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Editorial

Platelet-derived growth factor signaling in human malignancies

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Abstract

Platelet-derived growth factors (PDGFs) and their receptors were identified and purified decades ago. PDGFs are important during normal development and in human cancers. In particular, autocrine PDGF signaling has been implicated in various types of malignancies such as gliomas and leukemia. In contrast, paracrine signaling was found in cancers that originate from epithelial cells, where it may be involved in stromal cell recruitment, metastasis, and epithelial-mesenchymal transition. This editorial briefly discusses autocrine and paracrine PDGF signaling and their roles in human cancers, and introduces a series of review articles in this issue that address the possible roles of PDGFs in various processes involved in different types of cancers.

Key words Platelet-derived growth factor, cancer, tumor progression, drug resistance

Platelet-derived growth factor (PDGF) was first identified and purified from the platelets that stimulate proliferation of fibroblasts, smooth muscle cells, and glial cells[1-3]. Subsequent studies showed that the B chain of PDGF (PDGF-B) was closely related to the oncogene *v-sis* of simian sarcoma virus (SSV) and that autocrine PDGF-B signaling was sufficient for malignant transformation mediated by SSV[4,5]. These findings provided a paradigm describing how dysregulation of normal growth control machinery leads to malignant transformation.

Autocrine PDGF signaling has been implicated in gliomas[6], sarcomas[7], and breast cancers[8]. PDGF confers proliferation, survival, and tissue metastasis advantages to cancer cells and promotes angiogenesis from surrounding vasculatures. In several types of epithelial cancers such as breast cancer, autocrine PDGF signaling contributes to epithelial-mesenchymal transition (EMT) and tumor metastasis[9,10]. Paracrine PDGF signaling may play a role in malignant transformation by recruiting different types of stromal cells to the tumor mass. These stromal cells can then support tumor growth and survival, and promote tumor angiogenesis and metastasis[11,12]. Moreover, PDGF signaling in the tumor stroma contributes to the increased interstitial fluid pressure (IFP) observed in most solid tumors, implying that inhibition of PDGF signaling may improve the efficacy of chemotherapies[11]. This editorial provides an overview of previous studies of PDGF signaling in human cancers and aims to prepare the readers for the review articles published in this issue of the *Chinese Journal of Cancer*.

Activating Mutations of PDGFR and Autocrine PDGF Signaling in Tumor Progression

One of the best examples of how autocrine PDGF signaling contributes to malignancy is from studies of malignant gliomas. Co-expression of PDGF α–receptor (PDGFRα) and PDGF ligands are common in glioblastoma multiforme (GBM)[6,13] and frequently associated with p53 loss[14]. Enforced expression of PDGFRα and PDGF-A confers growth advantages to mouse and human glioma cells in the brain of immunodeficient mice[15]. Activating mutations of PDGFRα have also been described[16,17]. The role of PDGF signaling in normal central nervous system (CNS) development and human gliomas will be discussed in the first review article of this issue[18].

In addition to its role in gliomas, autocrine PDGF

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signaling is also involved in the development of soft tissue sarcomas. Because PDGF is a potent mitogen for various types of mesenchymal cells including fibroblasts and myofibroblasts, several studies using mouse models have been carried out to determine if PDGF overexpression can induce a malignant phenotype in these cells. As expected, a coding region in the *PDGF-B* gene corresponding to the *v-sis* oncogene was capable of inducing fibrosarcomas at the site of inoculation in newborn mice [19]. Subsequent studies showed that PDGFRs and PDGFs are expressed in various types of soft tissue tumors [7,20,21], suggesting a critical role for autocrine PDGF signaling in the development of these tumors.

Autocrine PDGF signaling has also been implicated during EMT in human breast cancer[12]. EMT is a process of switching polarized epithelial cells to a migratory mesenchymal type of cells, which are largely responsible for the progression and metastasis of human cancers that originate from epithelial cells. Studies involving the EMT process in breast cancers are discussed in the second review article in this issue[22]. Components of the PDGF signaling pathway are up-regulated during transforming growth factor-β (TGF-β)–induced EMT in breast cancer [9]. This observation is corroborated by studies demonstrating that autocrine PDGF signaling maintains EMT and promotes metastasis in mouse mammary carcinomas[10]. Interestingly, in gliomas, high TGF-β signaling confers poor prognosis in patients and promotes glioma cell proliferation by activating PDGF-B/PDGFR signaling [23], suggesting an evolutionarily conserved mechanism of regulating PDGF signaling in different types of human cancers.

Constitutive autocrine PDGF signaling can also be achieved by mutational activation of the genes encoding PDGF receptors or ligands. For example, a gene translocation event occurs in dermatofibrosarcoma protuberans (DFSP), a rare form of dermal sarcoma[24] resulting in a fusion gene between collagen 1A1 (*COL1A1*) and *PDGF-B*. The COL1A1/PDGF-B fusion protein over-produces PDGF-B and creates an autocrine loop that transforms NIH3T3 cells *in vitro* and *in vivo*[25,26]. Gene fusions involving PDGFRs have also been found in other human cancers. A subgroup of chronic myeloid leukemia without *BCR-ABL* fusion gene harbors a translocation-mediated fusion between *BCR* gene and *PDGFRA* gene, leading to over-activation of PDGFRα[27]. Gene fusion between Flip-like 1 (*FIP1L1*) and *PDGFRA* is also found in patients with hypereosinophilic (HES) symdrome[28], resulting in a fusion protein with constitutive tyrosine kinase activity and transforming capacity. Consequently, these HES patients often develop acute myeloid leukemia (AML). On the other hand, the *PDGFRB* gene is also a target of gene translocation-mediated activation. Gene fusion events between *PDGFRB* and the transcription factor *TEL/ETV6* as well as several other fusion partners take place in patients with chronic myeloid leukemia [11,12,29]. Additionally, a subset of gastrointestinal stromal tumors (GIST) with wild-type *c-Kit* often harbor intragenic mutations in *PDGFRA*, leading to a ligand-independent activation of the receptor and its downstream signaling pathways[30,31]. Lastly, gene mutations that constitutively activate PDGFRα are found in malignant human gliomas, which are discussed in the following review article of this issue[18].

Paracrine PDGF Signaling in Recruiting Tumor Stroma cells and Resistance to Therapies

PDGF signaling not only plays an essential role in promoting tumor malignancy but also contributes to the processes of tumor stromal recruitment, angiogenesis, and drug resistance [11]. Prevalent PDGFRα expression has been found in the stromal compartments of various types of solid tumors. PDGF ligands expressed by the neoplastic components of the tumor mass stimulate the recruitment of surrounding non-neoplastic stromal cells expressing PDGFR, including endothelial cells, pericytes, and fibroblasts, to the tumor[12]. In mouse fibrosarcomas[32], gliomas[33], and melanomas[34], paracrine PDGF/PDGFRβ signaling enhances pericyte recruitment to the tumor vasculature, thereby promoting tumor cell growth, survival, and vessel stabilization. In gliomas, paracrine PDGF signaling induces neo-angiogenesis by directly stimulating proliferation of PDGFRβ-positive tumor endothelial cells[8,35]. These studies suggest that inhibition of PDGF signaling by pharmacologic intervention can potentially suppress growth and survival of both tumor and tumor-associated stromal and endothelial cells[36,37].

PDGF signaling also supports tumor metastasis to the bone. Using an experimental prostate cancer mouse model, researchers demonstrated that blocking PDGFR thwarted the angiogenesis of tumors that had metastasized to the bone[38]. Additionally, as discussed in the third review article in this issue, PDGFRα signaling induces prostate cancer cell metastasis to the bone [39], further demonstrating that paracrine PDGF signaling enhances tumor growth, angiogenesis, and metastasis.

Another important component of the tumor stroma is fibroblasts[12]. Previous data suggests that recruited tumor fibroblasts are an integral part of various types of solid tumors and influence malignant transformation [40], angiogenesis[41], and tumor cell proliferation[42]. Therefore, blocking PDGF signaling in tumor stroma is effective in suppressing tumor growth in experimental tumor models[12]. Furthermore, the benefit of PDGF inhibition in tumor stroma could extend beyond suppression of tumor growth, angiogenesis, and metastasis. Some solid tumors frequently show high IFP, which restricts fluid convection rate across the capillary walls[12] and results in

low drug uptake and tumor resistance to cytotoxic drug treatments. One of the factors that contributes to high IFP within the tumor mass is PDGFRβ [43]. Indeed, inhibition of PDGFR signaling by imatinib reduces tumor IFP and enhances the drug uptake into tumor cells[44,45].

Summary

Autocrine and paracrine PDGF signaling contribute to several hallmarks of human cancers, including self-sufficient tumor growth, angiogenesis, stromal recruitment, and tumor invasion and metastasis to distant organs. Although inhibition of PDGF signaling holds promises for treatments of human cancers with activated PDGF signaling, carefully designed pre-clinical/clinical trials are necessary for the success of targeted therapies against components of this signaling pathway.

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