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Review

The secreted factors responsible for pre-metastatic niche formation: Old sayings and new thoughts

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ABSTRACT

Metastasis is a multistep process that requires acquisition of malignant cell phenotypes which allow tumor cells to escape from the primary tumor site. Each of the steps during metastatic progression involves co-evolution of the tumor and its microenvironment. Although tumor cells are the driving force of metastasis, new findings suggest that the host cells within the tumor microenvironment play a key role in influencing metastatic behavior. Many of these contributing cells are derived from the bone marrow; in particular, recruited bone marrow progenitor cells generate the "pre-metastatic niche" to which the tumor cells metastasize. Analysis of the molecular mechanisms involved in pre-metastatic niche formation has revealed that secreted soluble factors are key players in bone marrow cell mobilization during metastasis. In addition, membrane vesicles derived from both tumor and host cells have recently been recognized as new candidates with important roles in the promotion of tumor growth and metastasis. This review describes old ideas and presents new insights into the role of tumor and bone marrow-derived microvesicles and exosomes in pre-metastatic niche formation and metastasis.

1. Influence of the tumor microenvironment in metastasis

Cancer is the second leading cause of mortality, surpassed only by cardiovascular disease (CVD). As in CVD, it is now increasingly clear that cancer-related death is not due to a sudden spontaneous onset of catastrophic events, but rather a progressive series of increasingly irreversible changes that occur sequentially over a period of time. While in CVD these changes can be related to the development and progression of atherosclerotic plaque formation, cancer patient survival is not always directly correlated with the growth of the primary tumor. Patients most often succumb not to the primary tumor, but to the systemic fallout from its metastatic deposits. Previously, most cancer research had focused on primary tumors; as a result, primary tumor growth has been far better characterized than the metastatic microenvironment. However, there is constant active interaction between tumor cells and the surrounding nonmalignant cells and extracellular matrix. Indeed, the tumor microenvironment has been found to have an active role in the regulation of malignant cell behavior [1]. During tumor progression, bone marrow derived cells (BMDCs) have been shown to promote inappropriate growth, invasion and ultimately metastasis [1]. The molecular mechanisms underlying this process appear to involve secretion of specific molecules by the tumor cells to facilitate evasion from detection by the immune system. In fact, metastasis has been elegantly described as a process of selection whereby metastatic cells are challenged to acquire a specific and aggressive phenotype [2]. Indeed, it appears that this process of selection not only affects primary tumor cells but also influences the tumor microenvironment to create favorable conditions for metastasis to occur. Primary tumor-derived factors impact the cells in the tumor microenvironment; therefore, it is likely that during tumor progression there is a selection of specific phenotypes in cells composing the tumor microenvironment that co-evolves with the primary tumor. In this review we will focus on ways in which tumor cells influence BMDC behavior during metastasis by analyzing the main factors involved in this process, including soluble secreted molecules and shed microvesicles as potential new effectors of metastasis.

2. The pre-metastatic niche: laying the fertile soil

The growing field of metastasis research has been fostered by the early observation, in 1889 by Stephen Paget that mechan-

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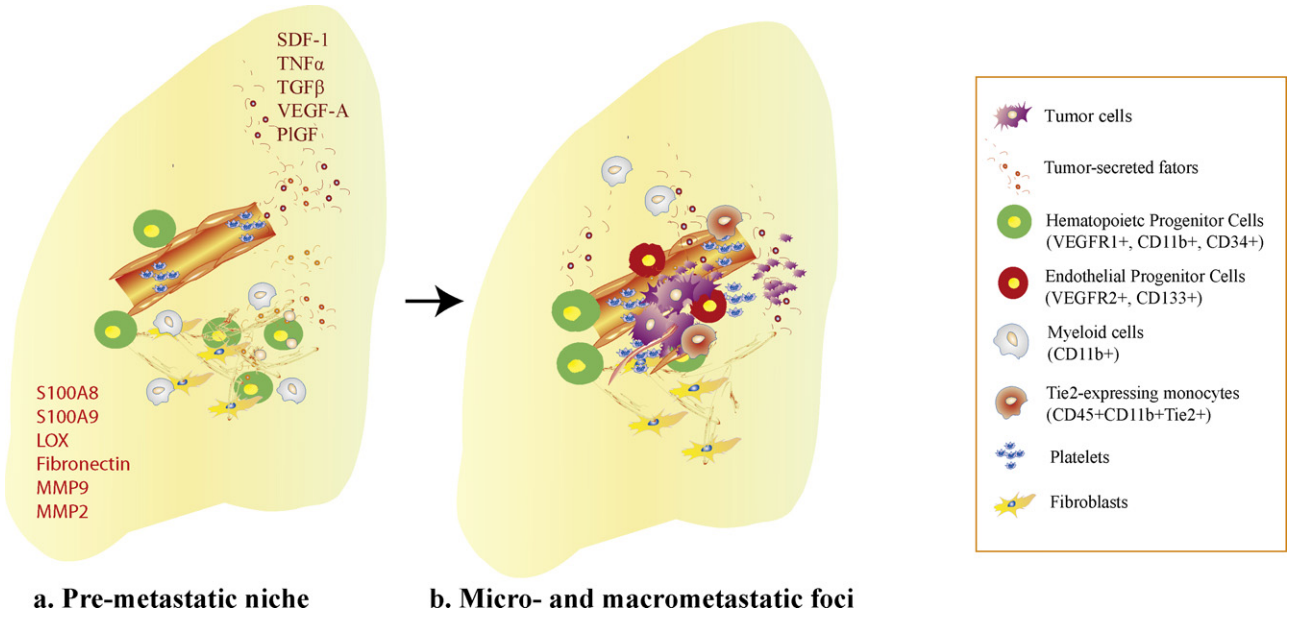

Fig. 1. Main secreted factors and cell populations involved in pre-metastatic niche formation and metastasis. (a) Tumor-secreted factors such as SDF-1, TNF-α, TGF-β, VEGF-A, and PlGF have been found to influence the recruitment of different cell types to pre-metastatic sites upregulating the expression of specific molecules in the niche like S100A8, S100A9, LOX, fibronectin, MMP9, MMP2. These molecules promote the recruitment of specific bone marrow-derived cells involved in pre-metastatic niche formation such as Hematopoietic Progenitor Cells (VEGFR1+, CD11b+, CD34+) and myeloid cells (CD11b+). Fibroblast and Platelets probably also contribute to pre-metastatic niche formation by secretion of pro-angiogenic and extracellular matrix-remodeling factors. (b) The formation of micro- and macrometastatic foci in later stages of metastatic disease involves the recruitment of Endothelial Progenitor Cells (VEGFR2+, CD133+) and Tie2+ monocytes (TEM) influencing a pro-angiogenic microenvironment.

ical forces alone could not account for a tumor's metastatic dissemination [3]. While the primary tumor clearly thrives and depends on the host's vascular supply and drainage, these factors by themselves do not account for a widely varied pattern of tumor metastasis that is seen in solid tumors. Seminal work by Fidler showed that, while circulating cancer cells are found in the vasculature of multiple organs, those cells do not give rise to metastatic disease, while other selective sites consistently develop metastatic tumor deposits [4]. Indeed, these results are consistent with clinical findings in cancer patients, which show that solid tumors have a propensity to home preferentially to distinct organs, as is seen in metastasis of melanoma to the lung and brain [5].

Just as certain plants and life forms thrive exclusively in distinct ecosystems that are favorable to their survival, so do the primary cancer's metastatic seeds. While mechanical forces are employed in the delivery of tumor cells to secondary sites, the successful engraftment and growth to a clinically relevant metastatic deposit is dependent on a receptive microenvironment [6]. Indeed, recent findings provide evidence that this distant microenvironment is primed and ready prior to the arrival of cancer cells, thereby creating a "landing dock" for future metastatic growth. In the setting of a primary melanoma, the lung microenvironment becomes a hotbed of local molecular activity, a concept referred to by Lyden and colleagues as the pre-metastatic niche [7,8]. In elucidating the process of pre-metastatic niche formation, recent findings have shown that it occurs as a temporal sequence of events, predating the influx of tumor cells, and effectually priming the target site of disease for the arrival, engraftment, and survival of incoming metastatic deposits. Importantly, the existence of the pre-metastatic niche implies that metastasis to a particular organ – the lung in this model – is not a random occurrence, but rather a predetermined event, with the cancer cell leaving its primary tumor setting having its target destination already defined.

In defining the pre-metastatic niche through its temporal and functional relationship to metastasis, Kaplan et al. demonstrated that bone marrow-derived hematopoietic progenitor cells (BMDCs) expressing the vascular endothelial growth factor receptor 1 (VEGFR-1) precede the arrival of even single metastatic tumor cells and macrometastatic disease at distant sites (Fig. 1a) [9]. These cells retained their progenitor status (as defined by expression of CD133, CD34, c-Kit), and expressed VLA-4 (also known as integrin α4β1), while tumor specific growth factors upregulated fibronectin, a VLA-4 ligand, at distant pre-metastatic sites. These events resulted in formation of a permissive niche for incoming tumor cells, and these observations provided the first evidence that non-neoplastic cells can bookmark a future site of metastasis. Furthering this hypothesis, and building on their previous findings that metastasis was increased by MMP9 induction in the pre-metastatic lung by endothelial cells and macrophages [10], Hiratsuka et al. demonstrated that secretion of VEGF-A, TNFα, and TGFβ by the primary tumor induces expression of the inflammatory chemoattractants S100A8 and S100A9, which in turn attracts CD11b+ (Mac 1+) myeloid cells to the pre-metastatic milieu [11]. Moreover, S100A8 and S100A9 were found to induce serum amyloid A (SAA) 3 in the pre-metastatic lung, which stimulated NFκB signaling via Toll-like receptor 4 (TLR) 4. This resulted in accumulation of CD11b+ myeloid cells and propagated a positive feedback loop for further chemoattractant secretion, all of which led to enhanced metastasis in the lung [12]. S100A9 is considered a marker of poor prognosis in patients with cancer [13].

S100A8 and S100A9 also induce inflammation-related pathways in the tumor microenvironment. In fact recently, inflammation has been considered as one of the potential driving forces for pre-metastatic niche formation by these two proteins [14]. Although inflammatory cytokines such as IL-1, TNF-α, and IL-6 secreted by bone marrow cells increase lung metastasis [15,16], secreted factors from the tumor (such as VEGF, TNF-α and TGF-β) also help generate a suitable microenvironment for metastasis and attract BMDCs [11,12]. Thus, S100A8 and S100A9 could be considered as key molecules playing important roles at multiple stages of the metastatic process.

More recently, Erler and colleagues uncovered an important role for lysyl oxidase (LOX) in the formation of the pre-metastatic niche.