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Review Article

The molecular composition of the metastatic niche

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ABSTRACT

In cancer, the microenvironment plays an important role of supporting the outgrowth of new tumors in distant organs i.e. the formation of metastasis. The interplay between cancer cells and the host stroma leads to generation of an active microenvironment termed a metastatic niche that effectively supports cancer progression and outgrowth of metastasis. The generation and development of the niche is intricately linked to cancer progression. Metastatic niches are highly dynamic interactions that can be forged by different mechanisms and continue to develop as the cancer progresses. The composition of the niche is increasingly being characterized and new niche components are being identified. The extracellular matrix (ECM), secreted enzymes, growth factors, cytokines and other molecules that carry information to cancer cells are essential parts of the metastatic niche. The sources of this molecular milieu are multiple cell types – local or recruited to the site of metastasis – and in some cases the cancer cells themselves. To understand metastatic progression it is essential to dissect the niche composition and identify the sources of niche components. With future analyses of the metastatic niche, significant opportunities can arise to identify novel targets for cancer therapy. Targeting the metastatic niche may be essential to treat and inhibit the progression of metastasis.

Contents

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Introduction

Metastasis is the spread of cancer cells from the primary tumor leading to outgrowth in distant organs. Despite being an inefficient process during which most cancer cells are eliminated, metastasis is the cause of most cancer related deaths. Metastatic cancer cells face and conquer great resistance as they enter distant organs. The selective pressure favors intrinsic characteristics induced through genetic and epigenetic means, many of which are already present in the primary tumor [1]. However, increasing evidence supports the notion that signaling cues from the microenvironment are essential for a successful colonization of distant sites [2]. A microenvironment favoring metastatic colonization has been termed as a metastatic niche, similarly to the endogenous stem cell niches that support continued maintenance of stem cells in an adult [3]. The endogenous stem cell niches provide a balanced availability of stem cells throughout the life of the organism and have specific locations within the tissue anatomy. Formation of a metastatic niche provides the cancer cells with functions necessary for their survival and propagation. Importantly, the metastatic niche lacks the structural organization and stability usually seen in endogenous stem cell niches.

The metastatic niche cannot be defined by a single location but is in fact any supportive microenvironment that promotes metastasis initiation. Niches develop as the cancer progresses and new ones may form while old ones perish. Importantly, there are distinct attributes within the metastatic tumor that are strongly linked to the functional state associated with the metastatic niche. These are manifestations like hypoxic pockets, invasive fronts and endothelial structures. In addition, cancer cells can take advantage of molecular components of endogenous stem cell niches suggesting that metastatic- and endogenous-niches may, at least in part, include overlapping components. It is important to identify recurring key components that lead to a niche formation and promote metastasis.

Formation of metastatic niches

Metastatic niches can develop by distinct yet connected biological processes (Fig. 1). These processes include systemic changes mediated by the development of the primary tumor, and others that occur at different stages of the metastatic progression. Moreover, cancer cells may take advantage of specialized microenvironment already existing at the distant site. Studies in animal models suggest that growth factors, cytokines, microvesicles and enzymes secreted by the primary tumor induce changes in distant organs. These changes can lead to extracellular matrix (ECM) remodeling, recruitment of stromal cells as well as changes in blood and lymphatic vasculature and have collectively been termed as a pre-metastatic niche [3]. The modified stroma involves mobilization of bone marrow-derived cells (BMDCs), stromal increase in fibronectin, matrix metalloproteinases (MMPs) and other enzymes leading to remodeling of the ECM and retention of BMDCs at distant organs [4]. Together, these attributes promote cancer cell adhesion and invasion favoring metastatic colonization.

In addition to actively modifying the stroma, cancer cells have been reported to take advantage of endogenous tissue anatomy like stem cell niches or endothelium to promote their own propagation. In prostate cancer metastasis to bone, cancer cells were shown to have affinity to the osteoblastic niche of hematopoietic stem cells (HSCs), likely through CXCL12-CXCR4 axis and competing for niche interaction [5]. The primary role of osteoblastic niches is to provide HSCs with the necessary factors to support long-term maintenance of stemness. Within stem cell niches, pathways are activated that play a major role in cancer cell propagation. These are stem/progenitor pathways like the Wnt, Notch, TGFβ, Hedgehog, phosphoinositide 3-kinase (PI3K) and JAK-STAT pathways [6]. Because of this overlap, cancer cells may benefit significantly from occupying endogenous stem cell niches. However, whether cancer cells colonize stem cell niches other than the bone marrow niche has not yet been determined and needs further studies.

Endothelial cells are receiving an increased attention as active participants in the crosstalk between cancer cells and stroma. The function of endothelial vasculature is considerably beyond their structural role to deliver oxygen and nutrients to tissues. A well characterized example of this type of interaction is the role of endothelial cells as components of the perivascular niche in gliomas of the brain where they promote viability and maintain self-renewal ability of cancer stem cells. [7]. Other examples further suggest importance for these interactions. Endothelial cells secrete interleukin and growth factors that promote survival mechanisms in squamous cell carcinoma cultures through STAT3, MAPK and PI3K pathways [8]. Moreover, in a recent study on colorectal cancer, endothelial cells were shown to promote cancer stem cell phenotype by inducing the Notch pathway [9]. Although the current functional evidence for the endothelial niche in cancer is mainly derived from studies on the primary tumor, there are indications suggesting that these mechanisms might also apply to metastasis. In xenograft mouse models for melanoma and breast cancer metastasis to brain, cancer cells were shown to maintain contact and co-opt the vessels post extravasation and this endothelial proximity was sustained and played a significant role during metastatic outgrowth [10,11]. Moreover, endothelial cells have been shown to be required for breast cancer metastasis to lung where the microRNA-126 inhibited recruitment of endothelial cells and prevented experimental metastasis in mice [12]. Evidence is starting to emerge for the significance of endothelial cells to metastasis, however, the mechanistic role still remains poorly defined.

Taking advantage of endogenous stem cell niches or endothelium might play an important role for metastasis initiation. However, through the progression of the disease, new microenvironmental processes are frequently produced such as invasive fronts and hypoxic regions. The invasive front is an actively moving intersection between the tumor and the adjacent stroma [13]. This front is often a highly vascularized part of the tumor and rich in stromal macrophages and myofibroblasts where significant interaction occurs between cancer cells and stromal cells [2]. At the invasive front, cancer cells are known to change significantly their phenotype

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