The selective nature of metastasis

James E. Talmadge

*Cancer Metastasis and Treatment Laboratory, NCI-Frederick Cancer Research Facility, P.O. Box B, Frederick, MD 21701, USA*

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**Summary**

The issue of whether metastases result from the random survival of cells released from a primary tumor or from the selective growth of specialized tumor subpopulations endowed with metastatic properties is important to our understanding of the metastatic process and to the development of therapeutic modalities against metastatic disease. We have found that the tumor cells populating spontaneous metastases are more metastatic than the cells populating the parent neoplasm, clearly indicating that metastasis is selective and not random. The selective nature of metastasis is a consistent observation, however, only when tumor cells are obtained from spontaneous metastases from mice bearing heterogenous, poorly metastatic tumors. Tumor cells from spontaneous metastases from mice bearing tumors that have been selected for metastatic potential or that are homogeneous (cloned) do not differ significantly in metastatic potential from tumor cells populating the parent tumor. Thus, under some conditions the process of metastasis can appear random. Although tumor cells from different individual metastases may be homogeneous with regard to a metastatic phenotype, they may be heterogeneous with regard to their sensitivity to chemotherapeutic agents. Thus, although metastasis selects for metastatic variants, resulting in the population of metastatic foci with tumor cells endowed with metastatic properties, it does not appear to select for phenotypes irrelevant to the process of metastasis such as sensitivity to therapeutic agents.

**Introduction**

Despite advances in the use of aggressive adjuvant chemotherapy and radiotherapy, which in combination with surgery are often successful in the eradication of the primary tumor, most deaths in cancer patients are caused by metastasis. Thus, an understanding of the mechanism whereby malignant tumor cells invade and metastasize to secondary sites is an important goal for cancer research. The recent studies of metastasis have greatly increased our understanding of the metastatic process which is influenced by both tumor cell properties and host–tumor cell interactions. Many of these studies have challenged established beliefs, resulting in the modification of experimental techniques and models used to study metastasis and altering our outlook on therapeutic protocols designed to treat established secondary foci.

A question important to our understanding of...
the pathogenesis of metastasis and to the improvement of cancer therapy is whether tumor cells that give rise to metastatic foci are random survivors of the cells within the primary tumor or represent a select subpopulation of tumor cells endowed with a unique metastatic phenotype(s) that preexists within the primary tumor population. If the metastatic process is selective, then the cells within a metastatic foci represent an enlarged pool of tumor cells with an increased metastatic potential for subsequent secondary metastasis. Furthermore, tumor cells within primary tumors are heterogeneous with regard to their metastatic potential and response to chemotherapeutic agents and other therapeutic modalities, thus they can be treated successfully only by modalities that circumvent this cellular diversity present not just in the primary tumor, but also among different metastases. Clearly, screening protocols for anticancer agents must not only monitor the response of the primary tumor to therapy but must also examine the efficiency of such protocols on the metastatic subpopulations within the primary tumor.

Heterogeneity of the primary tumor

Histological studies have long demonstrated morphologic differences among cells within the same tumor. For this reason, pathologists routinely examine several sections of a tumor to determine whether a tumor is benign or whether it contains nests of invasive and malignant cells. Dunn (1) examined the histiology of numerous primary murine mammary tumors and concluded that cancer does not represent a single alteration of one cell that reproduces itself without change. Foulds (2, 3, 4, 5) also noted that murine mammary tumors often have zones of tumor cells with different morphologies and that which each zone the cells appear homogeneous. To study this zonal heterogeneity, Henderson and Rous (6) fragmented tumors of mixed morphology which after transplantation as individual fragments, tended to develop into tumors with a uniform morphology.

At the time of diagnosis, most neoplasms are populated by subpopulations of cells with diverse phenotypes. Tumors have been shown to be composed of cells heterogeneous with regard to antigenicity (7-14) and immunogenicity (15-24). These variations in antigenicity and immunogenicity appear to profoundly influence the success of specific immunotherapy. Olsson and Ebbesen (25), using a number of AKR mouse lymphomas, showed that vaccination procedures against polyclonal tumors failed because only the dominant subclone was restricted in growth. The minor subpopulations, which did not constitute a sufficient mass in the vaccine to stimulate the immune response, proceeded to proliferate after the vaccination and eventually became the dominant population. Striking evidence that metastases of primary human tumors may not be uniformly susceptible to control by immunologic manipulation comes from a study performed by McCune et al. (26). These investigators used active specific immunotherapy directed against advanced renal carcinoma and its metastases by giving patients weekly injections of autologous, irradiated tumor cells obtained from the primary neoplasm, admixed with Corynebacterium parvum. They found that, not only did the degree of therapeutic efficacy vary from patient to patient, but that, in some patients whose overall response was favorable, some metastatic lesions regressed whereas others simultaneously progressed. This variable responsiveness of metastatic lesions even within the same patient was attributed to the antigenic diversity of the subpopulations of metastatic cells. These observations strongly suggest that antitumor immune responses can be evoked in renal carcinoma patients, but, most importantly, show that heterogeneity of the metastatic cells with respect to antigenicity is a problem that must be overcome if immunotherapy is to be truly effective in eradicating metastatic disease.

Tumor cell populations residing within a parent neoplasm can also be heterogeneous with regard to drug sensitivity. Cells isolated from rat hepatomas (27), methylcholanthrene-induced mouse sarcomas (28, 29), murine lung cancers (30); a murine melanoma (31) and a mouse mammary tumor (32) have different in vitro and in vivo sensitivities to various cytotoxic agents. Various human neoplasms, such as melanoma (33-35), colon adenocarcinoma (36, 37), gastric carcinoma (36, 37) ovarian carcinoma