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Role of Platelet-Derived Growth Factor-mediated signaling in carcinogenesis and metastasis

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Editorial

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ABSTRACT

Platelet-Derived Growth Factor (PDGF) mediated signaling has emerged as one of the most extensively studied cascades in cancer development and progression. Overwhelmingly increasing data obtained from preclinical and clinical studies has helped us to develop a near-complete resolution of PDGF/PDGFR signaling landscape. Phenotype- and genotype-driven studies have provided proof-of-concept that therapeutic targeting of PDGF/PDGFR signaling axis is necessary to improve clinical outcome. Kinase inhibitor drug discovery programmes have broadened their focus to include a wide variety of kinase targets. Based on the insights gleaned from previously published high-impact research, it is clear that different transduction cascades crosstalk with PDGF/PDGFR signaling during primary tumor invasion, dissemination and ultimate metastasis of cancer cells. In this commentary, we will focus on involvement of PDGF/PDGFR signaling in different cancers and how pharmacological targeting of this signaling cascade inhibits cancer progression.

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PDGFRα

PDGF ligand-receptor interactions and their downstream signaling effectors have a pivotal role in carcinogenesis. Functioning as molecular antennae that transduce downstream signaling, structural and functional studies related to PDGFRα/β-mediated downstream signaling offer plausible targets for cancer treatment. Topoisomerase IIB (TOP2B) modulates the transcription of different oncogenes in gliomas. There was a considerable decline in the levels of PDGFRα and MYC in TOP2B-silenced-BT142 cells. Intracranial implantation of TOP2B-silenced-BT142 cells followed by administration of doxycycline caused a reduction in the tumor growth (1).

Canertinib inhibited the activities of PDGFRA and EGFRvIII kinases. PDGFRα activity is necessary for EGFRvIII-driven glioblastoma formation in mice. GFRvIII and PDGFRα contribute to the activation of pro-survival PI3K-AKT and MEK-ERK signaling (2).

Regulation of PDGF/PDGFR by non-coding RNAs is also an area of exciting research. CircCDK14 interferes with miR-3938-mediated targeting of PDGFRα. There was a remarkable tumor growth in mice xenografted with circCDK14-silenced-U251 cells. Levels of PDGFRα, p-PDGFRα, Vimentin, ZEB1, GPX4 and SLC7A11 were found to be reduced in circCDK14-knockdown tumors (3).

LINC02283 gene co-amplifies with PDGFRα locus. LINC02283 interacts with PDGFRα and enhances its signaling as well as its downstream effectors (AKT and ERK) to promote the progression of GBM (4).

Knockdown of SNHG8 inhibited proliferation and invasive potential of gastric cancer cells. SNHG8 inhibited miR-491-mediated targeting of PDGFRα (5). Therefore, it will be intriguing to use miR-491 mimics in the inhibition of tumor growth in experimental mice.

Similarly, LINC00467 interfered with miR-509-3p-mediated inhibition of PDGFRα in HCC cells. Axitinib notably induced tumor regression in mice inoculated with LINC00467-silenced-Huh7 cells (6).

MDSCs (Myeloid-derived suppressor cells) centrally regulate the establishment of the metastatic microenvironment. Recombinant mouse-CXCL17 increased the number of metastatic nodules on the surface of the lungs in experimental mice orthotopically implanted with breast cancer cells (7). Moreover, in another experimental metastasis model, significant increase in the number and volume of tumor nodules was found in mice treated with recombinant mouse-CXCL17. There was a remarkable impairment of the spontaneous metastasizing capacity of CXCL17-knockdown 4T1 cancer cells. CXCL17 triggered the formation of pulmonary metastatic niches by the recruitment of PDGF-BB-expressing MDSCs. Intra-tracheally administered recombinant mouse-CXCL17 enhanced the infiltration and accumulation of CD11b+Gr-1+ MDSCs in the lungs of experimental mice. There was an evident increase in expression of PDGF-BB in CD11b+Gr-1+ MDSCs isolated from the lungs of CXCL17-treated mice. Importantly, significantly increased number of MDA-MB-231 cells was found in the lungs of mice after treatment with CXCL17. Treatment with recombinant mouse-PDGF-BB enhanced trans-endothelial migration and colony-forming ability of 4T1 cells. Conditioned media of CD11b+Gr-1+ MDSCs isolated from CXCL17-treated mice enhanced the colony-forming properties of 4T1 cancer cells (7).

VEGFR1+ hematopoietic progenitor cells play a principal role in the formation of pre-metastatic niches. There is an increase in the infiltration and recruitment of

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VEGFR1+CD133+ hematopoietic progenitor cells to the lungs during the progression of metastases. However, recruitment of VEGFR1+CD133+ hematopoietic progenitor cells to the lungs was reduced after the establishment of pulmonary metastasis. Co-culture of CD133+ hematopoietic progenitor cells with highly metastatic-MDA-MB-435s cells caused an increase in the secretion of PDGFRα, PECAM-1 and MMP9 by MDA-MB-435s cells. Combinatorial blockade of MMP9, PDGFRα and PECAM-1 significantly suppressed pulmonary metastasis of highly metastatic-MDA-MB-435s cells and the infiltration of VEGFR1+CD133+ hematopoietic progenitor cells to the lungs of experimental mice (8).

PDGFRβ

PDGFRβ played a central role in the progression of breast cancer. JAK2-STAT3-mediated signaling stimulated the expression of Myc. Consequently, Myc transcriptionally suppressed PDGFRβ in breast cancer cells. JAK2-mediated phosphorylation and proteasomal degradation of PDGFRβ. Nilotinib is an effective inhibitor of PDGFRβ. Combinatorial treatment of tumor-bearing mice with nilotinib and MEK1/2-JAK2 inhibitors caused significant regression of the tumor mass (9).

Seminal findings had shown that PDGFRβ and PD-L1/PD-1 signaling centrally regulated metastasis. Anti-human PDGFRβ aptamer and anti-PD-L1 mAb synergistically suppressed the metastatic dissemination and pulmonary metastatic nodules in experimental mice (10).

PDGFB efficiently promoted tumor growth and brain metastasis in rodent models that constitutively expressed active PDGFRβ (PDGFRβD849V). DB7 cells derived from mouse mammary tumors had high expression of PDGFB. Tumor growth was found to be severely impaired in mice orthotopically implanted with PDGFB-silenced-DB7 cells in mammary fat pads. PDGFRβ activation and tumor-derived PDGFB enhanced intracranial grown tumors. Crenolanib (PDGFR inhibitor) markedly suppressed the growth of the tumors in experimental models intracranially injected with PDGFB-expressing-DB7 cells into the brains of mice (11).

Dihydroartemisinin induced ubiquitination and proteasomal degradation of PDGFRα. Dihydroartemisinin significantly reduced the growth and mobility of PDGFRα-expressing SK-OV3 cells. PI3K/AKT and MAPK pathways are downstream effector pathways emanating from PDGFRα-driven signaling. Dihydroartemisinin inhibited PDGF-mediated phosphorylation of PDGFRα and activation of AKT and ERK. Dihydroartemisinin effectively inhibited metastatic nodules in BALB/c nude mice intraperitoneally injected with A2780 cells. Importantly, dihydroartemisinin and sorafinib worked with remarkable synergy and induced regression of the tumor growth (12).

NPM-ALK regulated the transcriptional expression of PDGFRβ by c-Jun and JunB. PDGFRβ expression accelerates ALK^+ tumor formation and metastatic dissemination. PDGFRβ deficiency caused significant reduction in the proliferation of the primary tumor cells and impaired tumor development. Experimental mice inoculated with a high density of wild-type-PDGFRβ-expressing cells achieved maximum tumor volume. PDGFRβ activated STAT5 and promoted tumor progression. PDGFRβ/STAT5 axis fuels malignancy and operates in parallel to the oncogenic NPM-ALK-STAT3 pathway resulting in disease aggressiveness (13).

Cancer-associated fibroblasts (CAFs) are involved in progression and drug resistance through interactions with gastric cancer cells. TGFβ1 transcriptionally upregulated PDGFRβ in CAFs (Akiyama). Therefore, PDGFD/PDGFRβ signaling promoted the growth of CAFs. It was shown that treatment with antagonistic antibodies against PDGFRα and PDGFRβ significantly inhibited CAF growth stimulated by PDGF ligands. CXCL1 and CXCL3 released from activated fibroblasts co-cultured with murine gastric cancer cells enhanced the chemotactic movement of PMN-MDSCs. Serially transplanted murine gastric tumors exhibited severe fibrosis along with increased CAFs and an immunosuppressive-microenvironment. $CD25^+FOXP3^+$ regulatory T cells were found to be significantly increased in fibrotic microenvironment. However, there was a notable reduction in CD8+ cytotoxic T lymphocytes in serially transplanted gastric tumors. Regorafenib restored the antitumor effects of anti-PD-1 antibodies in serially transplanted fibrotic tumors. There was a significant reduction in the number of tumor fibroblasts and PMN-MDSCs by regorafenib. Regorafenib and anti-PD-1 antibodies substantially enhanced infiltration of $CD8^+$ cytotoxic T lymphocytes (14).

TWIST1 transcriptionally upregulates PDGFRβ in cancer cells. Moreover, there was a notable increase in the activation of PDGFRβ in TWIST1-overexpressing cancer cells. Likewise, considerable increment in the levels of phosphorylated-FAK (focal adhesion kinase) and phosphorylated-Src was noticed in PDGFRβ-overexpressing breast cancer cells. Importantly, PDGFRβ mechanistically regulates the metastatic dissemination of breast cancer cells and cancer stem cells to the lungs and liver (15).

FOXQ1 transcriptionally upregulated PDGFRα and PDGFRβ. Ras-expressing human mammary epithelial cells demonstrated significant tumor-forming abilities. Accordingly, tumor growth was found to be considerably impaired in mice inoculated with PDGFRα/β-silenced human mammary epithelial cells (16). Overall, these findings indicated that the knockdown of PDGFRs blocked FOXQ1-promoted carcinogenesis and metastasis.

Pioneering research works have comprehensively characterized PDGF/PDGFR-driven signaling in different cancers. The synergy between the design and development of antagonistic antibodies and small molecule inhibitors has become the cornerstone of molecular oncology. PDGF/PDGFR pathway rewires downstream signaling cascades in carcinogenesis and metastasis. Therefore, there is a need to use a multipronged approach for pharmacological targeting of the PDGF/PDGFR pathway. Moreover, careful re-interpretation of molecular mechanisms will be needed for the development of rationally designed strategies for prevention of acquired resistance against PDGF/PDGFR inhibitors in wide variety of cancers.

References

1. Gonzalez-Buendia E, Zhao J, Wang L, Mukherjee S, Zhang D, Arrieta VA, Feldstein E, Kane JR, Kang SJ, Lee-Chang C, Mahajan A, Chen L, Realubit R, Karan C, Magnuson L, Horbinski C, Marshall SA, Sarkaria JN, Mohyeldin A, Nakano I, Bansal M, James CD, Brat DJ, Ahmed A, Canoll P, Rabadan R, Shilatifard A, Sonabend AM. TOP2B Enzymatic Activity on Promoters and Introns Modulates Multiple Oncogenes in Human Gliomas. Clin

Cancer Res. 2021 Oct 15;27(20):5669-5680. doi: 10.1158/1078-0432.CCR-21-0312.

2. Yeo AT, Jun HJ, Appleman VA, Zhang P, Varma H, Sarkaria JN, Charest A. EGFRvIII tumorigenicity requires PDGFRA co-signaling and reveals therapeutic vulnerabilities in glioblastoma. Oncogene. 2021 Apr;40(15):2682-2696. doi: 10.1038/s41388-021-01721-9.
3. Chen S, Zhang Z, Zhang B, Huang Q, Liu Y, Qiu Y, Long X, Wu M, Zhang Z. CircCDK14 Promotes Tumor Progression and Resists Ferroptosis in Glioma by Regulating PDGFRA. Int J Biol Sci. 2022 Jan 1;18(2):841-857. doi: 10.7150/ijbs.66114.
4. Goenka A, Song X, Tiek D, Iglesia RP, Lu M, Zeng C, Horbinski C, Zhang W, Hu B, Cheng SY. Oncogenic long noncoding RNA LINC02283 enhances PDGF receptor A-mediated signaling and drives glioblastoma tumorigenesis. Neuro Oncol. 2023 Sep 5;25(9):1592-1604. doi: 10.1093/neuonc/noad065.
5. Zhang P, Li S, Chen Z, Lu Y, Zhang H. LncRNA SNHG8 promotes proliferation and invasion of gastric cancer cells by targeting the miR-491/PDGFRA axis. Hum Cell. 2020 Jan;33(1):123-130. doi: 10.1007/s13577-019-00290-0.
6. Li W, He Y, Chen W, Man W, Fu Q, Tan H, Guo H, Zhou J, Yang P. Knockdown of LINC00467 contributed to Axitinib sensitivity in hepatocellular carcinoma through miR-509-3p/PDGFRA axis. Gene Ther. 2021 Nov;28(10-11):634-645. doi: 10.1038/s41434-020-0137-9.
7. Hsu YL, Yen MC, Chang WA, Tsai PH, Pan YC, Liao SH, Kuo PL. CXCL17-derived CD11b+Gr-1+ myeloid-derived suppressor cells contribute to lung metastasis of breast cancer through platelet-derived growth factor-BB. Breast Cancer Res. 2019 Feb 12;21(1):23. doi: 10.1186/s13058-019-1114-3.
8. Meng D, Meng M, Luo A, Jing X, Wang G, Huang S, Luo M, Shao S, Zhao X, Liu R. Effects of VEGFR1+ hematopoietic progenitor cells on pre-metastatic niche formation and in vivo metastasis of breast cancer cells. J Cancer Res Clin Oncol. 2019 Feb;145(2):411-427. doi: 10.1007/s00432-018-2802-6.
9. Kalimutho M, Sinha D, Mittal D, Srihari S, Nanayakkara D, Shafique S, Raninga P, Nag P, Parsons K, Khanna KK. Blockade of PDGFRβ circumvents resistance to MEK-JAK inhibition via intratumoral CD8+ T-cells infiltration in triple-negative breast cancer. J Exp Clin Cancer Res. 2019 Feb 18;38(1):85. doi: 10.1186/s13046-019-1075-5.
10. Camorani S, Passariello M, Agnello L, Esposito S, Collina F, Cantile M, Di Bonito M, Ulasov IV, Fedele M, Zannetti A, De Lorenzo C, Cerchia L. Aptamer targeted therapy potentiates immune checkpoint blockade in triple-negative breast cancer. J Exp Clin Cancer Res. 2020 Sep 7;39(1):180. doi: 10.1186/s13046-020-01694-9.
11. Thies KA, Hammer AM, Hildreth BE 3rd, Steck SA, Spehar JM, Kladney RD, Geisler JA, Das M, Russell LO, Bey JF 4th, Bolyard CM, Pilarski R, Trimboli AJ, Cuitiño MC, Koivisto CS, Stover DG, Schoenfield L, Otero J, Godbout JP, Chakravarti A, Ringel MD, Ramaswamy B, Li Z, Kaur B, Leone G, Ostrowski MC, Sizemore ST, Sizemore GM. Stromal Platelet-Derived Growth Factor Receptor-β Signaling Promotes Breast Cancer Metastasis in the Brain. Cancer Res. 2021 Feb 1;81(3):606-618. doi: 10.1158/0008-5472.CAN-19-3731.
12. Li X, Ba Q, Liu Y, Yue Q, Chen P, Li J, Zhang H, Ying H, Ding Q, Song H, Liu H, Zhang R, Wang H. Dihydroartemisinin selectively inhibits PDGFRα-positive ovarian cancer growth and metastasis through inducing degradation of PDGFRα protein. Cell Discov. 2017 Nov 21;3:17042. doi: 10.1038/celldisc.2017.42.
13. Garces de Los Fayos Alonso I, Zujo L, Wiest I, Kodajova P, Timelthaler G, Edtmayer S, Zrimšek M, Kollmann S, Giordano C, Kothmayer M, Neubauer HA, Dey S, Schlederer M, Schmalzbauer BS, Limberger T, Probst C, Pusch O, Högler S, Tangermann S, Merkel O, Schiefer AI, Kornauth C, Prutsch N, Zimmerman M, Abraham B, Anagnostopoulos J, Quintanilla-Martinez L, Mathas S, Wolf P, Stoiber D, Staber PB, Egger G, Klapper W, Woessmann W, Look TA, Gunning P, Turner SD, Moriggl R, Lagger S, Kenner L. PDGFRβ promotes oncogenic progression via STAT3/STAT5 hyperactivation in anaplastic large cell lymphoma. Mol Cancer. 2022 Aug 31;21(1):172. doi: 10.1186/s12943-022-01640-7.
14. Akiyama T, Yasuda T, Uchihara T, Yasuda-Yoshihara N, Tan BJY, Yonemura A, Semba T, Yamasaki J, Komohara Y, Ohnishi K, Wei F, Fu L, Zhang J, Kitamura F, Yamashita K, Eto K, Iwagami S, Tsukamoto H, Umemoto T, Masuda M, Nagano O, Satou Y, Saya H, Tan P, Baba H, Ishimoto T. Stromal Reprogramming through Dual PDGFRα/β Blockade Boosts the Efficacy of Anti-PD-1 Immunotherapy in Fibrotic Tumors. Cancer Res. 2023 Mar 2;83(5):753-770. doi: 10.1158/0008-5472.CAN-22-1890.
15. Yeeravalli R, Kaushik K, Das A. TWIST1-mediated transcriptional activation of PDGFRβ in breast cancer stem cells promotes tumorigenesis and metastasis. Biochim Biophys Acta Mol Basis Dis. 2021 Jul 1;1867(7):166141. doi: 10.1016/j.bbadis.2021.166141.
16. Meng F, Speyer CL, Zhang B, Zhao Y, Chen W, Gorski DH, Miller FR, Wu G. PDGFRα and β play critical roles in mediating Foxq1-driven breast cancer stemness and chemoresistance. Cancer Res. 2015 Feb 1;75(3):584-93. doi: 10.1158/0008-5472.CAN-13-3029.