Biological heterogeneity of cancer

Isaiah J. Fidler

Department of Cancer Biology, Metastasis Research Center; The University of Texas M. D. Anderson Cancer Center; Houston, TX USA

Despite significant improvements in diagnosis, surgical techniques, and advancements in general patient care, the majority of deaths from cancer are caused by the continuous growth of metastases that are resistant to conventional therapies. In a large number of cancer patients, metastasis may well have occurred by the time of diagnosis. The metastases can be located in different distant organs and in different regions within a single organ. The major obstacle for the eradication of metastases is the biologic heterogeneity of tumor cells that constitute primary cancers and metastases. Specifically, by the time of diagnosis, malignant neoplasms contain multiple cell populations with diverse biological heterogeneity in growth rate, karyotype, cell surface receptors, antigenicity, immunogenicity, marker enzymes, gene expression, sensitivity to different cytotoxic drugs, invasion, and metastasis. This biologic heterogeneity is not restricted to primary lesions. The cellular composition of metastases in the same organ or in different organs is heterogeneous, both within a single metastasis (intralesional heterogeneity) and among different metastases (interlesional heterogeneity). This heterogeneity is due to two major processes: the selective nature of the metastatic process, and the rapid evolution and phenotypic diversification of clonal tumor cell populations during progressive tumor growth resulting from inherent genetic and epigenetic instability of many clonal populations of tumor cells.

Clinical observations of human tumors have suggested that the tumors tend to undergo a series of changes during the course of the disease; for example, a

growth that initially appeared to be benign can develop into a malignant, lethal cancer. This process of tumor evolution and progression is most likely due to acquired genetic variability within developing clones of tumors, coupled with host selection pressures leading to the emergence of new clonal sublines with increasing growth or malignancy.

Tumor progression toward malignancy is accompanied by increasing genetic instability of the progressing cells. Indeed, multiple studies concluded that highly metastatic cells are consistently phenotypically and genotypically less stable than their nonmetastatic counterparts. This suggests that the rapid generation of diversity during progression may be due, at least in part, to the increased genetic instability of tumor cells. An additional mechanism for generating tumor cell diversity is that “epigenetic” phenomena could produce biological diversification through DNA modifications exclusive of DNA sequence alteration.

By the time cancer is diagnosed, the lesion can exceed 1cm³ in size, thus containing > 10⁹ cells. The destruction of 99.9% of the cells, a remarkable achievement indeed, still leaves 10⁶ cells to proliferate and rapidly generate biological diversity, including treatment-resistant variants. The three main areas where the biological heterogeneity of neoplasms is likely to prove of practical importance are in the detection of tumor deposits using monoclonal antibodies or tumor cell markers, in the design of screening procedures for new therapeutic modalities, and finally in applying therapeutic regimes other than surgical resection.

The implications of tumor cell diversity for the outcome of treatment of

Keywords: cancer, metastasis, heterogeneity, therapy, tumor

Submitted: 01/31/12

Accepted: 02/07/12

<http://dx.doi.org/10.4161/hv.19643>

Correspondence to: Isaiah J. Fidler;
Email: ifidler@mdanderson.org

cancer metastasis cannot be overstated. The heterogeneous nature of the response of malignant tumor cell subpopulations to cytotoxic drugs and other therapeutic modalities makes it unlikely that a single treatment regimen will be able to kill all the cells in a tumor. In many clinical situations, following completion of a treatment protocol using combined drugs that eliminates clinically detectable tumor burden, new regimens are implemented only when a patient presents some time later with clinical evidence of recurrent disease. Unfortunately, by the time the recurrent disease is diagnosed and subjected to a new therapeutic protocol, the tumor cells in the recurrent lesion(s) are likely to differ significantly from cells in the original tumor.

Over the years, numerous investigators have marshaled host immune mechanisms to control cancer metastases. Several approaches utilizing both specific and non specific immunologic manipulation have been employed to destroy tumor cells. In practice, however, there seem to be at

least three major components of successful application of immunologic techniques to the control of cancer metastasis: (1) the heterogeneous antigenic nature of malignant neoplasms; (2) the intrinsic antigenicity of metastatic tumor cells; and (3) the ability of the primary host to recognize and destroy susceptible tumor cells.

An active area of clinical research for the immune therapy of metastases is the use of monoclonal antibodies or immunoconjugates. Monoclonal antibodies alone may be useful to specifically block steps in the pathogenesis of metastasis. Immunoconjugates are being used to target these cytotoxic agents to metastases. One route to circumventing the problem of heterogeneity with monoclonal antibody therapy is to use different combinations of monoclonal antibodies targeted to different antigens.

Another approach to immunotherapy of metastasis is to stimulate host cellular immunity by vaccines consisting of tumor cells isolated from primary neoplasms or metastases. Antigenic heterogeneity of

cells populating metastases must be taken into consideration. The recognition that primary malignant tumors do not consist of uniform entities but contain subpopulations of cells with diverse biological properties requires a critical reappraisal of approaches to therapy. Heterogeneity exists among patients presenting with the same disease, and biological heterogeneity exists among cells populating a single tumor. This complexity and diversity of cancer suggest that we need to consider each cancer patient as presenting with a unique disease.

The biologic heterogeneity of primary tumors and metastases presents with three implications to therapy. First, targeted therapy requires a target. Second, heterogeneous disease cannot be treated by a homogeneous therapy. Third, a chronic disease cannot be treated acutely. Serious consideration of these principles should allow the design of better therapies for the fatal phase of cancer metastasis.