SHIP protein identified as a B-cell tumor suppressor

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Lymphoma is a cancer of the immune system. White blood cells divide again and again, spreading abnormally throughout the body. Lymphomas can arise from two types of white blood cells, T cells or B cells, which divide uncontrollably when the molecular mechanisms that keep them in check go awry. A new study led by Robert Rickert, Ph.D., professor and director of the Inflammatory Diseases Program at Sanford-Burnham Medical Research Institute (Sanford-Burnham), explores the roles of two enzymes, called SHIP and PTEN, in B cell growth and proliferation.

The results, published online on October 18 in The Journal of Experimental Medicine, show that SHIP and PTEN act cooperatively to suppress B cell lymphoma. This new information could impact several anti-lymphoma therapies currently in development.

"PTEN usually gets all the attention," Dr. Rickert explained. "But here we show for the first time that SHIP is also a major tumor suppressor in B cells."

T cells destroy infected cells, while B cells produce antibodies to neutralize foreign particles. To maintain enough of these cells to mount an immune response, but not so many that lymphomas develop, PTEN and SHIP keep a damper on PI3K, an enzyme that promotes cellular growth, survival and proliferation. PI3K signaling is altered in a number of different cancers. If PTEN is missing in T cells, the damper is removed, cells grow out of control and T cell lymphomas result. Surprisingly, this study showed that B cells deficient in either PTEN or

SHIP are fine. But if mouse B cells are engineered to lack both PTEN and SHIP, lethal B cell abnormalities develop.

Could PTEN and SHIP mutations actually lead to lymphoma in humans? In an earlier collaborative study with Michael David, Ph.D., at the University of California, San Diego, Dr. Rickert and colleagues showed that inflammation – such as occurs after infection or injury – reduces SHIP expression. The current study suggests that while PTEN mutation in B cells alone might not cause harm, a single mutation plus inflammation could be a double whammy that gives rise to lymphoma.

"People often talk about one gene relating to one cancer," Dr. Rickert said. "But cancer is multigenic – it takes multiple hits to subvert a cell from normal to abnormal. Here we have a model showing how that can happen in B cells."

In addition to increasing our understanding of B cell biology, this research has implications for lymphoma treatments currently in development. One such treatment targets drug-resistant B cells by depleting the body of BAFF, a compound that promotes their survival. In this new B cell lymphoma model, however, Dr. Rickert and colleagues found that B lymphoma cells still proliferate without BAFF.

On a more positive note, this study supports the development of anti-lymphoma drugs that mimic PTEN and SHIP activity by inhibiting PI3K. "Several companies are making PI3K inhibitors to treat certain kinds of lymphomas," Dr. Rickert said. "I think this system could provide a useful new preclinical model to study PI3K-dependent B cell malignancies. "

More information: Meletic AV, Anzelon-Mills A, Mills DM, Omori SA, Pedersen IM, Shin D-M, Ravetch JV, Bolland S, Morse III HC, Rickert R. Coordinate suppression of B cell lymphoma by PTEN and

SHIP phosphatases. *Journal of Experimental Medicine*. Published online October 18, 2010.