

Perspectives

Targeting PDGF Signaling in Carcinoma-Associated Fibroblasts Controls Cervical Cancer in Mouse Model

Rakesh K. Jain*, Johanna Lahdenranta, Dai Fukumura

Cervical cancer is one of the most prevalent malignancies in women worldwide and is the leading cause of cancer death for women in developing countries [1]. While early detection via the Pap test as well as treatment by surgery and chemoradiotherapy has reduced mortality from this disease, the prognosis is poor if the disease is detected at an advanced stage [2]. Thus new treatment strategies for cervical cancer are needed.

In this issue of *PLoS Medicine*, Kristian Pietras and colleagues, using a mouse model of cervical carcinogenesis, provide compelling evidence that targeting platelet-derived growth factor (PDGF) signaling, primarily in carcinoma-associated fibroblasts (CAFs), can slow the progression of this disease and even impair the growth of invasive carcinomas [3]. By offering preliminary evidence for the presence of PDGF receptors in a limited number of human cervical cancer biopsies, these authors also suggest that the drugs approved by the United States Food and Drug Administration (FDA) that target PDGF signaling, such as imatinib mesylate (Gleevec in the US; Glivec in Europe and Australia, Novartis), be tested in the clinic for this malignancy.

CAFs as Key Players in Cervical Carcinogenesis

The present study builds on previous work by this group and others where targeting PDGF signaling has been based primarily on the presence of PDGF receptors on the pericytes and endothelial cells of tumors. Targeting PDGF receptors on tumor pericytes

Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

Pietras K, Pahler J, Bergers G, Hanahan D (2008) Functions of paracrine PDGF signaling in the proangiogenic tumor stroma revealed by pharmacological targeting. *PLoS Med* 5(1): e19. doi:10.1371/journal.pmed.0050019

Douglas Hanahan and colleagues investigate a paracrine regulatory circuit centered upon PDGF receptor signaling in cancer-associated fibroblasts and pericytes of a mouse model of cervical carcinogenesis.

can destabilize tumor blood vessels, making them more vulnerable to anti-vascular endothelial growth factor (VEGF) therapies [4]. Targeting PDGF receptors on the tumor's endothelial cells can have direct anti-vascular effects [5]. In the new study, Pietras and colleagues offer evidence that targeting PDGF signaling in the carcinoma-associated fibroblasts plays a central role in the tumor response to PDGF receptor (PDGFR) blockade.

Using a previously developed model of cervical carcinogenesis, these authors show that PDGF receptors are primarily present in CAFs (PDGFR α and β) and pericytes (PDGFR β). In contrast, PDGF ligands (most abundantly PDGF-C) are present almost exclusively in cancer cells. They further show that blocking PDGF receptors α and β signaling in the CAFs—using either imatinib (a tyrosine kinase inhibitor) or monoclonal antibodies against these two receptors—can repress expression of fibroblast growth factor (FGF)-2, a potent pro-angiogenic molecule. This in turn can block angiogenesis in these tumors in which endothelial cells express fibroblast growth factor

receptor 1 (FGFR1). They also show that these agents reduce pericyte coverage on tumor blood vessels—as reported previously by a number of laboratories [4,6,7]. Finally, they show that imatinib decreases expression of FGF-7 (keratinocyte growth factor) in CAFs, and propose that this could potentially inhibit growth of FGFR-expressing cervical cancer cells. Putting this evidence together, these authors offer a potential approach to treat cervical cancer by targeting PDGF paracrine signaling between stromal and epithelial cells using imatinib.

Funding: This article was supported in part by National Cancer Institute grants including CA80124 and CA96915. JL is a Robert Black Fellow of the Damon Runyon Cancer Research Foundation. The funders played no role in the decision to submit the article or in its preparation.

Competing Interests: RKJ is a grantee of AstraZeneca and a consultant to AstraZeneca, Dyax, and Pfizer. He has received an honorarium from Roche. JL and DF declare that they have no competing interests.

Citation: Jain RK, Lahdenranta J, Fukumura D (2008) Targeting PDGF signaling in carcinoma-associated fibroblasts controls cervical cancer in mouse model. *PLoS Med* 5(1): e24. doi:10.1371/journal.pmed.0050024

Copyright: © 2008 Jain et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abbreviations: CAF, carcinoma-associated fibroblast; CML, chronic myelogenous leukemia; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GBM, glioblastoma multiforme; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor

Rakesh K. Jain, Johanna Lahdenranta, and Dai Fukumura are in the Edwin L. Steele Laboratory for Tumor Biology, Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, United States of America.

* To whom correspondence should be addressed. E-mail: Jain@steele.mgh.harvard.edu

The Perspectives section is for experts to discuss the clinical practice or public health implications of a published article that is freely available online.

The Complexity of Targeting PDGF Signaling

Originally developed as a bcr-abl kinase inhibitor, imatinib has served as a poster child for targeted therapy. Based on its dramatic effects on chronic myelogenous leukemia (CML), it was approved in 2001 by the FDA for CML and hailed as a “magic bullet” [8]. Later it was shown to be effective against gastrointestinal stromal tumors because of its activity against c-kit and PDGFR α expressed in cancer cells in this disease [9]. However, as a single agent, imatinib has not yet proven efficacious in PDGFR-expressing common solid tumors in any phase II clinical trials. Furthermore, although a small fraction of patients with glioblastoma multiforme (GBM) responded to imatinib, there was no correlation between patient survival and the tumor cell expression of the molecular targets of imatinib [10]. PDGFRs are also expressed on the vascular endothelium of glioblastomas [11]. Thus it is possible that imatinib might have led to a direct anti-vascular effect on these vessels in GBMs in addition to the indirect effect through FGF2 downregulation demonstrated in Pietras and colleagues’ study.

Despite these exciting results, several important issues remain to be solved. The potential benefits of targeting PDGFRs in the tumor stromal cells must be balanced by the adverse effects of imatinib on normal tissues, such as fluid retention, pleural effusions, and ascites formation [12,13]. Furthermore, the loss of pericytes in tumor vessels that results from blocking PDGFRs can

further destabilize tumor vessels and make them more abnormal. This abnormality, in turn, can impair blood flow, cause poor drug delivery when other agents are given concomitantly, and create a hostile microenvironment, characterized by hypoxia and acidosis, which makes tumors more aggressive and resistant to many treatments [14]. Lack of pericyte coverage may also facilitate tumor cell metastasis [15]. Finally, the phenotype of stromal fibroblasts is known to vary from one organ to the next. Thus, blocking PDGF signaling in CAFs might slow the growth of a tumor in its primary site, but might not have a similar effect on tumor metastases in secondary sites. These considerations underscore the complexity of targeting paracrine PDGF signaling between stromal and neoplastic epithelial cells.

These limitations notwithstanding, Pietras and colleagues’ study demonstrates how targeted alteration of CAF functions can lead to both anti-tumorigenic and anti-angiogenic effects, improving the disease outcome. These results offer a foundation for development of new approaches to the treatment of cervical cancer where suppression of PDGF-induced CAF functions in combination with conventional cytotoxic therapy and/or VEGF-dependent anti-angiogenic therapy might prove beneficial. ■

References

1. Ngoma T (2006) World Health Organization cancer priorities in developing countries. *Ann Oncol* 17 (Suppl 8): 9-14.
2. Waggoner SE (2003) Cervical cancer. *Lancet* 361: 2217-2225.
3. Pietras K, Pahler J, Bergers G, Hanahan D (2008) Functions of paracrine PDGF signaling in the proangiogenic tumor stroma revealed by

- pharmacological targeting. *PLoS Med* 5: e19. doi:10.1371/journal.pmed.0050019
4. Bergers G, Song S, Meyer-Morse N, Bergsland E, Hanahan D (2003) Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *J Clin Invest* 111: 1287-1295.
5. Kim SJ, Uehara H, Yazici S, Busby JE, Nakamura T, et al. (2006) Targeting platelet-derived growth factor receptor on endothelial cells of multidrug-resistant prostate cancer. *J Natl Cancer Inst* 98: 783-793.
6. Sennino B, Falcon BL, McCauley D, Le T, McCauley T, et al. (2007) Sequential loss of tumor vessel pericytes and endothelial cells after inhibition of platelet-derived growth factor B by selective aptamer AX102. *Cancer Res* 67: 7358-7367.
7. Song S, Ewald AJ, Stallcup W, Werb Z, Bergers G (2005) PDGFR β + perivascular progenitor cells in tumours regulate pericyte differentiation and vascular survival. *Nature Cell Biol* 7: 870-879.
8. Lemonick MD, Park A (2001 May 28) New hope for cancer. *Time Magazine*. Available: <http://www.time.com/time/magazine/article/0,9171,999978,00.html>. Accessed 20 December 2007.
9. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, et al. (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 347: 472-480.
10. Haberler C, Gelpi E, Marosi C, Rössler K, Birner P, et al. (2006) Immunohistochemical analysis of platelet-derived growth factor receptor- α , - β , c-kit, c-abl, and arg proteins in glioblastoma: possible implications for patient selection for imatinib mesylate therapy. *J Neurooncol* 76: 105-109.
11. Batchelor TT, Sorensen AG, di Tomaso E, Zhang W, Duda DG, et al. (2007) AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* 11: 83-95.
12. Hagendoorn J, Padera TP, Yock TI, Nielsen GP, di Tomaso E, et al. (2006) Platelet-derived growth factor receptor-beta in Gorham’s disease. *Nat Clin Pract Oncol* 3: 693-697.
13. Cohen MH, Williams G, Johnson JR, Duan J, Gobburu J, et al. (2002) Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. *Clin Cancer Res* 8: 935-942.
14. Jain RK (2005) Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 307: 58-62.
15. Xian X, Hakansson J, Stahlberg A, Lindblom P, Betsholtz C, et al. (2006) Pericytes limit tumor cell metastasis. *J Clin Invest* 116: 642-651.