REVIEW ARTICLE

Research progress on the regulation of tumorigenesis and development by the PDGF/PDGFR signaling pathway

Jinfeng Zhang[1, 2, †], Hong Xia[1, 3, †], Meng Xia[1, 4, †], Huixing Jiang[2], Shuqin Wang[3], Linhong Meng[3], Yong Zhang[5, *]

[1]Graduate School of Jinzhou Medical University, Jinzhou, Liaoning, China. [2]Department of Endocrinology, Jingmen Hospital of Traditional Chinese Medicine, Jingmen, Hubei, China. [3]Department of Medicine, Jingchu University of Science and Technology, Jingmen, Hubei, China. [4]Emergency Department of Chongqing Emergency Medical Center, Chongqing, China. [5]Department of Clinical Laboratory, Huangshi No.5 Hospital, Huangshi, Hubei, China.

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The platelet-derived growth factor (PDGF)/PDGF receptor (PDGFR) signaling axis is a master regulator of oncogenesis. By driving hallmark malignant behaviors including uncontrolled cell proliferation, invasion, and angiogenesis, it critically fuels tumor progression and metastasis. As a clinically relevant biomarker, its aberrant expression is linked to aggressive phenotypes and poor prognosis in solid tumors such as breast cancer, prostate cancer, and cholangiocarcinoma. Furthermore, the abnormal activation of the PDGF/PDGFR signaling is a core mechanism underlying the acquired resistance of tumor cells to targeted therapies such as cyclin-dependent kinase (CDK) 4/6 and fibroblast growth factor receptor (FGFR) inhibitors and traditional chemotherapy. It drives cellular plasticity and survival adaptation. Therefore, targeting this signaling axis has become a cutting-edge area in oncological research. Through the development of novel inhibitors, combination immunotherapies, or strategies to regulate the tumor microenvironment (TME), there is a hope to overcome treatment failure and improve patient prognosis. This review aimed to integrate the latest pre-clinical and clinical research evidence, systematically elaborate on the impact of the PDGF/PDGFR signaling axis on tumorigenesis and development, as well as its clinical value as a biomarker and therapeutic target, providing a new intervention paradigm for precision oncology.

Keywords: PDGF; PDGFR; cancer; targeted therapy; signaling pathway.

[*]**Corresponding author:** Yong Zhang, Department of Clinical Laboratory, Huangshi No.5 Hospital, Huangshi, Hubei 435004, China. Email: 1789087103@qq.com.

[†]These authors contributed equally to this work.

Introduction

Platelet-derived growth factor (PDGF), an autocrine granule component initially discovered in platelets, has attracted much attention since its discovery due to its indispensable role in vascular development [1]. PDGF exerts pleiotropic effects across multicellular systems, modulating stromal components, vascular compartments, neural interfaces, immunomodulatory effectors, and specialized lineages. These cells utilize PDGF to perform their

complex biological tasks through precise autocrine and paracrine mechanisms [2]. Contemporary research advancements have progressively revealed the intricate regulatory mechanisms of PDGF and cellular PDGF receptor (PDGFR) in physiological development and this expanding knowledge base has concurrently driven scientific attention toward their therapeutic applications in oncology [3].

A large amount of evidence shows that the PDGF/PDGFR signal transduction axis is a core regulatory mechanism in the process of cancer occurrence and development, and its role runs through all key stages from tumor initiation, progression to metastasis, showing a unique "baton" function. The PDGF/PDGFR axis critically enables tumorigenic progression in initial phases by driving aberrant cellular multiplication and maturation patterns [4]. As tumor progress advances, this signaling mechanism amplifies malignant cells' capacity to migrate and invade neighboring structures, thereby enabling tissue barrier penetration and regional spread [5, 6]. Of particular note is the critical function of PDGFR signaling pathways in facilitating blood vessel development during cancer progression. The dual action of enhancing endothelial activity and constructing vascular networks establishes a tumor-sustaining microenvironment, directly correlating with disease severity escalation [7]. Lymphangiogenesis is additionally mediated through this signaling mechanism, which not only opens a "highway" for tumor cells to metastasize to distant sites but also greatly promotes the systemic spread of the tumor, increasing the difficulty and complexity of treatment [8]. More seriously, excessive PDGFR signaling activity undermines vascular endothelial growth factor (VEGF) therapy effectiveness while simultaneously inducing cross-resistance to pharmacological interventions [9, 10]. For example, in breast cancer, the activation of PDGF-BB signaling can mediate resistance to cyclin-dependent kinase (CDK) 4/6 inhibitors [11], and the upregulation of PDGFR is associated with reduced treatment durability of fibroblast growth factor receptor (FGFR) inhibitors [12]. This discovery highlights the PDGF/PDGFR axis as both a persistent therapeutic challenge in oncology and a pivotal regulator in tumor pathobiology. In addition, clinical studies have shown that, in many types of cancers, the abnormal activation of the PDGF/PDGFR signaling pathway is often closely related to the poor prognosis of patients and has become an important indicator for predicting tumor prognosis [13].

Capitalizing on this signaling cascade's essential role in malignant transformation and advancement, PDGF/PDGFR-directed therapies now present a triple-pronged approach, which includes bypassing drug resistance mechanisms, potentiating cytotoxic therapies, and elevating survival trajectories. By precisely targeting and inhibiting the activity of the PDGF/PDGFR signal transduction axis, not only can the growth and spread of tumors be effectively blocked, but also the resistance of tumors to traditional therapies may be reversed, bringing more precise and effective treatment options for cancer patients. By synthesizing current knowledge of PDGFR-mediated regulatory networks and their associations with malignant phenotypes, this review discussed emerging intervention frameworks that might inform refinements in targeted cancer therapy.

Structure and function of PDGF/PDGFR and its signaling pathways

1. Structure and function of PDGF and its receptor

Structurally categorized within the receptor tyrosine kinase (RTK) type III superfamily, PDGFRs exist in two functionally distinct forms, PDGFR-α and PDGFR-β [14]. Distinct spatial allocation characterizes PDGFR isoforms with α-type receptors enriched in cancer cells and β-type receptors prevalent in microenvironmental support cells [15]. These receptors selectively associate with distinct PDGF isoforms, forming functional dimers that initiate downstream signaling cascades [1]. The α receptor subtype

exhibits primary affinity for PDGF-A, B, and C, in contrast to the β subtype's specific interaction profile with PDGF-B and D molecules [3]. This specific binding mode enables PDGFR to respond to different PDGF stimuli and produce corresponding physiological effects. In physiological states, PDGFR maintains ubiquitous expression across multiple cellular populations, executing critical biological roles essential for tissue homeostasis. However, in cancer, abnormal expression or mutation of PDGFR may lead to tumor growth, invasion, and metastasis [16]. Featuring a canonical VEGF-paralogous domain within its conserved core, PDGF achieves its bioactive dimeric state through strategically positioned disulfide bridges spanning monomeric and multimeric configurations [1]. Contemporary genomic research has identified four distinct genetic loci responsible for PDGF synthesis including PDGF-A, PDGF-B, PDGF-C, and PDGF-D. Both PDGF and VEGF demonstrate conserved cystine knot architectures, defining their membership in this evolutionary significant protein superfamily [17]. Evolutionary biology research suggests ancestral relationships between PDGF genes and VEGF homologs preserved in model organisms such as nematodes and fruit flies [18]. The PDGF family exhibits dimeric flexibility, combining identical subunits to create AA, BB, CC, or DD homodimers, or pairing different subunits to form heterodimeric variants like AB. In particular, the C-terminus of PDGF-BB contains a conserved motif that can bind to the extracellular matrix. The binding mechanism, though permitting receptor engagement, significantly reduces molecular diffusion capacity [19]. Inside or outside the cell, proteases can digest this motif and release soluble PDGF-BB, further exerting its physiological function [19].

2. Interaction of the PDGF/PDGFR signaling pathway with its upstream and downstream signaling pathways

The PDGF/PDGFR axis drives tumorigenesis and metastasis by activating multiple downstream pathways. It can activate the rat sarcoma/ mitogen-activated protein kinase (Ras/MAPK) pathway *via* growth factor receptor-bound protein 2 (GRB2) to regulate cell metabolism and division [20]. It can also trans-activate a protein coding gene (*Notch – 1*) through binding to PDGF (-BB/-DD), forming a positive feedback loop that upregulates VEGF/ matrix metallopeptidase (MMP)-9, promoting mitosis, extracellular matrix (ECM) remodeling, and metastasis [21]. This signaling axis can also increase MMP production to facilitate invasion [22], and regulate several key downstream molecules, which include that the expression ratio of PDGFR-α/β regulates the phosphoinositide 3-kinase/protein kinase B (PI3K – AKT) signal [23]; activated PDGFR or Janus kinase (JAK) can activate signal transducers and activators of transcription (STAT) proteins to drive proliferation [24]; its activation of phospholipase C-gamma (PLC – γ) is also crucial, so blocking either PDGFR or PLC-γ can effectively inhibit tumors [25]. In addition, transforming growth factor beta-1 (TGFβ-1) induced cancer-associated fibroblasts (CAF)-SULF2 expression can lead to multidrug resistance by activating the PDGFβ/STAT3 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signals in adjacent cancer cells [26]. The PDGF/PDGFR signaling complex acts like a "molecular rheostat", driving malignant phenotypes by coordinating signal crosstalk (Figure 1), providing new targets for cancer treatment. However, the crosstalk of this pathway can also reduce treatment efficacy. For example, the upregulation of PDGFRα can lead to resistance to epidermal growth factor receptor (EGFR) inhibitors in renin-angiotensin system (RAS) wild-type tumors [2, 27].

Role of the PDGF/PDGFR signaling pathway in tumors

The PDGF/PDGFR axis serves as a master regulatory module governing fundamental cellular programs of spanning mitotic progression, phenotypic specification, chemotactic motility, and neovascularization dynamics. However, in cancer, the abnormal activation of this signaling pathway has become

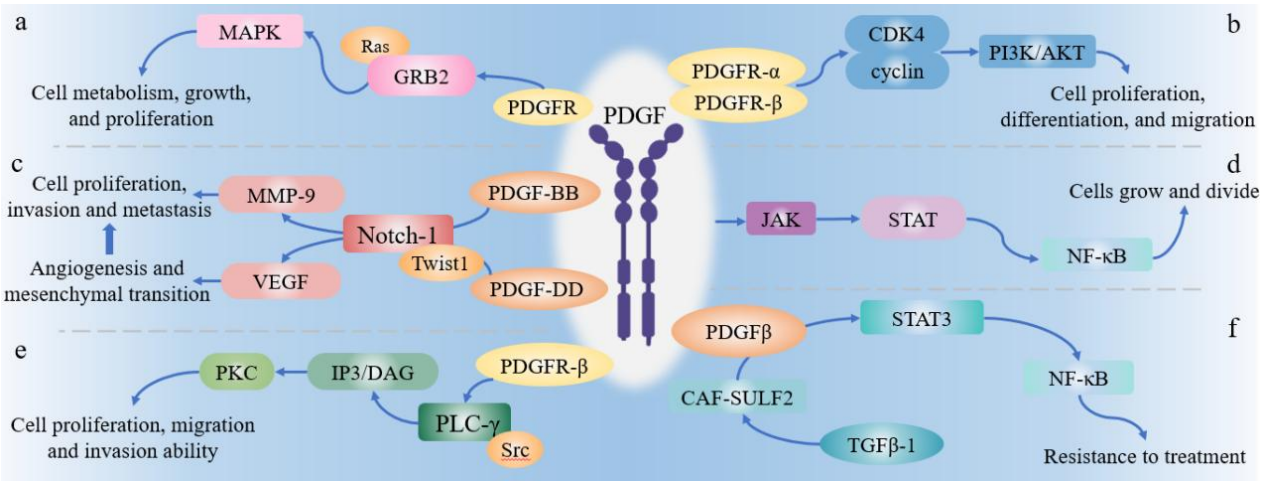

Figure 1. Interaction of the PDGF/PDGFR signaling pathway with its upstream and downstream signaling pathways in tumor progression. **a**. Ras-MAPK signaling pathway. **b**. PI3K/AKT signaling pathway. **c**. Notch signaling pathway. **d**. JAK/STAT signaling pathway. **e**. PLC-γ signaling pathway. **f**. TGFβ signaling pathway.

a key factor in promoting tumor growth, invasion, metastasis, and drug resistance.

1. Promoting tumor growth and invasion

(1) Directly stimulating tumor cell proliferation and invasion

The PDGF/PDGFR signaling pathway plays a significant role in the development of many tumors, and its mechanism of directly stimulating tumor cell proliferation is particularly remarkable. Clinical evidence confirms elevated PDGF/PDGFR expression in diverse malignant cellular populations with these ligand-receptor interactions directly stimulating tumor growth through localized autocrine-paracrine regulatory loops [2]. In gastrointestinal stromal tumors (GIST), oncogenic PDGFR-α mutations trigger sustained pathway signaling that serves as a key mechanism underlying malignant progression and metastasis formation [28]. In triple-negative breast cancer (TNBC), the PDGF/PDGFR signaling pathway promotes the proliferation and invasion ability of tumor cells by upregulating the activity of SH2 domain-containing protein-tyrosine phosphatase-2 (SHP-2), providing a new perspective for understanding the role of this pathway in tumor progression [5]. Meanwhile, PDGF-mediated signaling networks functionally integrate with other growth factor systems, cooperatively augmenting neoplastic cell division capabilities *via* pathway crosstalk. As exemplified in prostate malignancies, PDGF-D drives tumorigenic expansion through selective activation of the PDGFR-β signaling axis. This oncogenic cascade is mediated by sequential stimulation of ERK and AKT molecular pathways, demonstrating the intricate network of PDGF/PDGFR signaling in modulating neoplastic proliferation [29]. The study by Kolliopoulos *et al*. revealed that, after knocking out CD44 using CRISPR/Cas9 technology, the expression level of PDGFRA in U251MG glioblastoma cells decreased significantly, which suggested that CD44 might affect the proliferation ability of tumor cells by regulating the expression of PDGFRA [4]. Lin *et al*. investigated thyroid cancer and found marked PDGFC/PDGFRA co-upregulation with elevated PDGFRA expression, demonstrating strong prognostic correlation to diminished patient survival. After further knocking out the PDGFRA gene in the SW579 squamous thyroid cancer cell line using CRISPR/Cas9 technology, the proliferation ability of the cells was significantly inhibited. This result not only verified the core role of PDGFRA in the proliferation of thyroid cancer cells but also provided a strong basis for targeted therapy against this pathway [30].

(2) Inducing epithelial-mesenchymal transition

The epithelial-mesenchymal transition (EMT) constitutes a pivotal cellular reprogramming process that drives malignant dissemination by enabling tumor cell invasion and metastatic colonization. PDGF/PDGFR activation initiates transcriptional reprogramming to induce EMT, a pivotal process enhancing tumor cell migratory competence and metastatic colonization. The latest research results of Huang *et al*. further confirmed this point through comparative analyses that revealed distinct expression patterns of PDGF-D and its receptor between localized and metastatic osteosarcoma subtypes, demonstrating a direct correlation with malignant cell invasiveness [31]. In thyroid carcinoma investigations, CRISPR/Cas9-mediated PDGFRA knockout in SW579 cells resulted in marked downregulation of mesenchymal transition biomarkers, concurrent with upregulated expression of the epithelial differentiation marker E-cadherin. This mechanistic insight establishes PDGFRA-driven EMT modulation as a critical determinant of thyroid cancer metastasis, concurrently identifying this receptor tyrosine kinase as a therapeutic vulnerability through preclinical validation in orthotopic models [30]. In colorectal carcinoma, PDGF orchestrates EMT through functional engagement with the transmembrane receptor glycoprotein VI (GPVI) [32]. GPVI, as a specific receptor for collagen and fibrin, is originally expressed only in platelets and megakaryocytes. However, in colon cancer cells, when GPVI interacts with galectin 3 on the cell surface, it activates platelets and subsequently releases PDGF. PDGF secretion initiates PDGFR engagement on malignant cells, activating signaling pathways that significantly accelerate EMT development [32]. The process of PDGF/PDGFR signaling pathway-induced EMT also involves the complex regulation of multiple transcription factors. Twist1, a protein that acts as a transcription factor and an important EMT-inducing factor, can directly transcriptionally activate the expression of PDGFR-α, thereby promoting the invasion and metastasis process of tumor cells [33]. PDGF drives cholangiocarcinoma metastasis by coordinately upregulating MMP2/MMP9 expression and inducing EMT with mechanistic dependence on p38 MAPK pathway activation [6]. In addition, through PDGFR-β engagement, PDGF-BB triggers EMT progression, directly amplifying the capacity of malignant cells to infiltrate tissues and disseminate systemically [34]. This oncogenic adaptation demonstrates partial reliance on PI3K-AKT-mTOR axis orchestration coupled with Warburg effect remodeling, where pyruvate kinase M2 (PKM2) emerges as a metabolic-epigenetic nexus coordinating glycolytic flux tuning and mesenchymal transition programming. The PDGF-BB/PDGFR-β axis can regulate the expression and activity of aerobic glycolysis-related enzymes such as hexokinase 2 (HK2), muscle pyruvate kinase isozyme type M2 (PKM2), lactate dehydrogenase A (LDHA), and pyruvate dehydrogenase kinase 1 (PDK1) and affect the glycolytic process of human renal cancer Wilms (G401) cells, consequently emerging as a key modulator in the governance of the aerobic glycolysis pathway [34]. These studies jointly reveal the complex regulatory mechanism of the PDGF/PDGFR signal transduction axis in the EMT process and provide a new perspective for understanding tumor invasion and metastasis.

2. Driving angiogenesis

(1) Stimulating the proliferation and migration of vascular endothelial cells

PDGF functions as a robust promoter of angiogenesis, facilitating neovascularization by engaging multiple biological pathways. Hypoxia prompts tumor cells to produce various proangiogenic factors with PDGF representing a key cytokine. When these mediators engage PDGFR on endothelial cells, downstream signaling pathways are activated, thereby inducing the proliferation and migration of these cells. PDGF family members such as PDGF-B and PDGF-D can activate the PDGFR-β receptor and then initiate downstream signal transduction pathways such as PI3K/AKT and MAPK/ERK [35]. Phosphoproteomic analyses reveal these signaling axes coordinate endothelial activation

states through ERK/FAK phosphorylation cascades with the fold change large than 2.5, thereby orchestrating the angiogenic switch essential for neovascularization.

(2) Promoting the recruitment and differentiation of vascular pericytes

Pericytes associated with the vascular wall are pivotal in reinforcing the architecture of neovessels and preventing microvascular extravasation PDGF promotes the migration and differentiation of vascular pericytes by binding to PDGFR on vascular pericytes, thereby strengthening the stability of new blood vessels. Specifically, PDGF-B secreted by endothelial cells binds to PDGFR-β on the surface of pericytes and stimulates the migration and proliferation of pericytes, thereby participating in the process of angiogenesis and maturation [36].

(3) Fine regulation of key steps in angiogenesis

PDGF/PDGFR signaling orchestrates pivotal angiogenic events including vascular basement membrane proteolysis and lumen formation during vasculogenesis. PDGF stimulates both neoplastic and endothelial cells to secrete matrix metalloproteinases (MMPs), resulting in the degradation of the vascular basement membrane and thereby facilitating angiogenesis [2]. In parallel, PDGF enhances endothelial lumenogenesis and indirectly partakes in neovascularization through the regulation of alternative angiogenic mediators and their corresponding signal transduction mechanisms. PDGF can induce the expression of VEGF, thereby synergistically promoting angiogenesis. In addition, PDGF also acts in synergy with growth factors such as fibroblast growth factor (FGF) to jointly regulate the complex process of angiogenesis [7]. The PDGF/PDGFR signaling axis critically modulates both angiogenesis and lymphangiogenesis, coordinating vascular network assembly and lymphatic system ontogeny. PDGF-B promotes lymphatic vessel formation and orchestrates their maturation and functional attributes *via* the control of lymphatic endothelial cell proliferation and migration [8]. Moreover, for different types of PDGF, their mechanisms of action and effects may vary. For example, PDGF-C and PDGF-D may have unique functions in angiogenesis in specific tissues and organs [37]. Anti-angiogenic treatments involving PDGF family antagonism have demonstrated notable success against angiogenesis-related pathologies such as tumors. However, the onset of drug resistance persists as a critical issue. Research has underscored that dysregulated PDGF/PDGFR signaling often precipitates resistance to these agents, highlighting the potential of targeted PDGF/PDGFR inhibition to effectively reverse such resistance [38].

3. Affecting the tumor microenvironment

Beyond its direct impact on tumor cells, PDGFR is instrumental in modulating the tumor microenvironment. Belonging to the RTK family, PDGFR acts as a central regulator of extracellular signal transduction, orchestrating cellular responses to environmental cues through modulation of proliferation and migratory dynamics. In a hypoxic microenvironment, cancer cells secrete angiogenic cytokines such as PDGF. Binding of these ligands to endothelial cell receptors initiates a series of signaling pathways, specifically Akt/PIP3, Src, p38/MAPK, and Smad2/3, which converge to drive the proliferation and migration of endothelial cells [39]. In various tumor types, PDGFR has a specific effect on specific cell types such as mesenchymal cells and is regarded as a key regulator in the tumor microenvironment [37]. Studies have shown that, in tumors such as prostate cancer and breast cancer, high stromal PDGFR expression is closely related to the poor prognosis of patients [13].

(1) Cancer-associated fibroblasts and myofibroblasts

Cancer-associated fibroblasts (CAFs) constitute essential stromal components that drive tumor progression through paracrine secretion of pro-metastatic mediators including TGF-β, FGF2, and PDGF isoforms, orchestrating extracellular matrix remodeling and epithelial-mesenchymal transition programs. PDGF activates downstream signaling pathways by binding to PDGFR on CAFs,

thereby promoting the activation and proliferation of CAFs. In solid tumors, non-malignant stromal components account for the majority of the tumor mass, and CAFs are the dominant force among them. Mechanistic dissection reveals PDGF-BB-mediated CAF activation circuitry converges on PDGFR signalosomes, catalytically converting stromal quiescence into proliferative desmoplastic reaction that geometrically accelerates tumor kinetics while inducing epithelial-mesenchymal trophic shift. Exhibiting an activated phenotype, CAFs produce various growth factors and cytokines such as EGF, HGF, stromal cell-derived factor (SDF), PDGFs, interleukin-6 (IL-6), thereby promoting tumor proliferation and invasion [40].

(2) Tumor immune response

PDGF plays an immunomodulatory role in the tumor microenvironment. The PDGF/PDGFR signaling cascade suppresses immune effectors by inhibiting natural killer (NK) cells and T lymphocyte activation, thus weakening the immune response and aiding tumor immune escape [41]. In glioma models characterized by elevated PDGF-BB, a marked influx of macrophages that is negatively associated with patient survival has been documented [9]. Additionally, PDGFs potentiate monocyte chemotaxis and enhance MMP-2/MMP-9 expression through the Src-STAT3 pathway [42]. Furthermore, PDGF contributes to an immunosuppressive milieu by eliciting cytokine production and promoting the transformation of macrophages into the M2 phenotype [43].

(3) Resistance to anti-VEGF therapy

The PDGF signaling axis critically mediates therapeutic resistance to VEGF inhibition through hypoxia-driven feedback mechanisms. VEGF-targeted agents induce tumor microenvironmental hypoxia, triggering hypoxia-inducible factor 1-alpha (HIF-1α) stabilization, which transcriptionally activates compensatory angiogenic programs *via* dual induction of PDGF-BB and autocrine VEGF signaling. Studies have revealed that fibroblasts activated by PDGF-BB release PDGF-CC, erythropoietin (EPO), and FGF. Together, these mediators promote tumor angiogenesis independent of VEGF, which contributes to the development of anti-VEGF therapy resistance [9].

4. Participating in the development of tumor drug resistance

Due to its central involvement in tumor drug resistance and pathogenesis, the PDGF/PDGFR pathway is now a major target for intervention. Its expression is observed in many cancers, and higher levels correlate with increased invasiveness, larger tumor burdens, and reduced responsiveness to chemotherapy [44]. Taking GIST as an example, mutations in PDGFR-α observed in them can cause continuous activation of downstream signaling pathways, thereby exacerbating tumor cell drug resistance [28]. In such cases, targeted therapy drugs against PDGFR-α are expected to inhibit its activity and restore the sensitivity of chemotherapy drugs. In ovarian clear cell carcinoma (OCCC), PDGF produced by tumors activates PDGFR, which in turn induces CAF activation and survival. This cascade enhances HIF signaling, boosts PDGF expression, and fosters chemotherapy resistance in cancer cells [10]. Moreover, elevated PDGFRα expression in both tumor and stromal adenocarcinoma cells is linked to a RAS wild-type phenotype, suggesting its contribution to anti-EGFR therapy resistance and its potential utility as a precise or adjuvant treatment target [27]. Therefore, specific targeting of the PDGF/PDGFR axis is emerging as a promising strategy to improve chemosensitivity and overcome drug resistance. Central to tumor pathobiology, the PDGF/PDGFR axis coordinates a wide range of oncogenic programs across different cancers. It exerts its influence by directly stimulating tumor cell proliferation inducing epithelial-mesenchymal transition, enhancing angiogenesis, and modulating the functions of cancer-associated fibroblasts and immune cells. Additionally, aberrant activation of this pathway is linked to resistance against anti-VEGF therapies and chemotherapeutic agents and is a marker for poor prognosis. The co-expression of PDGF and its receptor further

reinforces an autocrine loop that drives tumor progression. Collectively, these observations support the rationale for targeting the PDGF/PDGFR pathway as a novel approach to overcoming drug resistance and heighten the efficacy of chemotherapy.

PDGF/PDGFR as Clinical Biomarkers in Cancer Management

In recent years, with the widespread application of high-throughput omics technologies and single-cell sequencing, the value of the PDGF/PDGFR signaling axis as a clinical biomarker has become increasingly prominent. Its expression level is not only closely related to the prognosis of various tumors but can also predict treatment response, providing an important basis for patient stratification and personalized treatment.

1. Prognostic and diagnostic value in solid tumors

There is a significant association between the expression patterns of PDGF/PDGFR pathway members in different tumor types and their clinical outcomes. However, this association is highly context-dependent, meaning that its prognostic value depends on specific ligands, receptor subtypes, and cancer types. In breast cancer, an analysis based on a large-scale genomic dataset (METABRIC) found that the mRNA expression level of PDGFB was significantly increased in high-grade, HER2-positive tumors. More importantly, patients with high PDGFB expression had a significantly shorter overall survival (P = 0.0001), indicating that PDGFB is a powerful biomarker of poor prognosis in breast cancer [45]. In cholangiocarcinoma (CCA), studies have confirmed that both the mRNA and protein levels of PDGF-CC are significantly higher in tumor tissues and patient sera compared to the normal control group. High-level PDGF-CC expression is closely associated with poor overall survival in patients, which not only makes it a potential prognostic indicator but also offers the possibility of liquid biopsy based on serum testing [46]. In castration-resistant prostate cancer (CRPC), single-cell analysis has revealed a specific CRPC-pericyte subset characterized by a significant upregulation of the PDGF signaling pathway. The enrichment of this cell subset is associated with shorter recurrence-free survival in patients and non-responsiveness to immunotherapy, suggesting that targeting the PDGF-signaling pericyte subset could serve as a biomarker for predicting the efficacy of immunotherapy [47]. However, the prognostic significance of PDGF ligands is not constant. In osteosarcoma, single-cell RNA sequencing (scRNA-seq) analysis presents a more complex picture. Contrary to the above findings, PDGFD has a higher expression level in non-metastatic osteosarcoma tissues, and its high expression is associated with longer metastasis-free survival and overall survival [31]. This discovery reveals the functional heterogeneity of PDGF family members. PDGFB may primarily drive invasive angiogenesis in breast cancer, while PDGFD may be involved in maintaining a more differentiated cell state with lower metastatic potential at specific stages of osteosarcoma. This functional difference emphasizes that, in clinical applications, it is essential to develop detection methods that can distinguish specific ligands and their cell origins, rather than evaluating "PDGF pathway activity" in a general way. In addition, in gastric cancer, lysyl oxidase (LOX) promotes the formation of vasculogenic mimicry (VM) through the PDGF-PDGFR pathway. Its expression level is higher in metastatic and advanced stage (T3 + T4) tumors and is positively correlated with VM formation, indicating a poor prognosis [48].

2. Matrix PDGFR expression: A key tumor microenvironment indicator

Tumor progression depends not only on cancer cells themselves but is also profoundly influenced by the tumor microenvironment (TME) in which they are located. PDGFR, especially PDGFR-β, is mainly expressed in stromal cells of the TME such as cancer associated fibroblasts (CAFs) and pericytes, and its expression level can serve as a "barometer" for measuring the state of the TME.

The PDGF system is a key regulator of tumor growth, metastasis, and drug efficacy. Variations in stromal PDGFR expression among patients are associated with prognosis and treatment response, suggesting that stromal PDGFR can serve as a clinical biomarker [49]. In breast cancer, the upregulation of PDGFR has been recognized as a phenotypic marker of CAFs and an indicator of poor prognosis [50], which directly connects the molecular biomarker with a crucial cancer-promoting cell type within the TME. Likewise, in prostate cancer, high expression of stromal PDGFR-β is independently associated with clinical and biochemical recurrence [13]. Therefore, the expression level of stromal PDGFR reflects whether the TME has been "hijacked" by the tumor to support its growth, angiogenesis, and immune escape. When stromal cells highly express PDGFR, it usually means that the TME is in a state that promotes cancer, suppresses the immune system, and resists treatment. Therefore, detecting the expression of stromal PDGFR can not only predict the efficacy of PDGFR inhibitors but also may predict the response to various treatment modalities including immunotherapy.

3. Liquid biopsy and omics-driven biomarkers

With technological advancements, the detection of PDGF/PDGFR biomarkers is evolving from traditional tissue biopsies to more non-invasive and comprehensive methods. The potential of liquid biopsy is demonstrated in the research of cholangiocarcinoma. The elevation of PDGF-CC levels in the sera of patients is associated with tumor burden and poor prognosis, suggesting that circulating PDGF ligands can serve as a non-invasive monitoring tool [46]. Advanced omics technologies provide a powerful impetus for the discovery of more precise biomarkers. Franciosa *et al*. conducted an in-depth analysis of ovarian cancer stem cells (OCSCs) from patients using quantitative proteomics and phosphoproteomics techniques and found that abnormal PDGFR activation was a common feature of chemotherapy-resistant OCSCs with stem cell-like properties [51]. This finding precisely linked PDGFR activation to a small subset of cells within the tumor that determined the success or failure of treatment, indicating that PDGFR was a potential target and biomarker for therapies targeting OCSCs.

Strategies and drugs for treating tumors by targeting the PDGF/PDGFR pathway

1. Cutting-edge therapeutic strategies targeting the PDGF/PDGFR pathway

With the deepening understanding of tumor heterogeneity, it has become possible to precisely target specific molecular subtypes. In myxoid glioneuronal tumor (MGNT), the unique PDGFRA K385I/L mutation is its molecular signature. The study by de Villenfagne *et al*. confirmed that these mutants were sensitive to FDA-approved tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and avapritinib, which provided clear targeted treatment options for patients carrying specific PDGFRA mutations [52]. In cholangiocarcinoma, the study by Luo *et al*. strongly demonstrated that PDGF-CC was a key factor driving tumor progression, which suggested that developing specific inhibitors or antibodies targeting PDGF-CC might have better efficacy and lower toxicity compared to using pan-PDGFR inhibitors that suppressed all PDGF signaling [46]. Combining PDGF/PDGFR inhibitors with other therapies to overcome drug resistance and reshape the TME is currently the most promising treatment direction. Immunotherapy has limited effectiveness in many tumors, one of the reasons being the immunosuppressive TME. In a castration-resistant prostate cancer model, Qiu *et al*. found that the upregulation of PDGF signaling driven by pericytes was a key factor leading to immunosuppression. Excitingly, the combination of a PDGFR inhibitor and an anti-PD-1 antibody could produce a significant synergistic anti-tumor effect [47]. The mechanism is that the PDGFR inhibitor can "reshape" the TME and weaken the immunosuppressive function of pericytes, enabling immune checkpoint inhibitors to function effectively. Ayers *et al*. found that, in metastatic breast cancer, the combined use of FGFR inhibitors and DNMT1 inhibitors could

prevent the upregulation of PDGFR caused by cell plasticity, thereby delaying drug resistance and prolonging survival [12], which provided a new idea for stabilizing the therapeutic effect through epigenetic regulation. In metastatic medulloblastoma, tumor cells secrete PDGF ligands to recruit and "reprogram" meningeal fibroblasts, thereby creating a microenvironment favorable for metastasis. The study by Abeysundara *et al*. demonstrated that the use of PDGFR-α neutralizing antibodies could block this process and significantly improve the survival rate of xenograft mice [53], which directly proved that targeting the PDGF/PDGFR interaction within the TME was an effective anti-metastasis strategy. Targeted drug delivery has emerged as a new treatment strategy in cancer treatment. Targeted drug delivery systems such as pH-sensitive nanosystems can improve the treatment effect and reduce side effects based on the differences between the TME and normal tissues [20]. A dual-targeted drug delivery system combining paclitaxel-loaded polyethylene glycol-polylactic acid nanoparticles with a cyclic peptide can selectively bind to PDGF/PDGFRβ and has been used to improve the treatment of multiple myeloma [54]. In addition to pH-sensitive nanosystems, other types of targeted drug delivery systems are also under study. Liposomes are a widely studied drug delivery system. There are already a variety of nano-drugs approved for clinical application with good biocompatibility and modifiability and can achieve targeted drug delivery through surface modification [55]. Exosomes are another highly promising biological nanocarrier. Tumor cell-derived exosomes can use molecules on the membrane to transmit signals and specifically transport drugs to tumor cells, improving the efficacy and reducing damage [56]. The virus-mimicking system is also an innovative drug delivery method. Functional modification can improve the targeting and treatment effect on tumor cells [20].

2. Related drugs targeting the PDGF/PDGFR pathway

(1) Antibodies and aptamers

Emerging from its established role in carcinogenic progression, PDGFR-targeted intervention has emerged as a paradigm-shifting approach in contemporary cancer therapeutics. Contemporary drug development has translated multiple targeted therapeutics into clinical testing, demonstrating promising clinical efficacy. As exemplified by Olaratumab (Lartruvo™), a humanized IgG1-class monoclonal antibody targeting PDGFRα, this therapeutic agent suppresses receptor activation and downstream signaling through competitive ligand binding inhibition, thereby disrupting PDGFRα-PDGF interactions [57]. Gint4.T is an RNA aptamer composed of 33 bases. It has a significant inhibitory effect on the lung metastasis of glioma cells and triple-negative breast cancer and can specifically bind to human PDGFRβ and inhibit its activity [58].

(2) Small molecule inhibitors

In addition to antibody and aptamer therapies, a variety of small molecule kinase inhibitors are under development. These drugs inhibit the kinase activity of PDGFR to block its downstream signaling pathways, thereby achieving the purpose of anti-tumor. By targeting both PI3K/Akt phosphorylation and PDGFR levels, Motesanib, a small molecule multi-kinase inhibitor, plays a significant role in curbing the growth of cancer cells [59]. In addition, as a tyrosine kinase inhibitor, Imatinib, a tyrosine kinase inhibitor, specifically targets PDGFR and is clinically authorized for use in GIST and several hematologic malignancies [60]. They inhibit the activity of the PDGF/PDGFR signaling pathway through different mechanisms and achieve anti-tumor effects, showing broad prospects and great potential in clinical applications and bringing new hope and treatment options for patients.

(3) Plant-derived inhibitors

Complementing synthetic small-molecule inhibitors, phytochemicals are gaining prominence in drug discovery pipelines owing to their favorable safety profiles and inherent polypharmacological properties. Studies have

shown that a variety of plant compounds such as coumarin [61], resveratrol nanoparticles [62], and ethanol extract of persimmon [62] have the effect of inhibiting PDGFR activity and exhibit anti-tumor activity across laboratory and live organism models. These natural products provide rich resources for the progression of anti-neoplastic agents. In addition, utilizing natural compounds as adenosine triphosphate (ATP)-competitive PDGFR/PDGFRs inhibitors can minimize the nephrotoxicity and hepatotoxicity linked to small-molecule drugs like Imatinib, Gefitinib, and Erlotinib [2].

Conclusions and perspectives

The PDGF/PDGFR axis emerges as a master regulatory scaffold in oncogenic transformation, governing tumor pathobiology through coordinated activation of regulatory networks encompassing the Ras-MAPK and PI3K-AKT-mTOR signaling axes. This mechanistic dissection reveals how PDGFR signalosomes recalibrate cellular homeostasis by modulating core neoplastic hallmarks including unrestrained proliferation, migratory plasticity, stromal invasion, and metastatic competency. These insights not only establish PDGF/PDGFR interactome centrality in tumor ecosystem evolution but also illuminate druggable network vulnerabilities, charting novel therapeutic trajectories for precision oncology interventions. Meanwhile, combined treatment strategies targeting the PDGF/PDGFR signaling pathway will also become one of the important directions of future cancer treatment. By comprehensively using a variety of treatment methods to modulate the PDGF/PDGFR signaling axis, it is believed that more effective treatment regimens and drugs targeting this pathway will emerge in the future, bringing new hope and options for cancer patients.

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