New Biomarker May Predict Leukemia Aggressiveness

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Scientists at the University of California, San Diego and the Moores UCSD Cancer Center have evidence of a potential new biomarker to predict the aggressiveness of an often difficult-to-treat form of leukemia. They found that high levels of a particular enzyme in the blood are an indicator that chronic lymphocytic leukemia (CLL) – the most common form of adult leukemia – will be aggressive and in need of immediate treatment.

The researchers, led by Paul A. Insel, MD, professor of pharmacology and medicine at the UC San Diego School of Medicine, say that the enzyme, PDE7B, is also critical to the development of CLL and a potential target for drugs against the disease. They present their results April 19, 2009 at the AACR 100th Annual Meeting 2009 in Denver.

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

In previous work, Insel's group had discovered that among a group of enzymes, cyclic nucleotide phosphodiesterases, one of the phosphodiesterases, PDE7B, was 10 times higher in CLL patients than in healthy individuals. PDE7B controls the levels of cyclic AMP (cAMP), a molecule that can promote programmed cell death, a process that is defective in CLL. Whereas most cancers have out-of-control cell growth, CLL is characterized by an overabundance of white blood cells that do not die when they should. High levels of PDE7B mean less cAMP and as a result, less cell death.

"The question was, could the level of PDE7B expression provide evidence for the clinical stage and diagnosis for individual patients?" Insel said. To find out if changes in PDE7B levels might reflect disease progression, Insel, postodoctoral fellow Linghzi Zhang, PhD, and their co-workers compared the amount of PDE7B in white blood cells in 85 untreated patients with CLL to those of 30 healthy adults, and watched for changes over time. They then divided the results into patients who had high levels of PDE7B and those who had low amounts.

"We found that individuals with high levels really had worse disease and showed that PDE7B expression had predictive value relative to other currently available markers for disease severity

and progression," Insel said. "In some cases, the level of PDE7B expression provided prognostic information that was additive to existing markers."

Zhang said that PDE7B can be used alone as a biomarker for CLL if the levels are high enough, but may be used with other markers if the level is lower and ambiguous. "PDE7B may not be good enough by itself if it's not high enough," she noted. "If it is low, other markers could be helpful."

Co-investigator and leukemia expert Thomas Kipps, MD, PhD, professor of medicine and deputy director for research at the Moores UCSD Cancer Center, said that the findings are potentially important because of the urgency for clinicians to be able to gauge early on what kind of disease the CLL patient has in order to design the best available therapy.

Insel said that their research to date implies that PDE7B has a role in prognosis and could also be a good drug target because it reflects part of the biology of the disease. "The more of this enzyme a patient has, the worse the outcome," he said. "This implies that if we can develop drugs to block this enzyme, which would raise cAMP and promote apoptosis – which is really at the heart of the underlying pathology."

The American Cancer Society estimated that in 2008, about 15,100 new cases of CLL occurred in the United States, with roughly 4,400 deaths from the disease.

Other UCSD authors include: Laura Rassenti, Minya Pu, Fiona Murray, Joan Kanter, Andrew Greaves and Karen Messer.

The Moores UCSD Cancer Center is one of the nation's 41 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer.

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