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Review

Metastasis suppressors and the tumor microenvironment

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ABSTRACT

The most lethal and debilitating attribute of cancer cells is their ability to metastasize. Throughout the process of metastasis, tumor cells interact with other tumor cells, host cells and a variety of molecules. Tumor cells are also faced with a number of insults, such as hemodynamic sheer pressure and immune selection. This brief review explores how metastasis suppressor proteins regulate interactions between tumor cells and the microenvironments in which tumor cells find themselves.

1. Introduction

Metastasis is the process in which neoplastic cells leave the site where a tumor formed, travel to nearby or distant discontiguous sites and proliferate into a macroscopic, clinically relevant mass(es) [1,2]. It has long been recognized that metastasis involves intrinsic (i.e., genetic) as well as extrinsic (i.e., tumor cell–microenvironmental signals) factors. Our objective is to explore the interface between specific genetic changes, specifically of metastasis suppressors, and the regulation by (or response to) the microenvironments with which tumor cells come into contact. Ultimately, the data presented here support the concept that several metastasis suppressors are key intermediaries between environmental signals and tumor cell response to environmental signals.

Over a century ago, Stephen Paget articulated the interactions between tumor cells and as-yet-undefined factors in bodily tissues that determine whether disseminated cells successfully colonize those organs [3]. Abundant data support the so-called Seed-and-Soil hypothesis; however, even in 2011, the molecular underpinnings are still not well characterized [4]. Disseminated tumor cells "seeds" recognize surface molecules in various soils to preferentially adhere there. The ability of cells to successfully grow following dissemination is determined by their ability to respond to growth promoting factors and/or resist growth inhibitors secreted by various tissues or matrix-associated factors [5–8]. Despite not yet knowing all of the detailed molecular interactions, Stephen Paget presented an important insight regarding tumor–host interactions.

It is clear that tumor cell interactions are crucial at every step of the metastatic cascade. Every communication – even between two cells – contributes enormous complexity. Neoplastic cells are dependent upon genetic alterations that distinguish them from their normal counterparts but are also exquisitely sensitive to

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extracellular factors that may, or may not, allow them to metastasize successfully. Tumor cells alter the microenvironment directly (e.g., proteolytic cleavage of the ECM) or indirectly (e.g., induction of nearby cells to secrete proteases). Reciprocally, tumor cells can be impacted by stromal cells (e.g., lymphatic or vascular) at each step in the cascade. Thus, it is important to focus beyond the genetic mutations, deletions or chromosomal translocations found within a tumor cell by recognizing that stromal factors are present and intimately involved in the process. What we learn from these interactions will help to provide insights that may allow development of new therapies targeting metastasis.

This review is based upon a simple tenet—some, if not most, of the genetic changes occurring within cancer cells either manipulate, or are manipulated by, the stimuli from the cells or matrices with which the tumor cells come into contact or the factors secreted by cells throughout a tumor cell's journey. This review is also submitted at a time when the field of metastasis research is evolving from a tumor cell-centric to a more holistic perspective that integrates both the neoplastic cell and the microenvironment. The breadth of the concepts cannot be covered in the space allowed. So, we will focus this review exclusively upon how changes in the expression of a new class of genes, metastasis suppressors, alter tumor microenvironmental changes.

2. Metastasis suppressors

Metastasis suppressors are defined as molecules whose expression results in the inhibition of a neoplastic cell's ability to metastasize while having little effect on primary tumor growth (reviewed in [1]). This family of molecules was first described in 1986, with the discovery of *Nm23*. Since then, more than thirty metastasis suppressors have been identified based upon this functional definition [1]. Still, the mechanisms of action for most are not yet known despite concerted efforts by many laboratories. It is clear, however, that metastasis suppressors are found both within cells and in the extracellular milieu, that their mechanisms of action are diverse, and that each regulates different steps of the metastatic cascade (reviewed in [1]). The metastasis suppressors discussed below are organized by cellular localization and functional class (Table 1).

2.1. Cell surface adhesion molecules and receptors

2.1.1. E- and N-cadherins

Epithelial cell–cell interactions are mediated by cadherins, transmembrane glycoproteins that form Ca^{+2}-dependent homotypic complexes [9]. In many tumor types, E-cadherin loss occurs during epithelial-to-mesenchymal transition (EMT, reviewed in [10–12]), which correlates with invasion and metastasis. Collectively, loss of E-cadherin is thought to be causative for invasion. E-cadherin expression can be regulated at transcriptional and post-transcriptional levels. In particular, the zinc finger transcriptional repressors Snail and Slug have been implicated in repressing E-cadherin transcription. Cadherins are regulated by catenins (α, β, γ, and p120 catenins), cytoplasmic proteins that functionally link cadherin complexes to cytoskeleton. β-Catenin is both a cell adhesion protein and a transcription factor.

Another putative metastasis suppressor is N-cadherin which, when ectopically expressed in an osteosarcoma line, inhibits pulmonary metastasis [13]. However, contradictory data showing that N-cadherin increases aggressiveness and metastasis in breast and melanoma cell lines raise questions regarding calling it a metastasis suppressor [14,15].

As cells growing in an epithelial layer decrease cohesion, they often produce cellular protrusions through reorganization of the cytoskeleton and plasma membrane that form new contacts with the surrounding microenvironment [1,2,34]. These new adhesive contacts promote migration through ECM. These observations also contribute to the conclusion that cancer cells, as they progress, become more autonomous and less reliant upon other cells and specific matrix interactions for survival signals.

It is important to emphasize, however, that EMT is not required for invasion or metastasis. Many carcinomas migrate as clusters of cells, suggesting that they have maintained vestigial epithelial-epithelial interactions (perhaps, though not directly tested to our knowledge, maintaining N- or E-cadherin expression). The EMT-based motility emphasizes migration of individual cells in a manner dependent upon proteolysis; whereas, individual cell movement independent upon proteases – the so-called epithelial-amoeboid transition – is becoming increasingly recognized [16].

Clearly, more work is required to define how cadherins play a role in metastasis suppression. Nonetheless, it is clear that different cadherins will play distinct roles in different tissues. This highlights an emerging theme in the metastasis suppressor field – context is critical.

2.1.2. KAI1

Kang-Ai1 (Chinese for anti-cancer; also known as CD82/C33/TIP30) was first identified in rat Dunning prostate cancer cells [17]. As for many of the metastasis suppressors, evidence for their existence was suggested by non-random losses of chromosomal material in late-stage cancers. For KAI1, human chromosome 11 was introduced into the metastatic prostate variants by microcell-mediated chromosomal transfer (MMCT). Chromosome 11-containing hybrids were significantly suppressed for metastasis without preventing primary tumor formation. Positional cloning identified KAI1 at band 11p11.2 [17–19]. Following demonstration that KAI1 inhibited metastasis of prostate cancer cell lines, it was also shown to suppress metastasis in breast and melanoma cells [20,21]. Consistent with its role as a metastasis suppressor, KAI1 expression is frequently down-regulated during progression of multiple tumor types, including prostate [17], breast [22,23], colorectal [24], ovarian [25], cervical/endometrial [26,27], oral [28] and non-small cell lung [29].

Tetraspanins, including KAI1, interact with other signaling molecules. KAI1 interacts with other tetraspanins, immunoglobulins, integrins and histocompatibility molecules, including the epidermal growth factor receptor which instigates EGFR endocytosis and migration signals. However, the most convincing studies regarding a mechanism of action for KAI1 came from the laboratory of Watabe and colleagues.

KAI1 directly interacts with DARC (Duffy antigen receptor for chemokines/gp-FY) on vascular endothelial cell surfaces to induce tumor cell senescence [30] when cells have intravasated. The story remains incomplete because senescence has been shown to occur even in the absence of KAI1-dependent activation of DARC signaling [31]. Collectively, their model proposes that KAI1-expressing cancer cells grow and invade locally, but upon intravasation and interaction with DARC-expressing endothelial cells, the tumor cells cannot complete subsequent steps in the metastatic cascade. Interestingly, KAI1-expressing melanoma cells injected into DARC knockout mice developed significantly more lung metastasis than in wildtype mice [30]. Thus, KAI1::DARC interaction-dependent metastasis regulation is controlled by the physiological balance of communication between the two molecules.

2.1.3. KISS1R

Although discussed in more detail below in the context of secreted metastasis suppressors, the KISS1 receptor (KISS1R, also known in the literature as GPR54, AXOR12, hOT7T175) appears to be involved in metastasis suppression in some tumor cells. KISS1R