Journal of Cancer Stem Cell Research (2018), 6:e1001
 ISSN 2329-5872
DOI: 10.14343/JCSCR.2018.6e1001
http://cancerstemcellsresearch.com

Research Article Open Access

Platelet Derived Growth Factor Receptor-β (PDGFRβ) Signaling: A Novel Therapeutic Target for Breast Cancer Associated Brain Metastasis

Anisha M. Hammer[1,2,#], Katie A. Thies[3,4,#], Blake E. Hildreth III[3,4], Luke O. Russell[1,5], Steven T. Sizemore[1,6], Anthony J. Trimboli[3,4], Raleigh D. Kladney[1], Sarah A. Steck[1,6], Manjusri Das[1,6], Chelsea M. Bolyard[1,6], Robert Pilarski[1,7], Lynn Schoenfield[1,8], Jose Otero[1,8], Arnab Chakravarti[1,6], Matthew D. Ringel[1,2], Zaibo Li[1,8], Balveen Kaur[9], Gustavo Leone[3,4], Michael C. Ostrowski[3,4], and Gina M. Sizemore[1,6]

[1]The Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio 43210, USA. [2]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, The Ohio State University, Columbus, Ohio 43210, USA. [3]The Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina 29425, USA. [4]Department of Biochemistry & Molecular Biology, Medical University of South Carolina, Charleston, South Carolina 29425, USA. [5]Department of Neurological Surgery, The Ohio State University, Columbus, Ohio 43210, USA. [6]Department of Radiation Oncology, The Ohio State University, Columbus, Ohio 43210, USA. [7]Division of Human Genetics, The Ohio State University, Columbus, Ohio 43210, USA. [8]Department of Pathology, The Ohio State University. [9]Department of Neurosurgery, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA.

Abstract: PDGFRβ is a receptor tyrosine kinase found in cells of mesenchymal origin such as fibroblasts and pericytes. Activation of this receptor is dependent on paracrine ligand induction, and its preferred ligand, PDGFB, is released by neighboring epithelial and endothelial cells. While expression of both PDGFRβ and PDGFB has been noted in patient breast tumors for decades, how PDGFB-to-PDGFRβ tumor-stromal signaling mediates breast cancer initiation, progression, and metastasis remains unclear. To test this important research question, we developed a mouse model of mesenchymal-specific PDGFRβ hyper-activation. PDGFRβ mutant mammary glands exhibit increased tertiary side-branching and epithelial proliferation confirming a stromal-specific PDGFRβ effect on neighboring epithelium during normal development. To test the effect of hyper-active mesenchymal PDGFRβ on tumor progression, orthotopic mammary tumor growth was evaluated. Interestingly, while we observed no significant difference in primary tumor growth, the incidence of brain metastases from the orthotopic site was significantly increased in the mutant animals. These findings were confirmed using experimental tail vein metastasis assays where we also observed prominent brain metastases in 50% of the PDGFRβ mutant mice ($n = 5/10$) with no brain lesions seen in controls ($n = 0/19$). In both the orthotopic and tail vein assays, there was no difference in the incidence of lung or liver metastases in the mutant mice suggesting a pro-metastatic function for PDGFRβ in the brain metastatic niche. To rule out dysfunction of the blood brain barrier contributing to the observed metastatic spread, we then intracranially injected mammary tumor cells, and as expected based on our metastasis assay, found that larger tumors formed in the brains of PDGFRβ mutant mice versus controls. To our knowledge, these combined findings are the first example where genetic manipulation of the stroma increases breast cancer associated brain metastases (BCBM). Given that these pre-clinical data suggest that primary breast tumors expressing high PDGFB could preferentially metastasize to the brain, we analyzed PDGFB protein expression in a tissue microarray comprised of HER2-positive and triple negative breast cancer (TNBC) primary tumors (total $n = 425$). While high PDGFB did not correlate with site-independent metastatic recurrence, it was prognostic of brain metastasis, mirroring our mouse data. Evaluation of PDGFB in a small cohort of matched primary breast tumors with associated brain ($n = 5$) and lung metastases ($n = 2$) revealed intense PDGFB staining in 100% of the brain metastases, but only 50% of the lung metastases. These findings further suggest that high primary tumor PDGFB expression defines a subset of breast cancer patients predisposed to brain metastases and that these patients may benefit from therapeutic inhibition of PDGFRβ signaling. To test this pre-clinically, we treated mice harboring intracranial tumors with the PDGFR specific inhibitor crenolanib. Excitingly, crenolanib treatment significantly inhibited the brain tumor burden in these mice. Combined, our findings to date (1) advocate that primary tumor expression of PDGFB is a novel prognostic biomarker for the development of BCBM and (2) support clinical trial evaluation of PDGFR inhibitors for the prevention and treatment of BCBM. Ongoing studies are evaluating how the PDGFRβ-expressing mesenchymal cells within the brain promote a pro-metastatic niche.

Keywords: PDGFRβ, PDGF-B, Tumor microenvironment, Breast cancer.

[#]Authors contributed equally to this work.

Received: November 15, 2018; Revised: November 15, 2018;
Accepted: November 15, 2018

ACKNOWLEDGMENTS

This work was supported by a Pelotonia Graduate Student fellowship to K.A.T., a Pelotonia Postdoctoral fellowship to G.M.S., a Department of Defense Breast Cancer Research Program Postdoctoral Fellowship to G.M.S. (W81XWH-14-1-0040), an NIH PO1 to M.C.O. (CA097189), and an NCI K22 to G.M.S. (K22CA218472-01). Research work was presented at the Cancer Stem Cell Conference (2018), Cleveland, Ohio, USA.