic version of the intracellular domain illustrate the split tyrosine kinase domain.

PDGFRα is critically involved in the development of the non-neuronal neural crest cells and in correct craniofacial anatomy. Functional PDGFRα-positive mesenchymal cells are also required for spermatogenesis and the formation of lung alveoli, intestinal villi and hair follicles. PDGFRβ is essential for proper investment of mural cells in blood vessels. PDGFRβ is also involved in kidney development through its effects on mesangial cells.

A common theme emerging form these analyses is a pattern of paracrine signaling where PDGFRs are expressed by mesenchymal cells and ligands produced by juxtaposed epithelial or endothelial cells.

3. Biological effects of PDGFRs in tumor stroma

Cell and developmental biology studies have identified PDGF receptors as important regulators of fibroblasts and pericytes. Prompted by these findings, a number of experimental studies in tumor models have demonstrated that stromal PDGFRs indeed can regulate multiple aspects of tumor biology including tumor growth, metastasis, immune surveillance as well as efficacy and uptake of drugs.

3.1. Effects of stromal PDGFRs on tumor initiation and growth

3.1.1. Effects of PDGFRs in stromal fibroblasts on tumor growth and initiation

Tumor growth stimulatory effects of stromal PDGFRs were first demonstrated in melanoma models where over-expression of PDGF-BB was shown to stimulate tumor growth in a manner associated with fibroblast recruitment and stimulation of angiogenesis [13]. Similar studies, relying on over-expression of PDGF ligands in receptor-negative cells, demonstrated the ability of PDGF-stimulated to support tumor growth in models of e.g. skin, breast and lung cancer [2,7,53,57,62]. Other studies, instead relying on use of PDGFR-inhibitors, have obtained independent support for the concept of growth-stimulatory effects of PDGFR-stimulated fibroblasts [46].

The potential involvement of PDGFR-expressing fibroblasts in earlier stages of tumor growth is less characterized. However, analyses of breast ductal carcinoma in situ (DCIS) lesions have implied activation of peri-glandular fibroblasts, occurring in association with basement membrane disruptions, as a critical step in the conversion from DCIS to invasive cancer (Strell, unpublished observation). Notably, this DCIS-induced re-programming of the mesenchyme includes a down-regulation of PDGFRα and an up-regulation of PDGFRβ in the affected fibroblasts.

3.1.2. Effects on tumor growth by PDGFRs on perivascular cells

The first study implying PDGFRβ-activation in pericytes as a stimulus for tumor growth used genetically engineered mice expressing a truncated hypomorphic form of PDGF-BB, which earlier had been shown to display reduced pericyte coverage. Tumor xenograft studies established that attenuated PDGFRβ signaling in this tumor model reduced tumor angiogenesis [1]. Follow-up studies demonstrated that over-expression of PDGFRβ ligands in cancer cells enhanced growth of melanoma xenografts in a manner that included increased pericyte coverage, occurring in the absence of changes in vessel density [18]. Studies in other cancer models have instead noted growth inhibitory effects by increased pericyte coverage, suggesting stage- and tumor type-specific effects [23,33].

3.2. Effects of PDGFRs on metastasis

3.2.1. PDGFR expression in stromal fibroblasts and metastasis

An ability of fibroblasts to support metastasis, through paracrine effects on juxtaposed malignant cells, was originally demonstrated by Karnoub et al. [25]. This concept has also been explored regarding PDGF-activated fibroblasts. A colorectal cancer model study demonstrated significantly reduced metastasis in an orthotopic model of colorectal cancer, after treatment the PDGFR-targeting tyrosine kinase inhibitor imatinib [54]. More mechanistic details were presented in analyses which demonstrated that PDGF-BB-activated fibroblasts enhanced colorectal cancer cell migration and invasion [43]. The key components in this pro-metastatic paracrine pathway remain to be conclusively identified, but some candidates have been suggested such as Stanniocalcin 1 [43].

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