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Interactive gene 'networks' may predict if leukemia is aggressive or slow-growing

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Rather than testing for individual marker genes or proteins, researchers at the University of California, San Diego (UC San Diego) and the Moores UCSD Cancer Center have evidence that groups, or networks, of interactive genes may be more reliable in determining the likelihood that a form of leukemia is fast-moving or slow-growing.

One of the problems in deciding on the right therapy for chronic lymphocytic leukemia (CLL) is that it is difficult to know which type a patient has. One form progresses slowly, with few symptoms for years. The other form is more aggressive and dangerous. While tests exist and are commonly used to help predict which form a patient may have, their usefulness is limited.

Han-Yu Chuang, a Ph.D. candidate in bioinformatics and systems biology program in the department of bioengineering in the UC San Diego Jacobs School of Engineering, senior author Thomas Kipps, M.D., Ph.D., professor of medicine and deputy director for research at the Moores UCSD Cancer Center, and their colleagues analyzed the activity and patterns of gene expression in cancer cells from 126 patients with aggressive or slow-growing CLL. The researchers, using complex algorithms, matched these gene activity profiles with a huge database of 50,000 known protein complexes and signaling pathways among nearly 10,000 genes/proteins, searching for "subnetworks" of aggregate gene expression patterns that separated groups of patients. They found 30 such gene subnetworks that, they say, were better in predicting whether a disease is aggressive or slow-growing than current techniques based on

gene expression alone.

They presented their results Monday, December 8, 2008 at the annual meeting of the American Society of Hematology in San Francisco.

"We wanted to integrate the gene expression from the disease and a large network of human protein interactions to reconstruct the pathways involved in disease progression," Chuang explained. "By introducing the relevant pathway information, we can do a better job in prognosis." Chuang, co-author Trey Ideker, Ph.D., professor of bioengineering at UCSD, and their co-workers have previously shown the potential of this method in predicting breast cancer metastasis risk.

"When you are analyzing just the gene expression, you are analyzing it in isolation," Chuang explained. "Genes act in concert and are functionally linked together. We have suggested that it makes more sense to analyze the genes' expression in a more mechanistic view, based on information about genes acting together in a particular pathway. We are looking for new markers – no longer individual genes – but a set of co-functional, interconnected genes," she said. "We would like to be able to model treatment-free survival."

The current work is "proof of principle," Chuang said. Clinical trials will be needed to validate whether specific subnetworks of genes can actually predict disease CLL progression in patients. She thinks that the subnetworks can be used to provide "small scale biological models of disease progression," enabling researchers to better understand the process.

Eventually, she said, a diagnostic chip might be designed to test blood samples for such genetic subnetworks that indicate the likely course of disease. The involved biological pathways could be drug targets as well.

The American Cancer Society estimates that, in 2008, there will be about 15,110 new cases of CLL in the United States, with about 4,390 deaths from the disease.

Source: University of California - San Diego