Chapter 1

METASTASIS-SUPPRESSOR GENES: A REVIEW AND PERSPECTIVE ON AN EMERGING FIELD

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Abstract

Metastasis is the most lethal attribute of a cancer. There is a critical need for markers that will distinguish accurately those histologic lesions and disseminated cells with a high probability of causing clinically important metastatic disease from those that will remain indolent. While the development of new diagnostic markers of metastasis was the initial motivation for many studies, the biologic approach used to identify metastasis-suppressor genes has provided surprising insights into the in vivo mechanisms regulating the formation of metastases. This chapter reviews the evolving view of the mechanisms that regulate metastasis and the importance of metastasis-suppressor genes in this process. The known metastasis-suppressor proteins or genes and the microcell-mediated chromosomal transfer strategy used to identify many of them are reviewed. New evidence for the role of these metastasis-suppressor activities (genes) in regulating the growth of disseminated cancer cells at the secondary site, the potential for the identification of novel therapeutic targets, and the multidisciplinary approach needed to translate this information into clinical tools for the treatment of metastatic disease are discussed.

1. THE CLINICAL PROBLEM: PREDICTING METASTATIC PROPENSITY

Our ability to detect and successfully treat localized cancers has improved appreciably in recent years. However, metastatic disease presents a continuing therapeutic challenge and is the most common cause of cancer-related death. Thus, there is an emphasis on the diagnosis of cancers at an early stage, when they are localized and most likely to be curable. Although screening for early stage disease is logical, its utility is limited by the inability of conventional diagnostic and histologic parameters to predict accurately the true extent and prognosis of a substantial proportion of clinically localized cancers (1-3). This
limitation is due, in part, to the inherent limitations and subjectivity of current grading and staging systems (4, 5).

The incidence of disease recurrence in surgical patients treated for prostatic and breast cancer illustrates this problem particularly well. Although we have a wealth of clinical and biologic information on these diseases, a large percentage of apparently resectable and theoretically curable lesions are found to be more advanced at the time of resection than envisaged, resulting in a substantial failure rate after attempted curative surgery (6-8). In studies of prostate cancer patients, even when patient selection excludes men with factors predicting poor prognosis (e.g. poorly differentiated histology, high prostate specific antigen [PSA] levels, clinical suspicion of local invasion) the relapse rate after radical retroperitoneal prostatectomy has approached 20%-30% (9-11). Similarly, one-third of surgical patients with node-negative breast cancer will develop metastases, while the other two-thirds, despite receiving no chemotherapy, do not (12). Even in patients with small tumors and tumor-negative lymph nodes (T1NO), there is a 15 to 25% likelihood of distant metastases (8).

Since the current staging systems for breast and prostate cancers do not accurately identify those patients curable by regional treatment alone, the evaluation of additional parameters associated with the metastatic phenotype will be very important for the differentiation of patients curable by surgery alone from those requiring systemic therapy. For instance, men at high risk for relapse of prostate cancer can be identified (e.g. serum PSA > 10 ng/ml, clinical stage T1 or T2 with greater than 50% of tissue at Gleason grade 4 (3, 4) on biopsy or clinical stage prostate cancer) and would be immediate candidates for adjuvant anti-metastatic therapies if they existed (10, 11, 13-16). Likewise, breast cancer patients with particularly poor prognoses can be identified by the detection of high microvessel counts concurrent with low expression of Nm23 and/or E-cadherin in the primary tumor (12-17). In fact, these parameters are better prognostic biomarkers than the conventional analysis of tumor size and grade. The information obtained from the simultaneous evaluation of biomarkers such as these have the potential to lead to a reduction in the morbidity in those patients not requiring chemotherapy, and possibly identify those patients requiring more aggressive therapies than indicated by current methods.

Overall, it is clear that there is a critical need for markers that will distinguish accurately those histologic lesions and disseminated cells that have a high probability of causing clinically important metastatic disease from those that will remain indolent (5, 15). Concerns have been raised that “metastasis” has often occurred by the time of diagnosis of the primary tumor, the implication being that it is then too late for anti-metastatic therapy to be of use (18). However, the mere spread of cancer cells into the vasculature or to a secondary site does not constitute metastasis. Development of clinically significant metastases requires that a cancer cell complete a series of well-defined steps,