New Method Holds Promise In Identifying Markers Of Non-Metastatic Versus Highly Metastatic Breast Cancer

April 22, 2005

Courtesy of the American Journal of Pathology Press Office Researchers at UCSD have used a new strategy to identify differences between non-metastatic and highly metastatic breast cancer cells. The article by Valerie Montel et al., "Expression profiling of primary tumors and matched lymphatic and lung metastases in a xenogeneic breast cancer model," appears in the May 2005 issue of *The American Journal of Pathology* and is accompanied by a commentary.

The significance of the study's findings lies in how the microarray method was employed. Previous studies have examined the patterns of genes that are active in primary human tumors, but the genetic differences that exist between individual patients can make interpretation of such results difficult. The beauty of the Montel et al. study is the use of microarrays to analyze variations in gene activity between cancer cell lines with differing capability to spread to distant organs (metastasize) but derived from *the same* human breast cancer. This eliminates the problem of irrelevant genetic variability among tumors derived from different patients.

The study, performed in the lab of Dr. David Tarin, used three cell lines that were weakly, moderately, or highly metastatic when injected into mice with compromised immune systems. Because the injected cells were labeled with green fluorescence protein (GFP), dissemination of the cancer cells could be tracked accurately due to their green glow.

Each of the three cell lines was injected into the mammary pads of mice, and metastasis was monitored by examining migration of cells to the lymph nodes and lungs. As expected, the weakly metastatic cells rarely moved to other sites while the moderately and highly metastatic cells migrated at increasing frequencies. The resulting primary and secondary (metastatic) tumors were then harvested for gene expression analysis by microarray technology.

Using a gene chip of 22,000 genes, the researchers determined which genes were turned "on" and "off" in primary versus metastatic tumors. Interestingly, few differences existed between the genes expressed in primary and secondary tumors originating from the same injected cell line. However, comparisons between non-metastatic and highly metastatic tumors identified several genes with altered expression patterns. This was further confirmed by analyzing RNA and protein levels from the tumors in vivo and the original cell lines in culture.

As envisioned by Dr. Tarin, "further work using this strategy will identify collections of marker genes (signatures) that predict the future behavior of a given human cancer from samples taken from the patient. The purpose is to find signatures of malignancy that indicate whether a cancer is more or less aggressive...The aim is to minimize over-treatment of those who do not need it and avoid under-treatment of those patients who do."

While the study provides several candidate genes that may prove useful for further clarifying the process of cancer metastasis, the authors caution that these results cannot be directly extrapolated to human tumors. That being said, the study still provides an important platform for future studies, in both animal models and human samples. The method holds great promise in identifying genes involved in metastasis of other cancers and may lead to better prognostics and therapeutics.

"Metastatic spread of cancer is the most important and urgent problem facing cancer doctors today," added Dr. Tarin. "The study outcome shows that progress is occurring in unraveling the issues, but more research dollars and effort need to be focused on this common clinical problem affecting cancer patients."

Media Contact: Nancy Stringer (619) 543-6163 UCSD