Mechanisms of Malignant Progression

Robert A. Weinberg
Whitehead Institute for Biomedical Research
Ludwig Center for Molecular Oncology
Department of Biology, MIT
Cambridge MA 02142 USA

Over the past three decades the mechanisms that lead to the transformation of a normal mammalian cell into a tumor cell have been studied through a variety of experimental approaches. Human cell transformation, in particular, requires perturbation of at least five distinct intracellular signal transduction pathways in order for a cell to become tumorigenic. While this problem seems to be solved, at least in conceptual outline, the mechanisms that allow cells within a primary tumor to become invasive and metastatic are less clear, in part because the process is extremely complex.

Cancer cells leave a primary tumor via a multi-step process termed the invasion-metastasis cascade. This involves initial local invasiveness, intravasation, travel through the circulation, extravasation, formation of a micrometastasis, and the final step of colonization, which involves the growth of a micrometastasis into a macroscopic metastasis. The complexity of this multistep process rivals the multistep process that previously generated the primary tumor, raising the question of how cancer cells acquire the multiple distinct capabilities required to complete this cascade.

In fact, many of these capabilities are acquired through activation of a normally latent cell-biological program termed the epithelial-mesenchymal transition (EMT), which is deployed during embryonic morphogenesis and certain types of wound healing. It appears that certain contextual signals received by cancer cells from the nearby tumor-associated stroma activate the expression of certain pleiotropically acting transcription factors, which in turn choreograph the EMT program. By creating cells with mesenchymal attributes, cancer cells acquire attributes such as motility, invasiveness, and an ability to resist apoptosis that together serve to enable them to disseminate to distant tissue sites in the body of a cancer patient.

Recently, we discovered that the product of the EMT is not a bona fide mesenchymal cells, but instead a cell that has many of the attributes of a stem cell, including the appropriate display of cell-surface markers and an acquired ability to self-renew. Accordingly, the EMT empowers cancer cells in two ways, by enabling them to disseminate and by imparting the trait of self-renewal, the latter trait being required for the growth of a micrometastasis into a macroscopic metastasis. This association between the EMT and the stem-cell state appears to operate for both normal epithelial cells and those that have undergone neoplastic transformation. Accordingly, and perhaps unexpectedly, normal epithelial stem cells seem to have many of the attributes of mesenchymal cells.