Embryonic Development Protein Active in Cancer Growth

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Silencing it impairs tumor growth, making ROR1 a potential therapeutic target

A team of scientists at the University of California, San Diego Moores Cancer Center has identified a novel protein expressed by breast cancer cells – but not normal adult tissues – that could provide a new target for future anti-cancer drugs and treatments.

Thomas Kipps, MD, PhD

Led by Thomas J. Kipps, MD, PhD, Evelyn and Edwin Tasch Chair in Cancer Research and Interim Director of the UC San Diego Moores Cancer Center, the scientists found that the tumor cells of patients with breast cancer frequently express the Receptor-tyrosine-kinase-like Orphan Receptor 1, or ROR1. They found that silencing expression of ROR1 impaired the growth and survival of human breast cancer cells. The findings are published in the March 5 online issue of *PLoS One*.

ROR1 was first identified in the early 1990s and labeled an orphan receptor because its purpose was unknown. Subsequent work found that ROR1 is expressed at high levels during embryogenesis, during which time it plays an important role in regulating embryonic muscle and skeletal development. During fetal development, however, the expression of this protein is turned off. Normal cells and tissues in adults do not typically express ROR1.

Cancer cells, however, are a different matter.

"Cancer cells tend to acquire features of less differentiated cells," said Kipps, interim director of the UC San Diego Moores Cancer Center and a professor of medicine in the UC San Diego School of Medicine. "They often can be found to have features of embryonic cells."

In recent years, Kipps and others have become increasingly interested in the role of ROR1 plays in the growth of cancer – and whether the protein might provide new options for stopping development of the disease. In 2008, for example, Kipps and colleagues reported that patients with leukemia treated with whole-cell vaccines could generate antibodies that reacted with their leukemia cells and the leukemia cells of other patients, but not with normal cells. They identified that such antibodies could target ROR1, accounting for the specificity of these antibodies in reacting with cancer cells. They identified another protein that could interact with ROR1 to stimulate the growth and/or survival of leukemia cells and that antibodies generated against ROR1 could block this function.

The discovery that ROR1 functions similarly in breast cancer heightens hopes. When the protein was silenced in human breast cancer cells, the cancer cells had slower rates of growth in the laboratory and in animal studies.

"There was a qualitative difference," said Kipps. "When ROR1 was knocked down, it took away some of the growth advantage enjoyed by cancer cells. Their capacity to survive also was impaired. This could affect the capacity of the cancer cells to survive treatment with other anti-cancer agents or generate tumors altogether."

The researchers report that expression levels of ROR1 correlate with the severity of at least some forms of breast cancer. The most aggressive cancers were the ones more likely to express ROR1. "That suggests ROR1 could be a good target for treating the most aggressive kinds of breast cancer, particularly the ones that lack expression of hormone receptors or the marker HER2/neu, which already can be targeted by monoclonal antibodies," Kipps said.

The discovery of ROR1's role in both blood and breast cancers also suggests it might have a similar function in other forms of cancer, a possibility Kipps said researchers will pursue.

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Co-authors of the paper are Suping Zhang, Liguang Chen, Bing Cui, Han-Yu Chuang, Jianqiang Yu, Jessica Wang-Rodriguez, Li Tang, George Chen and Grzegorz W. Basak, all at the UC San Diego Moores Cancer Center.

The article can be found online at http://dx.plos.org/10.1371/journal.pone.0031127

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