What Defines a Useful Marker of Metastasis in Human Cancer?

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In this issue of the Journal, O’Connell et al. (1) describe the identification of a region on the long arm of chromosome 14 that is apparently involved in the progression of breast cancer toward metastasis. Measuring loss of heterozygosity, the investigators found that the majority of lymph node-negative breast tumors did not amplify a region linked to D14S62 and D14S51, while lymph node-positive breast tumors retained heterozygosity for these same markers. These data could imply the existence of a metastasis-promoting gene. Alternatively, the observed molecular changes may be a marker of metastatic propensity.

Since metastasis is the most lethal attribute of a cancer, it is critical that tumors be diagnosed while still localized to achieve the highest probability of long-term survival and quality of life. In the absence of objective evidence that metastases do not exist, earlier diagnosis would accomplish three things: 1) increase the probability of diagnosis prior to spread, 2) decrease total tumor burden so that less therapy is required, and 3) decrease the likelihood of therapy-resistant tumor cell populations.

Detection of cancer has improved appreciably in recent years. However, there is still a critical need for markers that unambiguously distinguish weakly metastatic from highly metastatic lesions. This concept is underscored by the example of malignant melanoma where there is a direct relationship between primary lesion thickness and the likelihood of metastasis (2). For lesions that are overtly thin or thick, planning treatment is easy. However, for lesions of intermediate thickness, the decision is not straightforward. The subjectivity of the current grading criteria is demonstrated by the greater than 50% discordance in the diagnosis and staging of melanomas, even between preeminent dermatopathologists (3).

Choosing useful markers of metastasis requires a better understanding of the metastatic process (Fig. 1) and of how it is distinct from tumorigenicity. Tumorigenicity and oncogenicity refer to the ability of cells to proliferate continuously in the absence of the persistent stimulation by a triggering agent. Tumor progression is the evolution of already tumorigenic cells toward increasingly autonomous states (i.e., decreased dependence on host-derived growth factors and/or increased resistance to negative regulatory molecules). The distinction between oncogenesis and tumor progression is critical when one is determining whether a gene is important in controlling steps associated with malignancy or is simply involved in tumor formation [reviewed in (4–6)]. Some of the distinctions between malignant and metastatic are more subtle. Attributes of malignant cells include, but are not limited to, less differentiated morphology/cytology, vascular density, necrosis, high mitotic index, aneuploidy, and high nuclear:cytoplasmic ratio (7). The utility of these characteristics as markers is limited by some degree of subjectivity. In the end, the only incontrovertible hallmark of malignancy is the ability to invade through basement membrane and/or to metastasize.

What characteristics define a suitable marker of metastasis? In general, markers fall into two categories. The first category predicts metastatic propensity based on expression and/or activity of a molecule with an established role in metastasis. For example, matrix metalloproteinases would be expected to be more highly expressed in invasive and metastatic tumors than in their nonmetastatic counterparts. The second category includes markers for which there is no established mechanistic association with metastasis. This category includes known genes with potentially novel functions, novel genes, and molecular changes that correlate with metastatic ability. The markers reported by O’Connell et al. fall into this category, as do the vast majority of markers utilized today [reviewed in (8,9)].

Each of these categories can be further divided on the basis of whether the marker is increased or decreased. This criterion impacts the clinical utility of the marker. Assay sensitivity for molecules that are more highly expressed in metastatic primary tumors would be greater than for those expressed at lower levels because of tumor heterogeneity. It is well recognized that the majority of cells within a tumor cannot complete the multistep process of metastasis. Indeed, less than 0.1% of cells entering the bloodstream successfully form clinically detectable lesions (7). By inference, it follows that a similarly small percentage of cells within a primary tumor would display a marker of metastasis. Just as it is easier to see a single lighted candle in a dark room than to find the only unlit candle in a room full of lighted candles, it is easier to identify a single cell expressing a new marker against a background of nonexpressing cells than it is to find nonexpressing cells within a mass of cells that express a particular marker. This comparison does not even take into account quantitative differences in expression, which would further complicate the matter. For this reason, identification of metastasis-associated, positive regulators would be preferred by pathologists. Examples of such positive regulators include vascular endothelial growth factor, Ras, Mts1, Mta1, and Tiam1 [reviewed in (5,10)].

From experimental and treatment perspectives, however, identification of suppressors of metastasis offers advantages. To metastasize, cells must complete all steps of the metastatic cascade shown in Fig. 1. If a cell fails to complete any of these steps, it is nonmetastatic. Thus, it takes only one gene to block metastasis, whereas it takes the coordinated expression of many genes to allow metastasis (6,11). In experimental systems, it is fairly easy to find associations with metastatic ability; however, it is difficult to prove that a particular gene is essential. For example, if one were to transfect a bona fide metastasis-
Fig. 1. Pathogenesis of hematogenous metastasis. Metastasis is defined as the formation of secondary tumor foci at a site discontinuous from the primary tumor. Metastases can form following invasion and penetration into adjacent tissues followed by dissemination of cells in the lymphatics, blood vasculature (shown here), coelomic cavities, or epithelial cavities. Metastatic cells arise within a population of neoplastic/tumorigenic cells as a result of genomic instability. This subset of cells has accumulated mutations in addition to those that have already rendered the cells tumorigenic. Metastasis-competent cells have evolved so that they detach and migrate away from the primary tumor. During transport, cells travel individually or as emboli composed of tumor cells (homotypic) or of tumor cells and host cells (heterotypic). At the secondary site, cells or emboli arrest either because of physical limitations (i.e., too large to traverse a lumen) or by binding to specific molecules in particular organs or tissues. Once there, tumor cells then proliferate either in the vasculature or in the surrounding tissue after extravasation. To form macroscopic, clinically detectable metastases (on the order of mm), cells recruit of physical limitations (i.e., too large to traverse a lumen) or by binding to specific molecules in particular organs or tissues. Once there, tumor cells then proliferate.


(21) Welch DR. Tumor progression: analysis of the instability of the metastatic phenotype, response to radiation and chemotherapy. Houston (TX): The University of Texas; 1984.

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