Decoding Gene Expression in Cancer Tumors Using Non-Invasive Imaging

May 21, 2007 |

By correlating images of cancerous liver tissue with gene expression patterns, a research team led by a radiologist at the University of California, San Diego (UCSD) School of Medicine has developed tools that may some day allow physicians to view a CT image of a cancer tumor and discern its genetic activity. The study, designed to help doctors obtain the molecular details of a specific tumor or disease without having to do an invasive biopsy procedure, will be published online on May 21 in *Nature Biotechnology.*

According to principle investigator Michael Kuo, M.D., assistant professor of interventional radiology at UCSD, the study represents the convergence of two developing fields of medical research: the mapping of the human genome and advances in diagnostic imaging.

The research team, which included investigators from Stanford University School of Medicine, systematically compared features from CT images of liver tumors with gene expression patterns obtained from surgery and tissue biopsies. Once they pinpointed the genomic correlates of the features detected by CT imaging, the researchers found that the two very different aspects of studying cancer – how the tumor looks in a CT scan and how it behaves on a molecular level – had a very strong connection.

"We studied what the various genes were doing and the biological activity they were involved in such as angiogenesis or cell growth. We also looked at how the genes contributed to a particular phenotype in the liver tumor seen on the CT scans, for example, the presence of characteristics vessels, or the tumor's texture and other important diagnostic imaging traits," said Kuo.

The research process sought to reveal the relationship between genetic activity patterns in liver tumors and the tumor's appearance on CT scans, and provide a simple means of translation. The scientists initially began with approximately 135 basic tumor descriptors, and then narrowed down the multitude of traits to the 28 most important diagnostic descriptors, matching those imaging features with a vast stockpile of microarray data generated from human liver cancer samples.

"We found a rich association between the images and the gene expression," Kuo said, adding that out of approximately 7,000 genes in the tumors, the research team was able to consistently associate imaging traits with 75 percent of the genes.

Kuo first conceived of the project in 2001 while he was a radiology resident at Stanford University. "Radiology—while making great technological advances towards capturing more and more detailed information in a non-invasive manner—seemed to be largely unaware to a fundamental shift in medicine towards genomic, personalized medicine," he said. At the time, Stanford Medical School was the center of ground-breaking studies of DNA microarrays, lab tools that can screen thousands of genes at a time, developed by Stanford biochemistry professor Patrick Brown, MD, Ph.D. Microarrays were proving to be extremely useful for identifying groups of genes and their patterns in diseases such as cancer, enabling scientists to compare them with normal tissue activity.

Genomics expert Howard Chang, M.D., assistant professor of dermatology at Stanford, and the paper's lead author, Eran Segal, Ph.D., joined the project in 2004. Chang had been using the gene activity patterns of microarrays to predict cancer outcome. Segal developed algorithms during his doctoral studies at Stanford that played a critical role in the analysis of the massive amounts of data encompassed in the study.

"When we looked at noninvasive images, there were a lot of different patterns that had no known meaning," said Chang. "We thought that maybe we could come up with a way to systematically connect the gene activity seen with microarrays to imaging patterns, enabling us to translate images to gene patterns, and ultimately to the outcome of the disease process."

"Clearly, we are very far from clinical applications of these tools that we developed," said Segal, who is now a computational biologist at the Weizmann Institute of Science in Rehovot, Israel. "But the fact that we saw strong connections between the imaging features and the molecular gene activity data suggests that this could be a promising and fruitful research direction."

Such use of non-invasive imaging to determine unique molecular characteristics of disease could lead to more individualized diagnosis and treatment of patients, according to the researchers.

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The work was funded by part by a grant from the National Institutes of Health and the Israel Science Foundation.

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