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Mini-review

The influence of the pre-metastatic niche on breast cancer metastasis

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ABSTRACT

The emergence of metastatic disease constitutes a significant life-threatening development during cancer progression. To date, intensive efforts have been focused on understanding the intrinsic properties that confer malignant potential to cancer cells, as well as the role of the primary tumour microenvironment in promoting cancer metastasis. Beyond events occurring at the primary site, the metastatic cascade is composed of numerous barriers that must be overcome in order for disseminating cancer cells to form distal metastases. The most formidable of these is the ability of cancer cells to seed and grow in a completely foreign microenvironment. Interestingly, solid malignancies often display a particular tropism for specific tissue sites. For example, breast patients with metastatic disease will often develop bone, lung, liver or brain metastases. This mini-review will explore aspects of pre-existing and induced metastatic niches and focus on how the unique composition and function of diverse niche components, within common sites of breast cancer metastasis, enable the survival and growth of disseminated cancer cells. These common supportive functions of the niche are provided by a complex array of stromal components and molecular mechanisms that are, in part, reflective of the tissue in which the metastases arise. Finally, the metastatic niche is a dynamic structure that is continually altered and sculpted by the cancer cells during progression of the metastatic lesion.

Introduction

Our understanding of the molecular events and biological processes that contribute to the initiation, growth and spread of cancer cells continues to expand and deepen with the emergence of more sophisticated technologies and the development of better model systems. The manifestations of intrinsic cancer cell phenotypes, which are driven by complex genomic rearrangements, mutations and epigenetic changes within the tumour cell, are influenced and shaped by cues from the microenvironment. This concept is vitally important in the context of metastatic disease, where disseminated cancer cells must seed a distant organ or tissue. The ability of these cells to adapt to a foreign microenvironment, which is dramatically different from the tissue of origin, and "cultivate the soil" is essential for productive colonization and growth of nascent metastases. In this mini-review, we will discuss recent advances in understanding tumour/stromal interactions at the metastatic site that contribute to cancer metastasis. Our goal is to highlight particularly important concepts regarding pre-existing or cancer-induced features of the metastatic niche that permit the efficient colonization and outgrowth of metastases, with a particular emphasis on breast cancer.

Organotropism in breast cancer metastasis

When breast cancer cells spread from the primary tumour, they exhibit a propensity to metastasize to specific sites such as the bone, lung, liver and brain [1,2]. The developing metastatic microenvironments in these sites are composed of (1) unique resident cell types that are important for the physiological functions of the tissue, (2) extracellular matrix (ECM) components that are deposited and

Abbreviations: ALP, alkaline phosphatase; AXL, Axl receptor tyrosine kinase; Col-I, collagen-I; CSC, cancer stem cell; CTL, cytotoxic T lymphocyte; ECM, extracellular matrix; EPC, endothelial precursor cell; EV, extracellular vesicles; FN, Fibronectin; GAS6, growth arrest-specific 6; HDN, high-density neutrophil; HIF-1α, hypoxia-inducible factor 1α; HPC, haematopoietic progenitor cell; HSC, haematopoietic stem cell; IFN, interferon; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; LDN, low-density neutrophil; MDSC, myeloid-derived suppressor cell; NK, natural killer; OXPHOS, oxidative phosphorylation; PDK1, pyruvate dehydrogenase kinase 1; POSTN, periostin; PTH, parathyroid hormone; SITA, stable isotope tracer analysis; TAM, tumour-associated macrophage; TAN, tumour-associated neutrophil; TGFβ, transforming growth factor β; TNC, tenascin C; TYRO3, Tyro3 receptor tyrosine kinase; VCAN, versican.

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remodelled by diverse cell types within the growing metastatic lesion and (3) infiltrating cell populations (endothelial precursors, immune cells) that can eliminate or assist the metastatic tumour. Collectively, this diversity of cell types and multi-faceted cellular interactions has given rise to the concept of the metastatic niche [3]. This is an exciting and complex field of study in cancer biology. As such, there is a wealth of excellent data and we refer the reader to several recent and exceptional reviews on various aspects of this subject that we cannot discuss due to space limitations [4–7].

The communication between disseminated cancer cells and resident cells in these particular tissues is diverse. This has been most exhaustively studied during the formation of bone metastases, where breast cancer cells that colonize the bone must disrupt the normal physiological coupling between osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells) to favour the emergence of osteolytic metastases [8,9]. Indeed, bone-metastatic breast cancer cells secrete factors that directly induce osteoclastogenesis, or that act indirectly by stimulating the release of osteoclastogenic factors from osteoblasts [10–13]. In contrast, much less is known about the tumour–stromal interactions that support the survival and growth of liver metastases. Evidence suggests that heterotypic interactions between breast cancer cells and hepatocytes can induce E-cadherin expression in tumour cells, leading to enhanced survival in the liver microenvironment [14]. In support of this, liver-metastatic breast cancer cells upregulate Claudin-2 levels, a tight-junctional protein that mediates tumour cell interactions with hepatocytes and is required for the efficient formation of liver metastases [15,16]. Finally, emerging data suggest that astrocyte activation is a common feature of brain metastases, including those derived from breast cancers [17]. Mechanistically, astrocytes induce numerous gene expression changes within tumour cells, including upregulation of genes associated with cell survival [18]. Consistent with these observations, direct contact between breast cancer cells and astrocytes increases chemotherapy resistance in the tumour cells. Moreover, reciprocal interactions between breast cancer cells and astrocytes potentiate the expansion of breast cancer stem cells (CSCs). In this regard, breast cancer-derived IL-1β upregulates JAG1 expression in astrocytes, which in turn activates Notch signalling in breast CSCs to support their renewal [19]. Taken together, these observations indicate the importance of tumour–stromal interactions for the formation of metastases in organ-specific microenvironments.

While cancer cells clearly interact with resident stromal cells at the sites of metastases, there are emerging data to suggest that the metastatic microenvironment can be influenced at very early stages during tumour cell dissemination and can be dramatically shaped by the infiltration of different stromal cell types. This has given rise to the concept of the metastatic niche.

Pre-existing and “induced” metastatic niches

Metastatic niches can be divided into two types, which include pre-existing and induced niches. A pre-existing niche supports a specific physiological function within a tissue, which is co-opted by metastatic cancer cells to enhance their survival in a foreign microenvironment. A prominent example is the endosteal niche within the bone marrow, which normally functions to support haematopoietic stem cells (HSCs), and is exploited by metastatic cancer cells of epithelial origin, such as breast and prostate cancers [20]. The second is an induced or “pre-metastatic niche”, where changes in the expression of extracellular matrix components and mobilization of bone marrow progenitor cells create a conducive microenvironment for seeding and growth of disseminated cancer cells that subsequently arrive at metastatic sites [3].

The endosteal niche supports bone metastasis

The endosteal niche is a specialized structure that lines the inner bone surface [20]. Osteoblasts, which are derived from mesenchymal precursors and function to form new bone, are the principal constituent of the endosteal niche [21,22]. The first experimental evidence that cancer cells compete with HSCs for occupancy of the endosteal niche was provided using prostate cancer cell models [23]. Increasing the number of osteoblast niches, through administration of parathyroid hormone (PTH), increased the number of prostate cancer cells that could be detected in various skeletal sites. Conversely, ablating the endosteal niche, through targeted osteoblast elimination, resulted in fewer prostate cancer cells that seed the bone. These data provided the first evidence that disseminated cancer cells first establish within the privileged site of the endosteal niche [23].

Cancer cells can remain dormant for extended periods of time until the niche is physically disrupted or cancer cells overcome growth restrictions exerted by the niche. For example, in prostate cancer cells, the stoichiometric ratio of two receptor tyrosine kinases, Axl and Tyro3, may control the initial fate of disseminated cancer cells in bone [24]. These receptors compete for the GAS6 ligand, which is secreted by osteoblasts. While GAS6-stimulated activation of Axl signalling in prostate cancer cells favours their quiescence, a subsequent increase in Tyro3 expression on prostate cancer cells favours GAS6-mediated escape from quiescence, leading to Tyro3-dependent tumour cell proliferation and the eventual formation of macroscopic metastases [24]. Thus, the ability of stromal cells within the endosteal niche to prevent or support the growth of macroscopic bone metastases is controlled, in part, by signalling events within the cancer cells themselves (Fig. 1).

This concept has recently been validated in breast cancer models of osteolytic bone metastasis. Indeed, breast cancer cells experience a pre-osteolytic phase (little resorption) in the bone where tumour cells associate with alkaline phosphatase (ALP) and/or collagen-I (Col-I) positive osteoblasts. This period is subsequently followed by an osteolytic phase characterized by the identification of tartrate resistant acid phosphatase (TRAP) positive cells around the growing metastatic lesions [25]. These data support the notion that breast cancer cells initially establish in the endosteal or “osteogenic” niche, supported by osteoblasts, prior to progression to overt osteolytic metastases. In this study, an important role for heterotypic interactions between E-Cadherin expressed on luminal breast cancer cells and N-Cadherin expressed on osteoblasts was associated with enhanced breast cancer cell proliferation [25]. Subsequent activation of AKT/mTORC1 signalling within luminal breast cancer cells, which are in direct contact with osteoblasts, promotes osteoblast-induced breast cancer proliferation and the progression to overt bone metastases. These observations were made with a luminal breast cancer model, and raise the question of how claudin-low breast cancer cells, which lack E-Cadherin, engage the niche. It may be possible that they involve homotypic interactions between N-Cadherin molecules expressed on the breast cancer cells and the osteoblasts. Alternatively, a transient mesenchymal-to-epithelial transition, which increases E-Cadherin levels, may be required for effective occupancy of diverse breast cancer subtypes with constituents of the endosteal niche. However, whether or not one or both of these scenarios govern the bone metastasis potential of claudin-low breast cancers requires experimental validation. Combined, these data reinforce the importance of the endosteal or osteoblastic niche as a “privileged” site within the bone microenvironment, which allows metastatic cancer cells to colonize. We will undoubtedly discover additional examples of existing niches that cancer cells can exploit to enable their spread. Indeed, the concept of the “neural niche” is emerging as an intense area of interest in the study of brain metastases [26,27].

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