A New Member of the Growing Family of Metastasis Suppressors Identified in Prostate Cancer

Danny R. Welch, Kent W. Hunter

The molecular understanding of cancer metastasis has taken yet another step forward with findings published in this issue of the Journal by Fu et al. (1). The authors report that restoration of Raf kinase inhibitor protein (RKIP) expression is associated with the inhibition of prostate carcinoma metastasis but not with the suppression of tumorigenicity. In addition, the authors report an inverse association between RKIP expression and both the stage of disease and Gleason score. These properties epitomize metastasis suppressor genes, a recently described category of molecules defined by their ability to suppress metastasis without blocking tumorigenicity (2). RKIP is the thirteenth metastasis suppressor described in the literature for which functional data exist (the others are Nm23, KISS1, KAI1, BRMS1, TIMPs, E-cadherin, M KK4, TXNIP, CRSP3, DRG-1, SSeCKs, and RhoGDI2). Several recent reviews summarize what is known regarding the mechanisms of action of metastasis suppressors and the clinical and experimental data supporting their classification as metastasis suppressors (3–5). Additional molecules whose expression is associated with cancer progression but for which functional data are not yet published have also been described [reviewed in (4)], suggesting that the number of metastasis suppressors is likely to grow.

Metastases are discontinuous secondary cancer colonies that arise when cells dissociate from a primary tumor and are transported elsewhere in the body. The route of transport can be via the vasculature, the lymphatics, or within body cavities. Cancer cells must not only reach secondary sites, they must also proliferate after they get there. The entire process of metastasis is extremely inefficient (6,7). Between 1 and 4 million cancer cells are shed into the vasculature daily (8); fortunately, the vast majority never become macroscopic, physiology-affecting lesions (9). This fact highlights the distinction between mere local invasion and metastasis.

Single tumor cells or microscopic colonies of neoplastic cells can reside at secondary sites for extended periods (sometimes years) or until conditions become favorable for proliferation (10–13). Although the potential exists for disseminated tumor cells to convert to a proliferating mass, clinical and experimental data clearly show that most do not. There are a variety of reasons for this failure to convert from a dormant to a proliferative state. Among them are the balance between proliferation signals (such as those transduced by mitogen-activated protein/extracellular signal-regulated kinase [MEK] and [ERK]) and inhibition signals (such as those transduced by p38), as recently shown in an elegant series of experiments by Aguirre-Ghiso et al. (14) regarding the formation of macroscopic metastasis by head and neck carcinoma cells. Interestingly, MEK and ERK are in the same pro-metastatic pathway inhibited by RKIP. Analogous scenarios are likely to exist in other cell types and in different tissues.

Every step of the metastatic cascade is rate-limiting and depends on the cell type, the organ of origin, and the tissue of colonization (15). Examples of genes that are associated with the blockage of virtually every step of the metastatic cascade have been described [reviewed in (3–5)]. In the prostate cancer cell lines examined by Fu et al. (1), RKIP expression was associated with the suppression of invasion and angiogenesis. The authors concluded that diminished angiogenesis may not be the critical step controlling metastasis because primary tumors still grew (i.e., they must have recruited a neovasculature). However, it has yet to be firmly established that angiogenic mechanisms at primary and secondary sites are equivalent. In that respect, RKIP is like other metastasis suppressors in that its definitive mechanism of action is not yet known.

RKIP’s role as a metastasis suppressor is consistent with previously published data showing an association between Ras-induced oncogenic transformation and induction of the metastatic phenotype (16). Several Ras-induced proteins, including osteopontin (17) and MEK1 (18,19), have the ability to transform fibroblasts and induce metastatic capability. Therefore, it is not too surprising that RKIP, an inhibitor of the Ras/Raf/MEK/ERK pathway, would inhibit metastasis. Precisely which branch points in the pathway are critical for controlling metastasis remains elusive. Importantly, the article by Fu et al. (1) supports the notion that signaling pathways upstream of Ras are valid therapeutic targets for controlling metastasis. Because metastasis is, by far, the most lethal attribute of tumor cells, specific interventions to prevent tumor spread have a high probability of improving cancer patient survival and quality of life.

What does the existence of metastasis suppressors—and what

Affiliations of authors: D. R. Welch, Department of Pathology and Comprehensive Cancer Center, The University of Alabama at Birmingham; K. W. Hunter, Laboratory of Population Genetics, Center for Cancer Research, National Cancer Institute, Bethesda, MD. Correspondence to: Danny R. Welch, Ph.D., Department of Pathology, The University of Alabama at Birmingham, 1670 University Blvd., Volker Hall G-038, Birmingham, AL 35294–0019 (e-mail: dwelch@path.uab.edu). See “Notes” following “References.”

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is known about the step(s) of the metastatic cascade that they inhibit—tell us about the metastatic phenotype? First, cumulative data suggest that the process of metastasis requires traits superimposed upon those required for a cell to become a tumor. To successfully colonize different tissues, metastatic cells must coordinately regulate subsets of genes when those cells are in at least three different environments: in the local tumor, in transit, and at the secondary site. Tumor cell response to exogenous signals at each site could ultimately explain the century-old observation that metastases do not develop randomly (20). For example, the distribution of cancer cells from a primary tumor is nonrandom (i.e., cells move from efferent, not afferent, vessels or lymphatics). Adhesion of neoplastic cells at secondary sites is nonrandom [i.e., they arrest in the first capillary beds encountered (6,7) or they recognize tissue-specific addresses expressed on the surface of endothelial cells (21–26)]. Survival in the circulation is cell-dependent, as is the capacity to extravasate (27–29). And finally, tumor cells have different abilities to respond to tissue-derived chemotactic factors (30,31), growth factors, and growth-inhibitory factors (32,33). Together, these observations point to the existence of genes that determine which environments are suitable for metastatic cell survival and proliferation. A surprising number of the known metastasis suppressor genes block the last step of the metastatic cascade—colonization of the secondary site [reviewed in (3–5)].

Second, when metastasis suppressor proteins are arranged into “pathways” on the basis of their known or implied functions, it is apparent that metastasis is controlled at many levels within a cell and that the metastatic cascade has multiple rate-limiting steps (3–5). Metastasis suppressors are generally positioned within cells such that their functions serve to amplify signals, a situation that is necessary for controlling complex, multigenic phenotypes like metastasis. Metastasis suppressors exist within all cellular compartments (i.e., they consist of cell surface receptors [e.g., KAII, E-cadherin], intracellular signaling molecules [e.g., MKK4, SSeCKs, Nm23, RhodGD12, DRG-1, RKIP, TXNIP], secreted ligands [e.g., TIMPs, KISS1], and nuclear transcription factors and cofactors [e.g., BRMS1, CRSP3]). We anticipate that, like cell cycle regulation, higher order organization of metastasis regulation will become evident as additional metastasis regulators are discovered and characterized.

Interestingly, many metastasis suppressors function in diverse cell types, i.e., metastasis suppressor genes discovered in one tumor type (e.g., breast) also suppress metastasis of tumor cells of other origins (e.g., melanoma) [see references within (2–4)]. The extent of shared pathways that regulate metastasis in cells of different histiocytic origin will take many years to unravel, and the paucity of metastatic models (i.e., cells that metastasize in vivo) will be a major limitation.

It is encouraging that, for the majority of the metastasis suppressors that have been tested, expression of the suppressor in patient samples is associated with disease progression [reviewed in (3–5)]. The associations are generally found in small datasets and are imperfect but, collectively, they support the notion that metastasis suppressors may be independent prognostic markers. Although it is not yet known how, or whether, metastasis suppressors will play a role in predicting the propensity of tumor cells to metastasize in clinical cancer, information gained by understanding their mechanisms of action is providing insight into the fundamental mechanisms that control the spread of cancer.

The existence of genes that specifically control metastasis has been questioned (34,35). Yet functional data strongly argue that there are specific genes that control metastasis. Moreover, mouse breeding strategies have suggested the existence of metastasis efficiency genes (36–38). For example, crossing transgenic mice that express the polyoma virus middle-T protein under control of the mouse mammary tumor virus promoter (i.e., MMTV-PyMT mice) with mice of varying genetic backgrounds resulted in statistically significant differences in metastasis without altered tumor initiation or mammary tumor growth kinetics, depending on which mouse strain the MMTV-PyMT mice were crossed with. Furthermore, gene expression (observed using mRNA microarrays) varied between cancer populations. Because all tumors were initiated by the same oncogenic event (i.e., expression of MMTV-PyMT), differences in metastatic potential and gene expression in different mice are most likely due to genetic background. The data reinforce the importance of gene context in determining metastatic potential.

Changes in gene expression that are based on the location of cells within different tissues highlight another observation related to the mechanisms responsible for loss of metastasis suppressor gene expression: Anecdotal and published data suggest that many metastasis suppressor genes are not mutated but, instead, are differentially expressed [reviewed in (39)] at the protein translational level (40,41), or by mechanisms that involve gene methylation (42,43), histone acetylation (43–46), and mRNA or protein stability (47,48).

Thus, the growing numbers of metastasis suppressor genes represent new targets for cancer control. The fact that some of the known metastasis suppressors can now be arranged into pathways, in the same way that RKIP is involved in the Ras/Raf/MAPK cascade, signals a major step toward controlling the most deadly attribute of cancer cells.

REFERENCES


NOTES

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