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NEWS AND COMMENTARIES

Cancer Transcriptomics

Modeling metastasis

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In a recent issue of *Nature*, Minn *et al*[1] report an integrative strategy using microarrays to identify genes that might play functional roles in mediating breast cancer metastasis to the lung. These results support the idea that a tumor's proclivity for particular metastatic sites might be predictable and encoded in programs that are expressed relatively early in a tumor's evolution.

Metastasis, the spread of a tumor beyond its primary site, is the major cause of cancer-related deaths worldwide. However, its molecular basis is poorly understood likely because the complexity of the metastatic phenotype has been difficult to study using traditional approaches. Treatment for metastatic cancer thus remains largely empirical, inefficient, and poorly effective.

Part of the problem is the uncertainty that still surrounds the question of how a primary tumor becomes metastatic. A generally accepted model holds that rare metastatic cells arise in primary tumors relatively late in tumorigenesis, through the step-wise and stochastic accumulation of enabling mutations beyond those that cause initial transformation. The well-documented direct correlation between primary tumor size and the risk of metastatic recurrence supports this model as do classic animal studies in which poorly metastatic cell lines can spawn highly metastatic variants during *in vivo* passage and selection.[2] However, other observations are inconsistent with this strictly stochastic model: particularly, the well-known association of clinical features such as tumor grade with metastatic propensity and the nonrandom pattern of spread of particular tumor types.

If metastasis is largely a random process, it will not be possible to use whole-tumor molecular information from individual cancer patients to predict the propensity, site, and tempo with which metastases will appear. Recently, however, DNA microarrays have been used to identify specific transcriptional signatures in the bulk of primary human tumors that are destined to metastasize, despite the fact that limits in microarray sensitivity preclude the detection of rare cell subpopulations.[3,4] Hence, these results have led some to propose an alternative deterministic model of cancer metastasis, whereby at the time of clinical detection some primary tumors are actually predestined to metastasize while others will only grow as local tumors.[4,5]

The molecular basis of these observations remains an enigma. It is unclear when during carcinogenesis tumors that are destined to metastasize acquire these transcriptional changes, and whether metastasis-associated gene expression signatures directly cause metastasis or indirectly reflect propensity to metastasize.[6] Nevertheless, these observations are spurring the development of molecular prognostic tools for a variety of tumor types based on multi-gene expression patterns that can be used to determine the likelihood of cancer patients developing metastatic disease.[7,8]

If primary tumors are preconfigured to metastasize, an obvious next question is whether they might also be preconfigured to metastasize to specific sites? To address this question, the Massague group at Memorial Sloan-Kettering has made extensive use of the human breast cancer cell line MDA-MB-231.[1,9,10] This line was originally derived from the pleural effusion of a patient with widespread metastasis and has been carried in culture for many years. Interestingly, it is possible to isolate different sublines of MBA-MD-231 (through *in vivo* passage and selection) that predictably metastasize to different organs when injected intravenously into a mouse. Microarray profiling of these sublines shows that they express one specific set of genes that correlates with general metastatic propensity. In addition, these sublines express additional signatures that correlate with metastasis to specific sites.

In this new study, Minn *et al*[1] identify a set of 54 genes with differential expression in lung-tropic sublines compared with bone-tropic lines. Surprisingly, this signature is also found in a subset of human primary breast tumors where its expression correlates specifically with lung-metastasis-free survival. Furthermore, functional studies using both over-expression and siRNA-mediated gene knockdown demonstrate the functional importance of a subset of these genes in lung metastasis. Importantly, no individual gene fully encodes the metastatic phenotype and a number of signature genes are important not only for growth at metastatic sites but also for primary tumor growth. These findings are consistent with the idea that some primary breast tumors are preconfigured not only to metastasize but also to metastasize to specific organs.

Like all high-profile works, this report raises a number of yet unanswered questions. The reported organ-specific signatures are derived from rare cells that pre-exist in the parental MBA-MD-231 line, and yet these signatures are detectable in bulk profiles from primary breast tumors. This finding supports the idea that the metastatic behavior of a primary tumor is largely preconfigured in the bulk of its cells. However, it does leave one wondering why cells with lung-specific metastatic programs are so rare in the original cancer cell line? One potential answer is that lung-specific signatures increase fitness for growth in the lung (and perhaps other sites *in vivo*) but not for growth in the petri dish. Also, it remains unclear when exactly primary tumors acquire organ-tropic signatures. In this regard, the role of signature genes in both primary and secondary

tumor growth is an important observation, since selection for certain clones that are most 'fit' for primary growth might simultaneously result in selection for metastatic clones because of overlapping growth requirements between primary and secondary sites.

On a clinical level, an obvious question is whether these 54 lung-metastasis genes represent a 'magic' set that is responsible for all breast-cancer metastasis to the lung? This seems unlikely since only a small subset of primary human tumors expressed the signature in this study, while the lung is a common site of breast cancer metastasis. Thus it is possible that other similar signatures exist. From a therapeutic standpoint, most patients with metastatic breast cancer develop disease in multiple sites during the course of their disease. Do individual primary tumors express multiple signatures that are predictive of metastasis to different sites? Overall, these findings suggest that complex strategies, which account for genetic heterogeneity among metastatic cells both within and between patients with metastatic cancer, may be required eventually to treat and prevent breast cancer metastasis■

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Mouse Models

Psoriasis: an epidermal disease after all?

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In the September 15th issue of *Nature*, a research group from Austria reported a novel mouse model with epidermal specific double-knockout of the c-Jun and JunB genes with subsequent development of psoriasis-like skin phenotype and arthritic lesions.[1] In this interesting model, the authors show that epidermal changes precede and are independent of recruitment or function of T cells.

Psoriasis is a common chronic inflammatory and hyperproliferative skin disease characterized by complex alterations in epidermal growth and differentiation, as well as multiple inflammatory, immunological and vascular abnormalities.[2] A significant proportion of psoriasis patients also develop seronegative inflammatory arthritis.[3] Many lines of evidence indicate that the disease is genetic, although its mode of inheritance is usually multifactorial.[4] To date, no causative gene has been definitively identified.[5]

While the most prominent features of psoriasis are abnormal proliferation of epidermal cells (hyperplasia), and increased cutaneous blood flow, multiple lines of evidence indicate that infiltrating immunocytes initiate and maintain these changes.[6] For example, bone marrow transplantation from psoriatic donors has previously triggered psoriasis in donor recipients.[7] Moreover T-cell-specific immunosuppressants exert dramatic therapeutic effects on psoriatic patients.[2] Xenograft experiments in which uninvolved skin of psoriatic patients is grafted onto immunodeficient mice have shown a clear role for T-cells, as transformation into a psoriatic plaque is blocked when T-cell function is inhibited.[8]

Given these lines of evidence that implicate T-cell involvement in psoriasis these new data are surprising. The Jun proteins (c-Jun, JunB and JunD), together with the Fos proteins (Fos, FosB, Fra1 and Fra2) and some members of the ATF and CREB protein families, are the principal components of the activator protein 1 (AP-1) transcription factor.[9] C-jun plays an essential role in cell proliferation by regulation of cell cycle regulators such as p53 and cyclin D1, whereas JunB negatively regulates cell growth by activating the $p16^{INK4a}$ inhibitor and decreasing cyclin D1 expression.[10] It has been proposed that the