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Review Article

PDGF signaling in cancer progression

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Abstract: Platelet-derived growth factor (PDGF) is a pro-angiogenic factor that was isolated from human platelets. PDGF family is comprised of four different polypeptide chains encoded by different genes, which have been identified: PDGF-A, PDGF-B, and recently discovered PDGF-C and PDGF-D. PDGF is a variety of strong mesenchymal cell mitogenic agents and growth chemokines. PDGF, acting as a vascular endothelial growth factor, is closely associated with tumor development. PDGF signaling pathway has been extensively studied and well characterized because PDGF can regulate many cellular processes, including cell proliferation, migration, invasion, angiogenesis and metastasis. According to the available data, PDGF plays an important role in the development of breast cancer, stomach cancer, gastric cancer, prostate cancer, lung cancer, colon cancer, and other cancers. Effects of PDGF on cancer are complex and diverse, and further analysis is needed to confirm the predictive and therapeutic values of PDGF and its receptor. This article reviews the recent progress of PDGF in tumor progression.

Keywords: Platelet-derived growth factor, signal pathway, proliferation, migration, invasion, angiogenesis, metastasis, tumor progression

Introduction

Platelet-derived growth factor (PDGF) is a pro-angiogenic factor that was isolated from human platelets [1-3]. PDGFs are a variety of strong mesenchymal cell mitogenic agents and growth chemokines; they are also important modifiers for the normal and pathological vascular development [4-6]. PDGF, acting as vascular endothelial growth factor, plays a pivotal role in the development and progression of human malignancies. The latest findings show that PDGFs regulate tumor growth and metastasis by targeting malignant cells, vascular cells, and stromal cells [7-10].

PDGF and cancer cells

Cancer cell proliferation

PDGF stimulates cancer cell proliferation through autocrine and paracrine manners, since some cancer cells express the PDGF receptor and some do not. For example, Ustach *et al.* [11, 12] demonstrated that LNCaP cells auto-activate latent PDGFD into the active PDGF domain, which can induce the phosphorylation of β-PDGF receptor and stimulate LNCaP cell proliferation in an autocrine manner. Additionally, LNCaP-PDGFD-conditioned medium induces migration of the prostate fibroblast cell line 1532-FTX, indicating LNCaP-processed PDGFD acts in a paracrine manner as well. The PDGF signaling pathway combines with a variety of substrate protein signaling molecules, including SRC tyrosine kinase subfamily, phospholipase C (PLC-γ), phosphatidylinositol 3-kinase (PI3-K), GTPase activation protein (RAS-gap), growth factor binding protein (Grb2), tyrosine specific phosphatase (SYP), Src homology and cross-linked protein (SHC) and adaptation (Crk) protein, and non-receptor tyrosine kinase family (SRC) and so on, and forms a variety of signaling pathways, such as RAS-MAPK pathway, PI3-K pathway, the PLC pathway, and STAT pathway [13]. These signal molecules mediate cytoplasmic complex signaling networks, and play a role in cell membrane serine threonine residues, resulting in a variety of gene regulation and protein phosphorylation, thus promoting cancer cell growth and division

[14]. For example, PDGF has been proved to promote the proliferation of human meningiomas and mesothelioma cell through PI3-K pathway [15, 16]. Lu Y. demonstrated that hypoxia-induced PDGF-BB secretion by HCC cells stimulates HSCs to accumulate and proliferate in the tumor stroma [17]. Whereas angiogenesis inhibitor sorafenib downregulates the expression of PDGF-BB and TGF-β1 in the HSCs supernatant, and restrains the viability of the HSCs, resulting in suppressed proliferation and invasion in HepG2 cells [18]. Meanwhile, Platelet-derived growth factor receptor (PDGFR) signaling participates in different processes in solid tumors, including autocrine stimulation of tumor cell growth, recruitment of tumor stroma fibroblasts, and stimulation of tumor angiogenesis [19]. Moreover, malignant melanoma upregulates hyaluronan synthesis in fibroblasts by releasing PDGF-AA and PDGF-CC, which in turn stimulates the malignant melanoma cell proliferation in a paracrine manner [20]. PDGF also increases proliferation of Luminal breast cancer cells in the absence of estrogens [21]. In conclusion, PDGF induces proliferation and migration of tumor cells and inhibits apoptosis [21].

Cancer cells metastasis

Cancer cell metastasis begins with detachment of metastatic cells from the primary tumor, traveling of the cells to different sites through blood/lymphatic vessels, settlement and growth of the cells at a distal site [22]. During the process, metastatic cells go through detachment, migration, invasion, and adhesion [22]. For tumor metastasis, cardiovascular generation is required, which provides oxygen and nutrients for tumor growth and metastasis. PDGF can promote connective tissue to produce extracellular matrix proteins, which directly or indirectly induces tumor angiogenesis, significantly affecting tumor metastasis. PDGF-D-overexpressing tumors express higher levels of MMP-9 and PDGFD to induce renal cancer cells proliferation and migration, thus providing a molecular mechanism for the higher incidence of lung metastasis and pericyte coverage observed in PDGF-D-overexpressing tumors [23, 24]. PDGFD plays an important role in breast tumor aggressiveness and this process is mechanistically linked with the activation of Notch and NF-κB signaling [25]. A growing number of researchers believe that cancer growth, metastasis, and invasion depend not only on the tumor cells themselves, but also on the growth of tumor microenvironment, which supports cancer behavior. Studies have shown that PDGF-C in breast cancer activates the receptor by binding to the receptor, and activation of the receptor leads to tyrosine kinase pathway activation, which mediates fibroblast activation and is involved in the secretion of a variety of cytokines and the formation of cellular microenvironment [26]. Activated fibroblasts, known as cancer-associated fibroblasts (CAFs), promote the formation of tumor metastasis and directional vessel by secreting SDF-1/CXCR4. CAFs also can promote tumor growth and metastasis by secreting other factors such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), basic fibroblast growth factor (b FGF), and insulin-like growth factor (IGF). PDGF-DD secreted by gastric cancer-derived mesenchymal stem cells (GC-MSCs) is capable of promoting gastric cancer cell proliferation and migration *in vitro* and *in vivo*. Jieqiong Liu *et al.* [27] reported that overexpression of PDGF-D promoted tumor growth and lymph node metastasis through increased proliferation, decreased apoptosis, and induction of CXCR4 expression [28]. A study reports a mechanism of the interaction between perivascular cells and tumor-associated macrophages (TAMs) that promotes metastasis through the IL-33-ST2-dependent pathway in xenograft mouse models of cancer. While PDGF-BB upregulates IL-33 gene though stimulating the activation of pericytes SOX7 transcription factor. Gain- and loss-of-function experiments validated that IL-33 promotes metastasis through recruitment of TAMs. Pharmacological inhibition of the IL-33-ST2 signaling by a soluble ST2 significantly inhibits TAMs and metastasis [29]. Genetic deletion of host IL-33 in mice blocks PDGF-BB-induced TAM recruitment and metastasis [29]. Yasuhiko Kitadai discovered that expression and phosphorylation of PDGF-Rb by stromal cells and pericytes was higher in orthotopic tumors than in ectopic tumors and, therefore, was associated with the metastatic potential of the neoplasms [30]. PDGFs may also have a role in determining the preferential organ of metastatization. Indeed, PDGFs released by the tumor cells are potent chemoattractants and mitogens for host mesenchymal cells and could mediate the interac-

tions between cancer cells and the host environment of the preferred metastatic site [31]. PDGF plays an important role in epithelial mesenchymal transition. For example, it has been recently demonstrated that autocrine PDGF signaling maintains EMT and promotes metastatization in mouse mammary carcinoma and tumor dissemination [32]. PDGF promotes EMT via activation of STAT3 or PI3K pathway and PDGF-D over-expression was positively correlated with the expression of mesenchymal markers (vimentin and ZEB-2) in concomitant with expression of epithelial marker E-cadherin [25, 33, 34]. As is well known, epithelial-mesenchymal transition (EMT) enables the escape of epithelial cells from the rigid structural constraints of the tissue architecture to a phenotype more amenable to cell migration and, therefore, invasion and metastasis. All in all, PDGF affects tumor metastasis in many ways.

Chemotherapy resistance of cancer cells

Previous literature reported that PDGF is closely associated with chemotherapy resistance of cancer cells. A line of evidence demonstrates that chemo-resistance is associated with the acquisition of epithelial-mesenchymal transition (EMT) of cancer cells, and platelet-derived growth factor-D (PDGF-D) signaling pathway plays a critical role in the acquisition of EMT phenotype of GR HCC cells [35]. Rui Wang *et al.* demonstrates that overexpression of PDGF-D in gemcitabine-resistant (GR) HCC cells markedly inhibited miR-106a expression and subsequently upregulated Twist1 expression, whereas down-regulation of Twist1 reverses EMT to MET (mesenchymal-epithelial transition) in GR cells [36]. Some studies show that PDGF-C can promote tumor angiogenesis and tumor cell growth by upregulating VEGF level and activating VEGF independent angiogenesis pathway, which can produce VEGF-independent drug resistance [37]. VEGF inhibitors reduce the expression of VEGF and VEGFR, which can only inhibit VEGF-dependent angiogenic signal transduction pathways, while VEGF independent pathway is not suppressed, therefore anti-VEGF therapy can produce resistance. PDGFC plays an important role in drug resistance. It can promote angiogenesis through vascular cell pathway, inflammatory cell pathway, extracellular matrix pathway, but does not depend on VEGF. Exiting evidence demonstrates that the expression of platelet derived growth factor B can promote the cell recruitment in peripheral blood vessel wall and increase the stability of the structure [38]. The recruitment of peripheral blood cells increased blood vessel coverage which may lead to the resistance to anti-angiogenic drugs. In the study of Zhao Z *et al.*, PDGFD is one of the key candidate genes which may influence chemo sensitivity of glioblastoma (GBM) to Semustine (Me-CCNU) [39].

PDGF and cancer stroma or cancer microenvironment

PDGF and extracellular matrix (ECM)

The occurrence, development, invasion and metastasis of malignant tumors are often accompanied by changes in the expression of extracellular matrix (ECM) and their cell surface receptors [40]. The extracellular matrix can provide the raw materials for tumor metastasis, and the transformation of extracellular matrix components [41]. The extracellular matrix plays an important role in tissue homeostasis, therefore, it is crucial in tumorigenesis, development and metastasis [42]. PDGF has a close relationship with extracellular matrix.

Growth factors and the extracellular matrix have been shown to play important developmental roles in many embryonic systems. In the study of PDGF-AA and -BB homodimer isoforms, M, Pekny found that the paracrine activity of PDGF-AA and PDGF-BB homodimers are significantly different, and the local effect of PDGF-BB on tumor growth has greatly increased in the tumor when compared with PDGF-AA, which is very likely associated to the components of the extracellular matrix [43]. According to the latest research results of Wright JH *et al.*, receptors of PDGF-cc are localized on hepatic stellate cells (HSCS) that transform into myofibroblast-like cells that deposit in extracellular matrix (ECM) and promote the growth and transformation of the growth factor [44]. In different stages of tumor growth, the expression of extracellular matrix is enhanced and its distribution is different [45]. Extracellular matrix has a value in predicting the biological behavior of the tumor.

PDGF and angiogenesis

PDGF regulates tumor growth in tumor development, and a variety of environmental factors that can induce cell expression of PDGF stimu-

lates tumor growth. *In vivo* experiments confirmed that PDGF-mediated tumor angiogenesis provides nourishment for tumor growth [46]. At the same time, tumor blood vessels also provide a convenient route for the tumor cells to transfer tumor development-related signals, thus angiogenesis is a hallmark of cancer. Angiogenesis is one of the signs of advanced cancer, promoting the invasion and metastasis of cancer. Lu Y *et al.* found that PDGF-BB expression on HepG2 cells increased significantly under hypoxia. They show that hypoxia-induced liver cancer cell PDGF-BB stimulates the accumulation of HSC substance in the tumor stroma, enhances the expression of VEGF-A in hematopoietic stem cells, and promote angiogenesis [47]. Existing evidence show that PDGF promote angiogenesis primarily by aggregating pericytes which is a kind of mural cells for microcirculation. Pericytes and endothelial cells have a specific contact, and pericytes and endothelial cells have specific contacts at the vascular basement membrane [48, 49]. Many evidences have showed that PDGF/PDGFR-β, involve in the regulation of pericytes recruitment, the mechanisms governing pericytes migration and regulating angiogenesis, especially in cancers [50]. PDGF-D is the most recently discovered member of the PDGF family, regulating systemic arterial blood pressure, and suggests a role in maintaining vascular homeostasis [51]. Sennino found that new DNA aptamer AX102 is capable of specifically inhibiting PDGF-BB signal, resulting in tumor vascular pericytes loss and degradation of the tumor vasculature [52]. The impact of PDGF on pericytes is great, and PDGFR kinase inhibitors can reduce the accumulation of pericytes, which leads to reduced pericyte coverage and tumor blood vessel growth [53].

PDGF and stromal cells

Macrophages in the tumor microenvironment are key regulators of the immune response. The type of tumor associated macrophages was increasingly reported, and the research on the role of macrophages and PDGF are constantly advanced. Macrophage-derived PDGF can develop a series of factors to promote growth and development of tumor blood vessels. Dain Son have reported that pdgf-c-mediated signal pathway is involved in macrophage's anti-apoptotic effects, suggesting that tumor cells may promote enhanced malignancy via increasing tumor-associated macrophage survival [53]. Meanwhile, the anti-apoptotic role for macrophage signaling pathways mediated by PDGF-C was analyzed, and the researchers found that malignant human breast cancer cell line MDA-MB-231 produces high amount of PDGF-C; on the contrary, PDGF-C was not detected in benign MCF-7 cells. The conclusion is that the tumor cell-derived PDGF-C enhances the survival of tumor-associated macrophages, and promotes malignancy [54]. PDGF can be seen during the development of macrophages, which has a role in tumor growth.

Mesenchymal stem cells in bone marrow are a class of non-hematopoietic stem cells, which support and regulate hematopoiesis *in vivo*. Therefore, they have an effect on the occurrence and development of tumors. Recent studies show that PDGF-AA requires BMPRIA and PDGFRα receptor to activate the mesenchymal stem cells (MSC) bmp-smad1/5/8 channel [55]. Mesenchymal stem cells can be co-primary tumor lesion with other types of cells. A study showed that the presence of bone marrow mesenchymal stem cells/pericytes coverage of the target organ vasculature is necessary for effective melanoma metastasis to the bone marrow and liver [56]. The more interesting finding was that among patients with advanced breast cancer, bone marrow mesenchymal stem cells can change the migration of MCF-7 and MDA-MB231 cells. The levels of PDGF-AB, ICAM-1, and VCAM-1 in patient's bone marrow were significantly higher than those in healthy volunteers, suggesting that they may play a role in cancer cell extravasation, bone resorption, and cancer cell proliferation. This study shows that bone marrow mesenchymal stem cells may have similar function as PDGF-AB [57].

The relationship between platelet-derived growth factor and immune cells in the tumor is unclear. Agrawal *et al.* demonstrated that human PDGF inhibited dendritic cell (DCs) maturation and induced IL-10 secretion. They also found that PDGF induced the expression of C-type lectin-like receptor member 2 (CLEC-2) receptor on DCs, leading to the induction of regulatory T cells [58].

Neutrophils have dual role in tumor: they can inhibit the cancer development; on the other hand, they promote tumor growth and invasion

[59]. Thus, it is necessary to investigate the relationship between neutrophils and PDGF. Platelets release Platelet-derived growth factor (PDGF) and attract inflammatory cells such as monocytes and neutrophils. MG Houghton *et al.* determined the effect of neutrophil elastase on tumor progression. Their results show that neutrophil elastase degradation of insulin receptor substrate 1 (IRS-1) can increase the interaction between phosphatidylinositol 3-kinase (PI3K) and platelet-derived growth factor interaction receptor (PDGFR), thus distorting the PI3K-axis toward tumor cell proliferation [60].

MDSC can suppress innate immune cell-NK cell and NKT cell-mediated tumor cytotoxicity, as well as $CD4^+$ $CD8^+$ T cell-mediated adaptive immunity, and will gradually become resistant to anti-tumor immune responses [61]. In the study of breast cancer in metastatic sites, Kaplan *et al.* found that VEGFR and bone marrow-derived haematopoietic progenitor cells are among the first to arrive at the pre-metastatic sites before the arrival of breast cancer cells to promote the formation of microenvironment called pre-metastatic niche (pre-metastatic niche) for tumor cell growth [62]. MDSC derived VEGF cytokine directly contribute to the formation of the pre-shift niche [63]. Research reports that MDSC, VEGF, and PDGF have similar functions, and they may all promote the formation of pre-metastatic niche.

Tumor associated CAF is an important participant in tumor proliferation. Desmoplastic malignant tumor such as cholangiocarcinoma is rich in tumor-associated fibroblasts [64]. CAF, as primary or metastatic tumor stroma, is an important component in tumor formation and progression [65]. Chu TY's team studied the impact of the crosstalk between cancer cells and cancer associated fibroblasts (CAFs) on the proliferation and survival of irradiated cancer cells, and found that CAF-cancer cell crosstalk has protective effect on radiated cancer cells. They identified various growth factors, including PDGF at CAF-cancer cell crosstalk which may affect the radiation protective effects of cancer cells [66]. The latest results show that PDGF-activated CAF upregulates puma, which causes the proapoptotic change of Bak, resulting in enhanced cell apoptosis *in vivo* [26]. PDGF is an important protumor factor that causes fibroblast transformation. Activation of Src and ERK can activate collagen integrin signaling pathway and improve the production of PDGF-A, a key regulator for fibroblast recruitment [67].

Clinical application of PDGF detection in cancer

Diagnosis

As a tumor growth factor, PDGF stimulates tumor growth, invasion, and metastasis and is also involved in chemotherapy resistance. A study has shown that cancer can cause increased serum PDGF content [68]. Cancer induced increase in the content of serum PDGF may be associated with a variety of factors: tumor cells release bone marrow stimulation substance which functions as thrombopoietin to stimulate the pluripotent stem cells, thus contributing to the increased platelet production following the increase of serum PDGF [68]. Their data also suggest that PDGF content in the serum of liver cancer patients was significantly higher than that in normal people, and benign liver disease patients' serum PDGF levels are slightly higher than that in the normal serum, but the difference did not reach statistical significance [68]. Therefore, the content of serum PDGF is not only an ideal marker for HCC diagnosis in liver cancer, but also a reference that is valuable in differential diagnosis among liver benign lesions such as liver cirrhosis, chronic hepatitis, and liver hemangioma [68]. Many studies have shown that cancer cells highly express PDGF. For example, Lei Xu *et al.* revealed that PDGF-D was homogenously strongly expressed in the tumor tissues of all histologic types, Jieqiong Liu *et al.* revealed that human breast cancers express high levels of PDGF-D, and Miguel Torres-Martin *et al.* identified that PDGFD was upregulated in meningiomas and schwannomas when compared with their respective healthy tissues [23, 30, 69]. Moreover, a study confirmed that the serum VEGF and PDGF levels in malignant ovarian tumors (MOT) increased compared with those in benign ovarian tumor (BOT) and the normal control group; serum VEGF and PDGF levels in BOT group were similar to those in the normal control group; and there was no significant difference between VEGF and PDGF. Thus, the serum VEGF and PDGF levels are associated with ovarian tumor malignant behavior and have certain value in the diagnosis of ovarian

tumors [70]. Overall, these results suggest that increased serum VEGF and PDGF levels may be associated with the formation of cancer. However, Zheng Li *et al.* found that the serum PDGF content slightly decreased in several cancers [68]. In addition, D Matei *et al.* claimed that measurable levels of PDGF were of no predictive value for the diagnosis of ovarian malignancy [71]. It can be seen that the application of PDGF in the diagnosis of cancer is still controversial and need to be further explored.

Monitoring

PDGF plays an important role in tumor development. Monitoring the expression and sites of PDGF may monitor the tumor development. Studies have shown that there are differences in the expression of PDGF in cancers in different stages. For example, the levels of VEGF and PDGF in low differentiated tumors (G3) and late stage tumors (FIGO stage III and IV) were higher than those in highly differentiated tumors (G1, G2) and early stage tumors (FIGO I + II) in malignant ovarian tumors [70]. Moreover, VEGFA contributes to lung cancer progression by significantly induced the secretion of a variety of angiogenic factors, such as PDGFB, which might offer potential for monitor and therapeutic intervention [72]. NRASQ61 mutations are associated with hypomethylation of PDGFD, which consequently increases the gene expression of PDGFD and subsequently dysregulates downstream regulatory cascades. Hence, we can monitor the process of NRASQ61 mutations by monitoring the PDGF gene and downstream regulation genes [73]. In addition, a study has proved that in the liver metastasis of gastric cancer, serum PDGF levels were markedly increased to a level that was significantly higher than that of patients with primary gastric cancer and normal people, indicating that serum PDGF has a value in determining and monitoring the course of gastric cancer. In gastric cancer patients with serum PDGF levels increased significantly, the possibility of liver metastasis should be considered [70]. Yuan Wang *et al.* demonstrated that PDGF-D was commonly over-expressed in endometrial cancer, which was associated with late stage deep myometrium invasion and lymphoma vascular space invasion [74]. Both *in vitro* and *in vivo* experiments showed that PDGF-D could promote tumor growth and invasion through up-regulating MMP2/9 and inducing EMT. Compared with that in matched normal endometrial cases, PDGF-D was up-regulated in endometrial cancer patients. Expression of PDGF-D protein, found in 78% of the cases, was associated with nonendometrioid histologic type (P=0.028), FIGO stage III/IV (P=0.039), >50% solid tumor growth (P=0.048), pelvic LN metastasis (P=0.035), and ER and PR negativity (P=0.04 and 0.002, respectively) [75]. PDGF-D expression was also significantly associated with the expression of VEGF-A (P=0.021) [75]. Collectively, these results suggest that increased serum VEGF and PDGF levels may be associated with the formation and malignant behavior of tumor and the serum VEGF and PDGF levels before the operation of ovarian tumor may have certain diagnostic value.

Prognosis prediction

Prognosis (tumor size, lymph node status, and histological grading, etc.) and treatment-predictive factors are routinely used for the classification and guidance of subsequent treatment decisions in tumor. Staging of the cancer, determined by tumor-node-metastasis (TNM) staging system, can be divided into prognostic subgroups, and several markers in tumor cells are useful to predict the prognosis of the patients. Previous studies have pointed out that the PDGF receptor can be used as a prognostic and predictive marker of tumor. For example, Donnem *et al.* studied the prognostic value of PDGF in NSCLC tumor cells and stromal cells (including endothelial cells, immune cells, fibroblasts, etc.) and found that high tumor cell PDGF-B and PDGFR-β expression were independent negative prognostic factors for disease-specific survival, whereas in stromal cells high PDGF-A expression had an independent positive survival impact, which may due to the fact that high levels of PDGF-A in interstitial cells can activate adaptive anti-tumor immunity [76, 77]. High expression of PDGFRβ in stroma of pancreatic adenocarcinoma correlates with a worse prognosis [78]. Moreover, PDGF-β receptor expression in tumor stroma was correlated with HER-2 positivity, and the expression loss of PDGF-β receptor in tumor stroma was correlated with TNBC (triple negative breast cancer) [79]. Thus, stromal PDGF-β receptor expression significantly correlates with less favorable clinicopathological parameters and shorter survival in breast cancer [80].

Because tumor metastasis depends on the tumor microenvironment, which may be related to activation and differentiation of fibroblasts, pericytes recruitment, and extracellular matrix (ECM); Whereas PDGF induces fibroblast differentiation, pericyte recruitment, and ECM formation, thus PDGF can act as a reliable tumor prognostic marker [81]. It is demonstrated that the PDGF signature captures biological properties that are not captured by other stroma-derived predictors, therefore is of prognostic significance [82]. Sigve Andersen *et al.* proved that PDGF expression in tumor emerged as an independent poor prognosticator for disease-specific survival in non-small cell lung cancer, and Kawai T *et al.* also reported that immunohistochemistry for PDGF B-chain may predict the outcome for lung carcinoma patients [83, 84]. PDGF-D expression proved to be an independent prognostic factor in addition to histologic grade and FIGO stage, and patients with high expression levels of PDGF-D had a significantly poorer overall survival rate compared with patients with no expression [85]. Continued characterization of PDGFR expression in human tumors should present opportunities for improved accuracy in prognosis and also allow novel biomarker-based clinical studies exploring the efficacy of PDGFR-directed tumor therapies.

Therapy

The fact that PDGF and/or PDGF receptors are overexpressed or mutated in different tumors makes it desirable to investigate whether PDGF or PDGF receptor antagonists can be used to treat patients with these diseases. Many studies have proved that PDGF ligands are expressed by cancer cells, whereas PDGF-Rs are expressed mainly by stromal cells. Directed therapy targets both PDGF and stromal PDGFR, which can be activated so as to be closely associated with recruitment and activation of fibroblasts and significant deposition of extracellular matrix (ECM) [80, 86]. A large number of studies have shown PDGF targeted therapy is effective in a variety of tumors, including thyroid nodules, recurrent goiter, pancreatic adenocarcinoma., leukemia, cholangiocarcinoma, lymphoma, gastric cancer, colon cancer, and prostate cancer etc. [78, 87-92]. Several potent PDGF receptor kinase inhibitors have been developed, including imatinib, sunitinib, sorafenib, pazopanib, and nilotinib, etc., which often get better results by combined use. For example, nilotinib and everolimus in combination reduced both the growth rate and stromal reaction in gastric cancer [91]. Also, monoclonal antibodies directed against PDGF or PDGFR have gradually been used to test whether they can delay and improve tumor development. For instance, IMC-3G3 specifically binds to human PDGF receptor α (PDGFRα) with high affinity and blocks PDGF ligand binding and PDGFRα activation; IMC-2C5 is directed against PDGFRβ from an antibody phage display library [93, 94]. However, a study shows that the resistance mechanisms limit the success of such treatments, and anti-PDGF receptor therapy is most likely to achieve lasting remission when combined with other signal transduction inhibitors, chemotherapy, or other treatments [11]. Marya F. *et al.* revealed that treatment of PDGF-BB-overexpressing tumors with imatinib mesylate (PDGFR inhibitor) resulted in increased growth and decreased total pericyte content compared with those in untreated PDGF-BB-overexpressing tumors [95]. Thus, Single-agent therapy targeting PDGF receptor must be used with caution when PDGFR is not the target on tumor cell itself. Further developments rely on clinical studies where systematic analyses of target status in malignant cells and in cells of the tumor stroma are included. It remains to be studied that how to further reduce the side effects of combination therapy with selective PDGFR inhibitors.

PDGF signaling has a key role in cancer progression, stimulating tumor cell proliferation, invasion, migration, and chemotherapy resistance. Through autocrine or paracrine secretion, PDGF binds to its receptor to activate series of protein signals to stimulate the growth of cancer cells, inhibit apoptosis, and directly or indirectly support cancer metastasis by acting on tumor cells or in tumor microenvironment. By promoting epithelial mesenchymal transition and VEGF dependent or independent angiogenesis, and recruitment of peripheral blood cells, PDGF signaling is involved in the chemotherapy resistance of cancers. A large number of studies have shown that due to the close relationship between PDGF and tumor progression, PDGF has certain clinical value in the diagnosis and monitoring of cancers. In addition, usually PDGF highly expression is typically associated with a poor prognosis. Finally, many researchers have studied the therapeutic

effects of PDGF signaling-targeting agents. However, effects of PDGF on cancer are complex and diverse, and further analysis is needed to confirm the predictive and therapeutic values of PDGF and its receptor. In addition, how to target PDGF signaling pathway to more effectively control the occurrence and development of cancer remains to be explored.

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Disclosure of conflict of interest

None.

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