The Crossroads of Oncogenesis and Metastasis
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The treatment of cancer is generally based on histologic grade, resectability, and the presence or absence of metastasis. Because interventions after the manifestation of metastasis are notoriously ineffective for most cancers, great effort has been invested in the development of targeted therapies to eradicate or suppress the growth of micrometastatic disease. In three recent studies, investigators implicate potential targets: proteins that mediate both transformation and metastasis. These studies also provide a potential clue to why some cancers have already metastasized at the time of diagnosis.

The implicated proteins, twist homolog 1 (Twist-1) and two members of the zinc-finger-protein Snail family, are transcription factors associated with transition from an epithelial phenotype to a mesenchymal phenotype (epithelial-to-mesenchymal transition) and cancer dissemination. The studies by Mikkelsen, Mani, and Ansieau and their colleagues ratchet back the point at which Twist-1 and the Snail proteins are known to be relevant to neoplastic transformation, suggesting that some metastatic capabilities of cancer cells can be acquired early during malignant conversion. The ability of proteins encoded by TWIST-1, snail homolog 1 (SNAI1), and snail homolog 2 (SNAI2) to suppress the expression of E-cadherin, a powerful intercellular adhesion molecule, is thought to be pivotal in both of these processes, which involve cell migration.

Mikkelsen et al. asked whether somatic cells can be reprogrammed to a pluripotent state through the ectopic expression of defined transcription factors. They observed that the immediate response to the induction of the reprogramming factors is characterized by a reversal in differentiation of the mouse embryonic fibroblast and concomitant up-regulation of proliferative genes, including Sna1 and Sna2, which are associated with epithelial-to-mesenchymal transition. Consistent with these observations is the study by Mani et al., who report that the induction of epithelial-to-mesenchymal transition in nontumorigenic, immortalized human mammary epithelial cells by ectopic expression of either Twist-1 or Snai1 transcription factors results in the production of stem cell–like cells, which, in turn, are capable of generating cancer stem cells. Moreover, Mani et al. found that stem cell–like cells that are isolated from mouse and human mammary glands and carcinomas express markers for epithelial-to-mesenchymal transition. These results suggest that epithelial-to-mesenchymal transition can contribute to cell transformation. The study by Ansieau et al. extends the reach of epithelial-to-mesenchymal transition even further by showing that the Twist-1 transcription factor can protect cells from senescence induced by the Ras oncogene.

The classic model of cancer development proposes that transcription factors involved in the promotion of epithelial-to-mesenchymal transition are activated in rare cancer cells residing at the invasive edge of advanced cancers. According to this model, the activation of proteins associated with epithelial-to-mesenchymal transition does not provide a growth advantage within the primary tumor but, rather, mediates the final step in tumor progression (that is, metastasis). In contrast, the findings of the three recent studies indicate that metastatic dissemination occurs continually throughout the course of primary tumor development, at least in some cancers (Fig. 1).

The expression of Snail proteins is repressed in response to DNA damage, which fuels the hypothesis that this repression is a physiological defense against tumorigenesis. Supporting this hypothesis is the finding that Snail proteins regulate molecular pathways that promote the invasion of tumor cells. Thus, under physiologic conditions, DNA damage decreases the expression of Snail proteins and probably inhibits or contributes to the inhibition of the migratory capacity of tumor cells. Constitutive expression of
Snail proteins during transformation would impede this control. The expression of proteins involved in epithelial-to-mesenchymal transition, including that of Snai1 and Snai2, is associated with tumor recurrence in patients and a poor prognosis in a variety of cancer types. It is therefore possible that the detection of the expression of such proteins may identify patients who may benefit from more aggressive chemotherapy or other therapeutic regimens.
The need for accurate mouse models of human cancers represents a hurdle that lies between studies such as these and a successful, rational therapeutic strategy. It will also be important to identify endogenous repressors of migration in order to understand how cells stop migrating when they reach their target tissues. The development of inhibitors that specifically interfere with the delamination of cells from primary tumors is also a goal. The inactivation of proteins involved in epithelial-to-mesenchymal transition might curb invasiveness and render invasive cells more susceptible to destruction. Certainly, a hypothesis worth testing is that agents that target such proteins will find the Achilles’ heel of at least some forms of human cancer.

Dr. Sánchez-Garcia reports holding patents pertaining to the use of Slug protein and its targets in the context of cancer and a patent on transgenic mammals used as models of human diseases originating from stem cells. No other potential conflict of interest relevant to this article was reported.

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