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Perspective Article

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Overview of metastasis and metastases

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The metastatic process

Metastasis is defined as the formation of progressively growing secondary tumor foci at sites discontinuous from the primary lesion[1]. The metastatic process is not a simple process, but rather a complex cascade composed of many steps. The metastatic cascade requires that tumor cells first detach from the primary tumor, invade through extracellular matrix, intravasate into the bloodstream, migrate to the target site, attach to target endothelium, extravasate and invade into the target tissue, and establish tumor growth including vascularization. As each of these steps is required for metastases to develop, inhibition of any one step should inhibit metastases from developing. Tumors of different tissue origins seem to have predispositions to metastasize to different target organs. The mechanism accounting for this tissue selectivity has received much attention in the cancer research field. Perhaps the theory that has received the most support to account for the tissue selectivity of metastases is the "Seed and Soil" hypothesis.

Seed and soil hypothesis

The observation by Dr. Stephen Paget that breast cancer metastasized to specific tissues led him to suggest that metastasis was not a random process but rather that the tumor cells (the "seed") has a specific affinity for the target organs (the "soil"), which provide the appropriate microenvironment for the seed[2]. Experimental evidence for the "Seed and Soil Hypothesis" was provided by the observation that B16 melanoma cells injected into mice metastasized to selective organs[3]. In terms of skeletal metastasis, it has been suggested that growth factors in the bone matrix are released upon osteolysis[4]. These growth factors then promote tumor growth at the site of their release. Although strong formal proof of this hypothesis has not been published, the observations that inhibiting bone remodeling diminishes tumor growth in bone are supportive of this possibility. Regardless of the target organ, the complexity of the metastatic cascade suggests that there are many factors that control the ability of a cancer cell to reach its target site.

Metastasis suppressor genes

It is possible that metastasis can be blocked by inhibiting one gene since inability to complete any step of the metastatic cascade should render a cell non-metastatic[1]. In support of this possibility is evidence that loss-of-function of specific genes, known as metastasis suppressor genes (MSGs), is an important event during the progression toward a malignant phenotype[5-8]. MSGs suppress the formation of overt metastases without affecting the growth rate of the primary tumor[5]. These genes are different from tumor-suppressor genes, which suppress growth of primary tumors. To date, only a handful of metastases suppressor genes have been identified. Furthermore, the mechanisms through which these genes and their protein products suppress metastasis *in vivo* are not well defined and demand extensive investigation due to their importance in cancer pathophysiology. Some may act to prevent the early steps of the metastatic cascade (i.e. initial migration and intravasation); whereas others may act to prevent late steps (i.e., endothelial adhesion, extravasation, angiogenesis).

A variety of MSGs have been identified including: Nm23: The first reported MSG, Nm23 RNA levels were initially described as highest in cells and tumors of relatively low metastatic potential compared to those with high metastatic potential[8]; KAI1: was shown to suppress metastasis when introduced into rat AT6.1 prostate cancer cells[9]. Experimental studies in colon and breast cancer cell lines have shown that KAI1 over-expression is associated with decreased invasiveness and metastatic behavior[10]; MKK4: Mitogen-activated protein kinase kinase 4 (MKK4) suppresses AT6.1 Dunning rat prostate cancer metastases *in vivo*[11]. Furthermore, MKK4 expression is inversely correlated with Gleason pattern[12];

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MKK4 was identified on chromosome 17 as a factor that invoked dormancy in metastases[13]. This finding suggests that MKK4 works on the late steps of metastasis; Maspin: Maspin, a member of the serpin family, is a secreted protein. Maspin has been reported to inhibit the invasiveness and motility of prostate cancer tumor cells and angiogenesis from breast cancer cells[14-16]. Maspin appears to suppress metastasis, in part, through inhibition of urokinase-type plasminogen activator system[17]; BRMS1: breast-cancer metastasis suppressor 1 maps to human chromosome 11q13.1-q13.218. When stably transfected into breast carcinoma and melanoma cell lines, the cells still form progressively growing, locally invasive tumors but are significantly less metastatic[18,19].

Bone metastases

The bone provides a unique environment, compared to soft tissue, for the establishment of metastases. This includes a variety of aspects unique to bone including the sinusoidal characteristics of the marrow; the mineralized matrix in the bone, and the extracellular matrix, which is rich in growth factors. There is emerging evidence that bone metastases establish and thrive in the skeleton due to cross-talk between the bone microenvironment and tumor cells. This cross-talk is mediated by both cell-to-cell contact[20] between cancer and bone cells, as well as soluble factors that mediate effects between these cells[21]. Specifically, bone provides chemotactic factors, adhesion factors, and growth factors that allow the cancer cells to target and proliferate in the skeleton. The cancer cells reciprocate through production of osteoblastic and osteolytic factors that modulate bone remodeling. The cancer-induced osteolysis promotes release of the many growth factors within the bones extracellular matrix thus further enhancing the progression of the metastases and in effect creating a vicious self-perpetuating cycle of bone osteolysis, release of growth factors, and metastatic proliferation[4]. Understanding the signalling mechanism through which cancer and bone cross-talk to foster metastasis may help identify important therapeutic targets. To this end, high-throughput screening methods, such as gene array[22] and tissue microarrays[23] should help facilitate recognition of putative factors important in the promotion of bone metastasis.

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