Molecular markers of breast cancer metastasis
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Hard-wired genotype in metastatic breast cancer

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ABSTRACT

Recently, we showed by gene-expression profiling that the molecular program established in a human primary breast carcinoma is highly preserved in its distant metastases. According to the predominant model of metastasis, the capacity of a primary tumor to metastasize is acquired only rarely and late in tumorigenesis. Our findings challenge this common theory and imply that the metastatic nature of 'poor prognosis profile' breast carcinomas is an inherent feature, and not reserved to advantageous subpopulations.

Metastases—the spread of cells from the primary breast carcinoma to distant organs—are the main cause of death for breast cancer patients. The question of how metastases arise from the primary tumor is not only of importance for the understanding of the molecular mechanisms of cancer progression but will also have implications for the clinical management of the disease. The long-standing concept about the development of metastases is that a few rare cells within a primary tumor acquire mutations over time which provide some type of proliferative advantage. This advantageous genetic alterations enable these cells to escape the primary tumor mass and form new solid tumors at distant sites (Fig. 1A). This genetic selection model is based on in vitro culturing of tumor cell lines subsequently transplanted into mice. Others however have shown that metastases develop through stochastic events from the average tumor cell that enters the blood circulation. More recent studies performed on human tumor material challenge the genetic selection metastasis model and suggest that the acquisition of the metastatic phenotype may actually happen relatively early during tumorigenesis (Fig. 1B). Bernard and Weinberg even suggested that some of the genetic alterations acquired by tumor cells early in their development are the ones that later enable metastasis. This hypothesis was mainly based on the finding that expression profiles, obtained by microarray analysis, could predict the risk of disease outcome of breast cancer patients. A 'poor prognosis signature' is strongly predictive for the development of distant metastases, in contrast to the 'good prognosis signature'. A study by Ramaswamy et al. showed that several types of primary adenocarcinomas harbor a gene-expression signature associated with metastases, supporting the notion that not just a few rare cells in a tumor acquire metastatic ability, but that indeed all cells are able to metastasize. Different observations support the assumption of the relatively early acquisition of metastatic features during tumorigenesis. Micrometastases have been frequently observed in patients with small, low stage tumors and metastases with unknown primary tumors are also a common clinical diagnostic phenomenon.

Interestingly, our comparison of pairs of human primary breast carcinomas and their metastases developed years later at distant sites by gene expression profiling revealed and thereby further substantiated their genetic similarity. On average, more than 92% of the significantly expressed genes are co-regulated between primary and matching metastatic tumors. Hence, also significant biological characteristics are likely to remain similar between a tumor and its distant outgrowth. Until now, basic knowledge on the acquired metastatic potential was largely based on 'single gene' overexpressing cell lines injected into mice. Our study challenges the concept that the acquisition of a metastatic phenotype and the translocation of a tumor cell to a distant site in the body includes major changes in the gene expression of a tumor. In fact, the changes in expression of a metastatic colony are much more subtle than expected. Furthermore, we did not observe metastasis-specific gene sets for the primary tumors as compared to the metastases, groupwise nor within pairs. It cannot be ruled out that this is due to the small sample size. If the average 8% of differentially expressed genes observed within pairs would be responsible for metastasis development, as assumed in the 'single gene' overexpressing type of metastasis experiments, then in all eight primary tumors investigated a different set of genes is involved in the
metastatic spread. However, close analysis of these anti-regulated genes between primary and metastatic tumors showed us mostly tissue-specific genes from the site of metastasis (data not shown).

A frequent question our study provoked was whether the similarity we detected between primary tumors and distant metastases was based on patient-specific genes only. To disprove this assumption we tested breast cancer patients who developed a second primary tumor in the ovaries (confirmed by histopathology and loss-of-heterozygosity analysis). The hierarchical cluster analysis revealed that primary breast tumors obtained from different patients are more similar to each other than to their second primary tumor (data not shown). Furthermore, Alon et al. compared paired normal colon and colon carcinoma tissue obtained from the same patient by gene expression profiling. They showed in a very elegant paper that clustering distinguished tumor and normal samples from the same patient even when the genes used for clustering were chosen to have only small average difference between tumor and normal samples. These findings combined with the fact that no classifier could discriminate the primary from the metastatic tumors underscores that the observed similarity in gene expression between primary breast tumors and their distant metastases is rather remarkable.

References
