

Viewpoint

Osteopontin: a new role for a familiar actor

Nicholas IF Johnston and Mohamed K El-Tanani

Centre for Cancer Research and Cell Biology, Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK

Corresponding author: Mohamed K El-Tanani, m.el-tanani@qub.ac.uk

Published: 1 December 2008

This article is online at <http://breast-cancer-research.com/content/10/6/306>

© 2008 BioMed Central Ltd

Breast Cancer Research 2008, **10**:306 (doi:10.1186/bcr2199)

Abstract

Our understanding of the events that occur in cancer progression has been enhanced by the use of cell lines *in vitro*. Changes in gene expression, induction of signalling, and cell motility can all be investigated in this setting. However, other aspects of progression can be revealed only *in vivo*, especially the interactions of tumour cells with host cells and organ systems. In one such *in vivo* model, described by McAllister and colleagues, it proved possible to establish a novel function of an already well-characterised protein, osteopontin, adding to its attractiveness as a target in cancer therapy.

Laboratory-based cancer research involves making choices about the experimental approach best suited to address the question at hand. *In vitro* work has provided a vast amount of relevant information with respect to tumour cell-specific processes. For example, it has been possible to define differences between tumours of varying malignancy and to suggest candidate genes responsible for these differences [1]. But such observations are only part of the story: *in vivo* work provides a richer picture of the consequences of presenting transformed cells to living organisms. The tumour microenvironment is an essential element of the 'success' of any cancer, and the ability to disrupt established growth should be a valuable weapon in the treatment of solid tumours. For research to progress beyond basic characterisation of cancer cells, it is necessary to examine the interaction between tumour cells and the host organism.

In a recent paper, McAllister and colleagues [2] described the use of a mouse model to examine the effect of the presence of transformed cells of more than one type and the interaction of these cells with the host organism. Different tumour cell lines were injected into contralateral flanks of nude mice. Cell lines designated as 'instigators' were capable of inducing the growth of other cells – 'responders' – that developed into larger and more viable tumours when instigators were injected at the site opposite to the one at

which Matrigel or non-instigators (cell lines that seemed to have no effect on responders) were injected. The instigators did not affect the responders directly or migrate to responder tumours but instead acted by activating and mobilising specific bone marrow cells (BMCs) that moved to the responder tumour. Furthermore, activated BMCs were able to induce the growth of responding tumours when injected into experimentally naive mice without the injection of instigators. Comparison of the blood plasma of differently treated mice suggested that osteopontin was responsible for this tumour instigation. Instigating cells also increased the frequency of lung metastases formed by circulating non-metastatic cells; inhibition of osteopontin by short hairpin RNA abrogated this effect. It was also demonstrated that the use of instigating cells allowed the propagation of a human colon tumour obtained from a surgical procedure.

The work described in the paper (including the supplemental data) is exciting for many reasons. Osteopontin, a secreted glycoposphoprotein, is known to be pleiotropic; it is capable of inducing 'the hallmarks of cancer' described by Hanahan and Weinberg [3] in breast cancer cells [4]. Osteopontin expression has been observed in many cell lines that are metastatic in nature [5]. However, these are largely examples of an action of osteopontin on cancer cells themselves (with the exception of its role in angiogenesis [6]). The work described in this paper establishes a novel role for osteopontin in recruiting host BMCs to create a sustaining environment for tumour growth, in either a primary tumour or a metastatic setting.

The use of this model will make it possible to screen other molecules; osteopontin may not be the only molecule capable of inducing instigation. Also, the effect of disruption of the movement of BMCs to tumours can be assessed. The use of BMCs expressing green fluorescent protein is particularly valuable as it provides an immediate index of what cells a tumour consists of.

BMC = bone marrow cell.

The work is also exciting because of the questions that remain unanswered. The significance of the specificity of the BMCs activated by osteopontin is unclear. It is noteworthy that PC3 cells (a prostate cancer cell line) forcibly over-expressing osteopontin develop many features of migratory metastatic cells [7] but do not act as instigators in this model. It is concluded that an additional factor, as yet unidentified, is required for instigation. Although this is feasible, it is also the case (but not discussed in the paper) that alternative splicing and post-translational processing can alter the functional range of osteopontin [8-10]. It seems necessary to carry out further work to confirm that the PC3-derived osteopontin is functionally comparable to that produced by other, instigating, cell lines. In addition, activated macrophages can secrete osteopontin that is functional *in vitro* [11]. Together, this observation and the PC3 work described raise interesting questions about the provenance of osteopontin and the specific cell surface participants in osteopontin-mediated processes in cancer.

This paper emphasises the involvement of osteopontin in many aspects of tumour biology and extends our appreciation of its repertoire. It also reinforces the argument that osteopontin is an attractive target for cancer therapy development [12,13]. Suppression of expression, or inhibition of downstream signalling pathways [14], of osteopontin could be a potent method to inhibit tumour growth and check disease progression. It may also be possible to grow clinically derived samples, hitherto difficult to sustain, using osteopontin and so use it as a vehicle in the downfall of cancer, which would be a fitting role.

Competing interests

The authors declare that they have no competing interests.

References

1. Alizadeh AA, Ross DT, Perou CM, van de Rijn M: **Towards a novel classification of human malignancies based on gene expression patterns.** *J Pathol* 2001, **195**:41-52.
2. McAllister SS, Gifford AM, Greiner AL, Kelleher SP, Saelzler MP, Ince TA, Reinhardt F, Harris LN, Hylander BL, Repasky EA, Weinberg RA: **Systemic endocrine instigation of indolent tumor growth requires osteopontin.** *Cell* 2008, **133**:994-1005.
3. Hanahan D, Weinberg RA: **The hallmarks of cancer.** *Cell* 2000, **100**:57-70.
4. Cook AC, Tuck AB, McCarthy S, Turner JG, Irby RB, Bloom GC, Yeatman TJ, Chambers AF: **Osteopontin induces multiple changes in gene expression that reflect the six 'hallmarks of cancer' in a model of breast cancer progression.** *Mol Carcinog* 2005, **43**:225-236.
5. El-Tanani MK: **Role of osteopontin in cellular signaling and metastatic phenotype.** *Front Biosci* 2008, **13**:4276-4284.
6. Rodrigues LR, Teixeira JA, Schmitt FL, Paulsson M, Lindmark-Mansson H: **The role of osteopontin in tumor progression and metastasis in breast cancer.** *Cancer Epidemiol Biomarkers Prev* 2007, **16**:1087-1097.
7. Desai B, Rogers MJ, Chellaiah MA: **Mechanisms of osteopontin and CD44 as metastatic principles in prostate cancer cells.** *Mol Cancer* 2007, **6**:18.
8. Sodek J, Ganss B, McKee MD: **Osteopontin.** *Crit Rev Oral Biol Med* 2000, **11**:279-303.
9. He B, Mirza M, Weber GF: **An osteopontin splice variant induces anchorage independence in human breast cancer cells.** *Oncogene* 2006, **25**:2192-2202.
10. Shinohara ML, Kim HJ, Kim JH, Garcia VA, Cantor H: **Alternative translation of osteopontin generates intracellular and secreted isoforms that mediate distinct biological activities in dendritic cells.** *Proc Natl Acad Sci U S A* 2008, **105**:7235-7239.
11. Cheng J, Huo DH, Kuang DM, Yang J, Zheng L, Zhuang SM: **Human macrophages promote the motility and invasiveness of osteopontin-knockdown tumor cells.** *Cancer Res* 2007, **67**:5141-5147.
12. Tuck AB, Chambers AF, Allan AL: **Osteopontin overexpression in breast cancer: knowledge gained and possible implications for clinical management.** *J Cell Biochem* 2007, **102**:859-868.
13. Johnston NI, Gunasekharan VK, Ravindranath A, O'Connell C, Johnston PG, El-Tanani MK: **Osteopontin as a target for cancer therapy.** *Front Biosci* 2008, **13**:4361-4372.
14. Kurisetty VV, Johnston PG, Johnston N, Erwin P, Crowe P, Fernig DG, Campbell FC, Anderson IP, Rudland PS, El-Tanani MK: **RAN GTPase is an effector of the invasive/metastatic phenotype induced by osteopontin.** *Oncogene* 2008, Sep 15. [Epub ahead of print].