Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Protein deregulation associated with breast cancer metastasis

Ka Kui Chan [a,e], Kyle B. Matchett [a], Paul M. McEnhill [a], El Habib Dakir [a], Mary Frances McMullin [a], Yahia El-Tanani [a], Laurence Patterson [d], Ahmed Faheem [c], Philip S. Rudland [b], Paul A. McCarron [c], Mohamed El-Tanani [d,*]

[a] Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast BT9 7BL, United Kingdom
[b] Institute of Integrative Biology, University of Liverpool, Crown Street, Liverpool L69 7ZB, United Kingdom
[c] School of Pharmacy and Pharmaceutical Sciences, Ulster University, Cromore Road, Coleraine BT52 1SA, United Kingdom
[d] Institute of Cancer Therapeutics, University of Bradford, Bradford, West Yorkshire BD7 1DP, United Kingdom
[e] Department of Pathology, The University of Hong Kong , Hong Kong Special Administrative Region

ARTICLE INFO

Article history:
Received 17 April 2015
Accepted 20 May 2015

Keywords:
Breast cancer metastasis
EMT
TGF-β
Osteopontin
PEA3

ABSTRACT

Breast cancer is one of the most prevalent malignancies worldwide. It consists of a group of tumor cells that have the ability to grow uncontrollably, overcome replicative senescence (tumor progression) and metastasize within the body. Metastases are processes that consist of an array of complex gene dysregulation events. Although these processes are still not fully understood, the dysregulation of a number of key proteins must take place if the tumor cells are to disseminate and metastasize. It is now widely accepted that future effective and innovative treatments of cancer metastasis will have to encompass all the major components of malignant transformation. For this reason, much research is now being carried out into the mechanisms that govern the malignant transformation processes. Recent research has identified key genes involved in the development of metastases, as well as their mechanisms of action. A detailed understanding of the encoded proteins and their interrelationship generates the possibility of developing novel therapeutic approaches. This review will focus on a select group of proteins, often deregulated in breast cancer metastasis, which have shown therapeutic promise, notably, EMT, E-cadherin, Osteopontin, PEA3, Transforming Growth Factor Beta (TGF-β) and Ran.
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1. Introduction

Approximately 10–15% of patients with a breast cancer diagnosis will develop distant metastases within 3 years [1]. Metastasis is initiated when tumor cells detach from the primary site and extravasate into the blood or lymph circulation (Fig. 1). The disseminated tumor cells (DTC) survive in the circulation and then intravasate and colonize new tissues by forming micro-metastases and subsequent macrometastases [2]. Metastatic breast cancer is difficult to treat because, once the tumor cells spread from the original site and become DTCs, they are relatively undetectable and can remain dormant for many years after the primary tumor has been removed. Thus, it is crucial to understand the underlying mechanisms of metastasis in order to improve detection of micrometastases and develop new therapeutic agents to manage the disease. It is still elusive as to how and when these tumor cells disseminate and migrate. Two fundamental models, known as linear progression and parallel progression, have been proposed to account for the systemic progression of a primary tumor [3–6]. In the linear progression model, as the development of the primary tumor progresses, tumor cells acquire an invasive phenotype resulting from alterations in gene expression and multiple genetic and epigenetic perturbations [7]. This resulting phenotype leads to tumor cells becoming DTC, leaving the primary site and migrating to secondary organs [8]. In contrast, the parallel progression model suggests that the metastatic founder cells appear long before the diagnosis of a primary tumor and may progress in parallel at different rates in various organs.

Both models have limitations when applied to different sets of clinical data. It has been observed that the parallel progression model can account for the kinetics of metastases formation. In contrast, the commonly used tumor size (cm), local lymph node spread, distant metastatic spread (TNM) system for tumor classification can, in some instances, be explained using the linear model, particularly in instances where metastasis is associated with increasing tumor size. However, it is less accurate in other

* Corresponding author. Tel.: +44 1274 23536; fax: +44 1274 233234.
E-mail address: M.El-Tanani@bradford.ac.uk (M. El-Tanani).

http://dx.doi.org/10.1016/j.cytogfr.2015.05.002
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Please cite this article in press as: Chan KK, et al. Protein deregulation associated with breast cancer metastasis. Cytokine Growth Factor Rev (2015), http://dx.doi.org/10.1016/j.cytogfr.2015.05.002

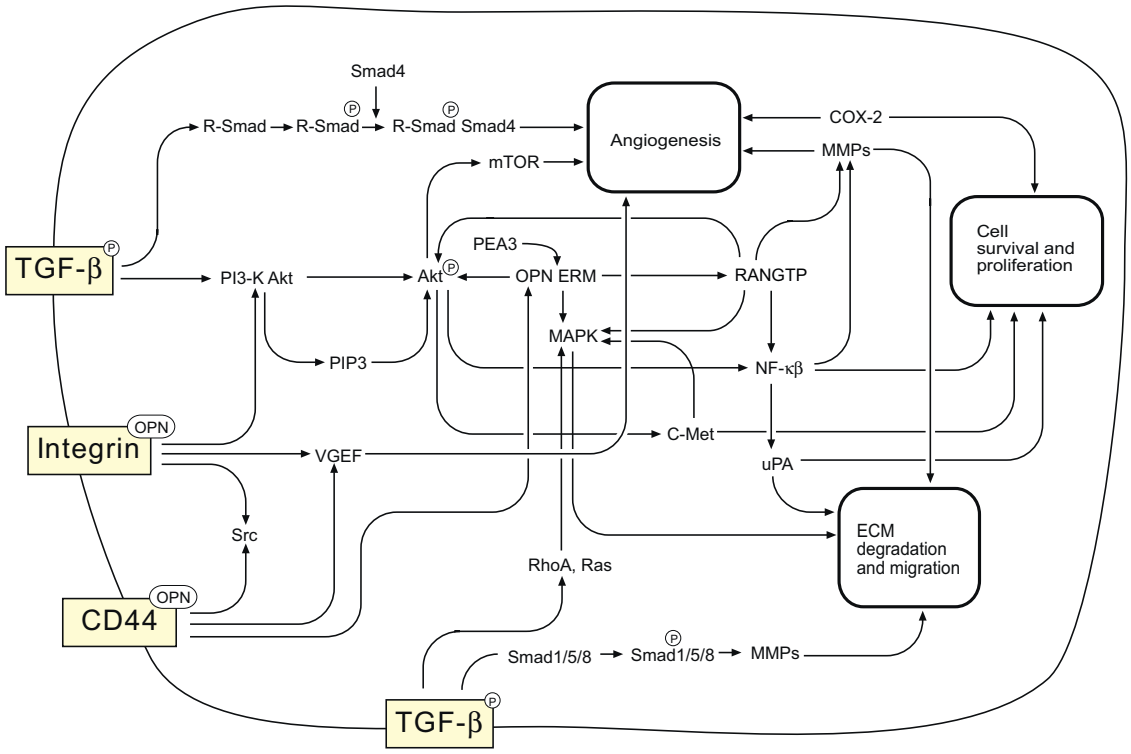

Fig. 1. Integrated networks of TGF- β, osteopontin, integrin and CD44 for cell migration and invasion. OPN has a well described role in promoting metastasis. It can be mediated through interacting with TGF-β, integrin and CD44 and activated downsteam pathways. This includes the PI3 K/Akt, VGEF, C-Met and Ran GTP pathways and induces metastasis. Moreover, Smad and MEK/ERK signaling mediators of TGF-β increases cell survival and angiogenesis.

occasions, such as when the diagnosis of metastasis is at an early stage of tumor development (T1M1) [4]. An integrative and modified model of the mechanisms of metastasis may, therefore, be more useful in developing and selecting specific treatments to generate the best outcome in patients with varying breast cancer subtypes.

Initial infiltration into the tissue environment of the secondary site through penetration of blood vessel endothelium can be driven either by the intrinsic capacities of tumor cells themselves or extrinsic attractant signaling molecules released from the distant organs. The intrinsic capacity may be derived from their original cell lineages or through specific gene expression acquired upon transformation (Fig. 2), which confers the ability to interact with endothelial surface molecules of the target sites. For example, αvβ6 integrin on breast cancer cells interacts with laminin 5 on the basement membrane of lung capillaries as part of an

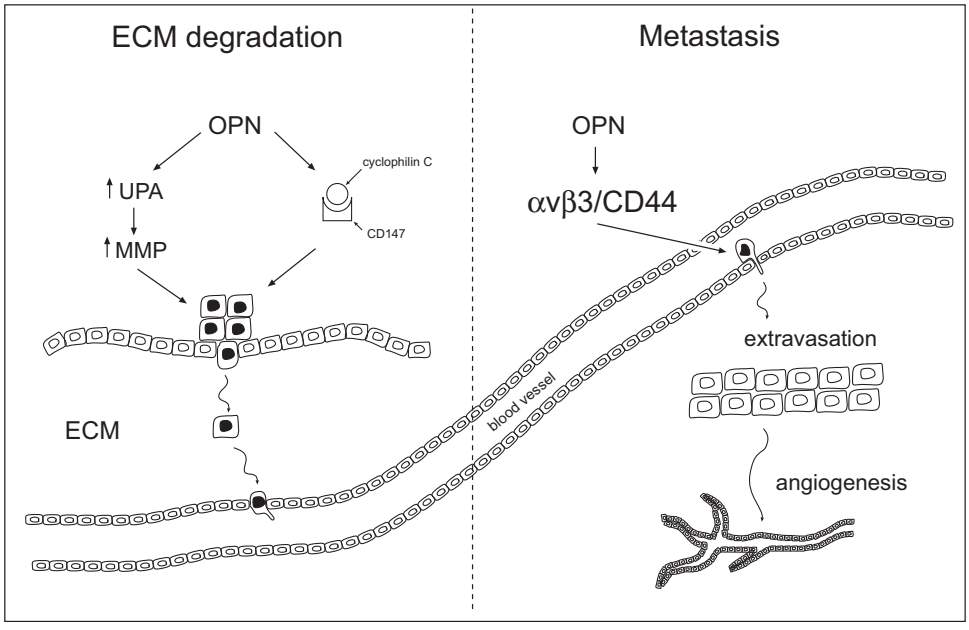

Fig. 2. Role of osteopontin in cancer metastsis. OPN increases the activation of uPA and matrix metalloproteinases (MMPs)-mediates cell motility and invasion into the surrounding tissue. Moreover, the interaction of OPN and αvβ3 integrin and/or CD44-mediates cell migration, adhesion and activated endothelial cells, which are crucial during angiogenesis.

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