The mouse that ROR'ed: ROR1 oncogene combines with another to accelerate, worsen blood cancer

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Researchers at the University of California, San Diego School of Medicine report that an oncogene dubbed ROR1, found on chronic lymphocytic leukemia (CLL) B cells but not normal adult tissues, acts as an accelerant when combined with another oncogene, resulting in a faster-developing, more aggressive form of CLL in mice.

The findings, published in the Dec. 30, 2013 Online Early Edition of *PNAS*, suggest ROR1 could be an important therapeutic target for patients with CLL, the most common form of blood cancer. Prevalence of CLL in the United States is high: 1 in 20 people over the age of 40 could have apparently pre-cancerous CLL-like cells in their blood. These people may develop actual CLL at a rate of about 1 percent per year. More than 15,000 new cases of CLL are diagnosed each year in the United States. Roughly 4,400 patients with CLL die annually.

The work by principal investigator Thomas Kipps, MD, PhD, Evelyn and Edwin Tasch Chair in Cancer Research, and colleagues continues a series of discoveries about ROR1. Previously, for example, they found an association between ROR1 and the epithelial-mesenchymal transition – the process that occurs during embryogenesis when cells migrate and then grow into new organs during early development. CLL cells exploit ROR1 to spread disease. Called metastasis, it is responsible for 90 percent of cancer-related deaths.

In the *PNAS* paper, Kipps and colleagues created transgenic mice that expressed human ROR1, then observed that these mice produced B cells (a kind of white blood cell) that were abnormal and resembled human CLL cells while non-transgenic littermates did not.

Next they crossed the ROR1 mice with another transgenic mouse-type that produces an oncogene called TCL1. Oncogenes are genes that can lead to cancer development if over-expressed or mutated. The progeny of these cross-bred mice possessed both oncogenes – ROR1 and TCL1 – and consequently displayed an even greater proclivity toward developing aggressive, fast-acting CLL.

When researchers treated the mice with an anti-ROR1 monoclonal antibody that reduces levels of ROR1, the CLL cells were impaired and more vulnerable to treatment and destruction. Based on these findings, Kipps said investigators at UC San Diego Moores Cancer Center are planning clinical trials in 2014 using a humanized monoclonal antibody that has the same type of activity against human leukemia or cancer cells that express ROR1.

Provided by University of California - San Diego

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