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Review

Breast cancer osteomimicry and its role in bone specific metastasis; an integrative, systematic review of preclinical evidence

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ABSTRACT

Metastasis accounts for most of the deaths from breast cancer and the preference of invasive breast cancer metastasising to bone has been widely reported. However, the biological basis of breast cancer osteotropism is not fully understood. This paper provides, for the first time, an integrative, systematic review of evidence of molecular factors that have functional roles in the homing of metastatic breast cancer to the bone.

Pubmed, Web of Science and EBSCOhost were searched using keywords and synonyms for molecular, metastasis, breast cancer and bone to identify articles published between January 2004 and August 2016. 4491 potentially relevant citations were retrieved. 63 articles met the inclusion criteria, which were primary studies reporting evidence of molecular factors that have functional roles in predisposing breast cancer bone metastasis *in vivo*. 12 of those 63 articles that additionally met quality criteria were included in the review. Extracted data were tabulated and key findings that indicated biological mechanisms involved in breast cancer metastasis to bone were synthesised.

15 proteins expressed by breast cancer cells were identified as factors that mediate breast cancer bone metastasis: ICAM-1, cadherin-11, osteoactivin, bone sialoprotein, CCN3, IL-11, CCL2, CITED2, CXCR4, CTGF, OPN, CX_3CR1, TWIST1, adrenomedullin and Enpp1. Upregulation or overexpression of one or more of them by breast cancer cells resulted in increased breast cancer metastasis to bone *in vivo*, except for CCL2 where bone-metastatic cells showed a reduced expression of this factor. All factors identified, here expressed by breast cancer cells, are proteins that are normally expressed in the bone microenvironment and linked to physiologic bone functions. All have a functional role in one of more of the following: cell proliferation and differentiation, bone mineralization and remodelling, cell adhesion and/or chemokine signalling. Six of them (cadherin-11, ICAM-1, OPN, CX_3CR1, CCN3 and osteoactivin) have a reported function in cell adhesion and another eight (CCN3, osteoactivin, Enpp1, IL-11, CTGF, TWIST1, adrenomedullin and CITED2) are reported to be involved in cell proliferation and differentiation.

This review collates and synthesises published evidence to increase our understanding of the biology of breast cancer osteomimicry in the development of bone metastasis. Findings of this review suggest that changes in expression of proteins in breast cancer cells that confer osteomimicry facilitate homing to bone to enable the development of bone metastasis.

Introduction

Paget suggested that cancer cells are more likely to metastasize to a tissue that has the necessary components to support their growth, just as a seed would only grow in soil in which it can thrive [1]. This concept implies that cancer cells migrate to environments that are biologically favourable for colonisation in terms of growth factor production, receptor expression and other stromal characteristics, such as tissue origin. If this 'seed and soil' theory were always true one would expect that cancers in paired organs, like breast and kidney, would commonly metastasise to the contralateral organ. However, clinical evidence indicates that metastases rarely form in a contralateral paired organ. Furthermore, there is a 98% chance that a breast cancer in the contralateral breast is due to a second, unrelated primary tumour [2].

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Ewing proposed, in contrast, that metastatic site specificity was purely mechanical; the first organ that tumour cells passed via blood circulation was the most likely site of metastasis owing to their physical entrapment there [3], as in the example of breast cancer metastases forming in the lungs. However, a large volume of blood from breast tissue also passes through the heart and spleen and breast cancer metastases rarely form in these organs [4]. Evidently, beyond the anatomical exposure to cancer cells, there seems to be a requirement for host-tumour compatibility and specific interaction for metastasis to occur. Hence Paget's theory of related biological factors is, on balance, more favoured [5].

Bone is the commonest and often the earliest site of distant metastasis in breast cancer [6]; 50% of individuals newly diagnosed with advanced breast cancer have bone metastases, compared to 30%, 26% and 7% with liver, lung, brain metastases, respectively [7]. About 70% of women who die from breast cancer have bone metastases [8], which is where the majority of the tumour burden resides at the time of death [2].

Breast cancer metastases characteristically cause osteolytic lesions, though osteoblastic tumours are found in 25% of cases [2]. There is a growing body of evidence that breast cancer cells interact with bone stroma facilitating the process of metastasis [9]. For example, breast cancer cells secrete parathyroid hormone related peptide (PTHrP), which stimulates osteoblasts to produce RANKL. This in turn activates osteoclasts, which create osteolytic lesions, and consequently release growth factors stimulating further growth of the breast cancer cells that produce more PTHrP; hence a vicious cycle of positive feedback develops [9].

Osteoclast resorption of the bone has been described as a key characteristic that creates a favourable environment for tumour growth. During resorption, osteoclasts secrete proteolytic enzymes that degrade the bone matrix and release abundant growth factors, cytokines and chemokines, all of which attract circulating tumour cells and support their growth [10]. Bussard and colleagues [11] suggested that the continuous bone turnover, together with the resultant release of chemotactic and trophic factors, could explain site specificity of bone metastasis in most cancers, including breast cancer. However, despite such metastatic favourability, bone metastases are very rare in some other common solid tumours, such as colorectal cancers [7]. This suggests that beyond the growth promoting environment in bone, a significant level of specific interaction is required between cancer cells and bone tissue for bone metastases to establish successfully.

A systematic search of relevant databases for review papers concerning breast cancer metastasis to bone identified those focussing on the bone as a common site of metastasis for many cancers [11–13] and factors involved in breast cancer metastasis to different host organs [6,14]. One review that specifically evaluated factors involved in breast cancer metastasis to the bone was found [8]; however, no *systematic* reviews were identified. Therefore, herein, for the first time, we report an integrative, systematic review of molecular factors that are shown to have functional roles in homing of metastatic breast cancer to the bone.

Method

Literature search

A systematic search of articles published in English between January 2004 and August 2016 was conducted in the electronic databases Pubmed®, Web of Science™ and EBSCOhost using keywords and synonyms for molecular, metastasis, breast cancer and bone to search 'all terms'. Boolean operators and truncations of keywords were employed to both expand and restrict the search. Search expansion was performed using citation chaining in Web of Science™ and snowballing of reference lists of articles that met inclusion criteria. Using this method only one article published prior 2004 was identified that met the inclusion criteria for this review.

Inclusion and exclusion criteria

Studies that reported *primary* research findings about molecular factors that have a functional role in breast cancer bone metastasis were included in this review. Included studies were also deemed to have been ethically conducted, for example ethical approval was reported in the study, and met defined quality criteria, as follows. Included studies were designed prospectively with a focus on bone as a metastatic site from breast cancer. Studies entirely carried out *in vitro* without *in vivo* testing were excluded in order to ensure that findings included in the review considered the role of the tumour microenvironment. Studies using bone tropic models that specifically demonstrated osteotropic effects of specific gene products were included. This was because the review aimed to identify evidence about gene products that exerted osteotropic effects in breast cancer. The same genes may have additional roles in metastasis, including enabling metastasis to develop in tissues other than bone, but those effects were not the focus of this study, so data about additional putative roles were not extracted as part of this review. Studies that focused on assessing experimental techniques, clinical data, or therapeutic testing were also excluded. The inclusion and exclusion process is depicted in a PRISMA flow chart adapted from Moher et al. [15] (Fig. 1).

Exclusion process

Initially citations were screened by OA at the level of the title and then abstract by OA and VL for relevance using parameters set by the inclusion and exclusion criteria. Citations that met or potentially met inclusion criteria at the level of the title and abstract were obtained in full text for further assessment against the inclusion and exclusion criteria. Potentially relevant sources were independently reviewed in full by OA and VL for internal validity. In addition, full texts of all studies included in the review were assessed by OA and SB for eligibility against the inclusion criteria.

Quality appraisal

Studies obtained in full text that met the inclusion criteria were assessed for quality by OA and SB using a checklist for critiquing scientific research described by Kuyper [16]. Studies were assessed to identify whether the following criteria were appropriate and reliable, and clearly reported: title, study aims, study design and method (e.g. *in vivo*, cell lines, animal model), and reporting of results. Details of the quality appraisal for each included study are shown in Table 1. Authors' conclusions were also appraised to assess whether they reflected the findings of the study and whether any limitations of the study were identified within the publications reviewed. Studies that met the quality criteria described above were included in the review. The strength of evidence presented by the studies was also assessed in order to judge their significance in contributing to the review and thus identify the strengths and limitations of the review (Table 1).

Data extraction

Data were independently extracted and tabulated by OA and SB in order to aggregate, sort, compare and integrate findings [17]. Extracted data were author and publication date; functional factors identified; wild type function of molecular factor(s) (if known);