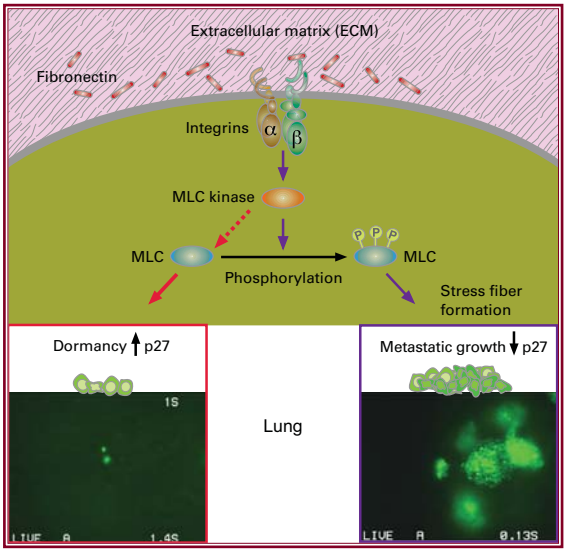
Letting Sleeping Micrometastases Lie



(*Image: J. Kelly*)

A network of interactions within the extracellular matrix (ECM) activates dormant tumor cells, resulting in post-treatment metastases. When the intracellular enzyme MLC kinase is blocked, tumor cells remain dormant. This suggests that treatments that inhibit MLC kinase may effectively perpetuate dormancy in micrometastatic cells.

One of the most insidious aspects of the spread, or metastasis, of cancer cells is its stealth. Metastatic tumors can appear months or even years after treatment for primary cancers. Recent evidence suggests that during this time, tumor cells lie dormant in their new host tissues. Because most chemotherapy agents target actively dividing cells, the dormant tumor cells are able to survive this time untouched, waiting for a signal to awaken and grow.

The nature of the signal(s) is unclear, though this knowledge would give researchers and clinicians an opportunity to develop ways of keeping cancer cells permanently in a dormant state. A team of researchers led by Research Fellow Dalit Barkan, Ph.D., and Jeffrey Green, M.D., Head of the Transgenic Oncogenesis and Genomics Section in CCR's Laboratory of Cancer Biology and Genetics, applied a three-dimensional (3D) culture technique to model dormancy, allowing them to identify at least one of the external cues for waking dormant breast cancer cells. Their results were published in the August 1, 2008, issue of the journal *Cancer Research*.

The majority of *in vitro* cell culture experiments are conducted using two dimensional (2D) cultures. However, these cultures do not reflect the true nature of the tumor microenvironment. With their 3D cultures, Barkan, Green, and their collaborators attempted a more realistic assessment of the signals exchanged between dormant breast cancer cells and the extracellular matrix (ECM), the structural framework that provides cells with environmental stimuli for growth, survival, angiogenesis, and other activities.

What they discovered was a complex set of interactions within micrometastatic cells and between micrometastatic cells and the ECM that regulate dormancy. The researchers found that their cell lines exhibited remarkably different growth characteristics when grown in 2D versus 3D cultures, more accurately reflecting their metastatic behavior *in vivo*. According to their results, tumor cells remain dormant by applying a molecular brake on their life cycle. Expression of a protein called fibronectin, often found to be increased in the ECM of carcinomas, triggered rearrangements in their cytoskeletons that effectively released the brake. Blocking an intracellular enzyme called MLC kinase, which mediates fibronectin's cytoskeletal effect, prolonged cell dormancy in both 3D cultures and in an *in vivo* metastasis model.

The researchers noted that while it is unlikely that fibronectin is the only ECM factor involved in switching on dormant micrometastases, their results suggest that pathways that regulate the cytoskeleton might serve as good targets for treatments that keep dormant micrometastatic cells inactive permanently.

Read more about the research conducted by Drs. Green and Barkan at http://ccr.cancer.gov/staff/staff.asp?profileid=13662.