# Breast stem-cell research: Receptor teamwork is required and a new pathway may be involved

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Breast-cancer researchers at the University of Wisconsin-Madison have found that two related receptors in a robust signaling pathway must work together as a team to maintain normal activity in mammary stem cells.

Mammary stem cells produce various kinds of breast cell types. They may also drive the development and growth of malignant breast tumors.

Published recently in the Journal of Biological Chemistry, the research also suggests that a new signaling pathway may be involved, a development that eventually could take cancer-drug manufacturers in a new direction.

"We wanted to know if we could use this knowledge to inform us about what might be the transition that occurs to start tumor growth and maintain it," says senior author Dr. Caroline Alexander, professor of oncology at the McArdle Laboratory for Cancer Research at the School of Medicine and Public Health.

The paper describes new information about the Wnt signaling pathway. Wnt signaling underlies numerous activities in normal development, but when the system is unregulated, cancer often occurs.

"Wnt signaling is very important for both stem cells and tumor growth. We need to know the details of the signaling process so that we can use

the positive aspects of Wnt signaling for regenerative medicine, and eliminate the negative cancer-causing aspects," says Alexander, a member of the UW Carbone Cancer Center (CCC).

Regenerative biologists typically add Wnt proteins together with other agents to guide the differentiation of lung, bone and heart stem cells, she notes.

The UW researchers zeroed in on two related Wnt receptors on the cell surface--LRP5 and LRP6. The receptors normally respond to Wnt ligands that approach cells to initiate a signaling cascade inside.

Scientists have known that when some abnormality causes over-expression of Wnt signaling, many types of cancer can arise. They think that the over-expression of the LRP6 receptor may be important to some of the worst-outcome triple-negative breast tumors. On the other hand, LRP5 is clearly necessary for mammary stem cells to work.

Wnt ligands typically attach at the cell surface to a multi-component receptor complex that includes an LRP or to another receptor called Frizzled. Binding with specific receptors ultimately leads several different types of signal to travel down specific arms of the pathway to activate Wnt-target genes located in the nucleus.

In earlier research, Alexander and her team found that LRP5 and LRP6 serve different functions in the mouse mammary gland. The current research examined the signaling potential of each receptor.

"Our hypothesis was that different Wnt ligands activate the Wnt pathway by preferentially signaling through either LRP5 or LRP6," Alexander says.

To test the hypothesis, researchers treated embryonic mouse cells with

different physiologically relevant Wnt ligands. They found that both LRP5 and LRP6 were required to respond optimally to one group of Wnt ligands.

Over-expression of either LRP5 or LRP6 overcame the need for both receptors to be present, suggesting that this was a way to sidestep the natural controls that regulate stem cell function during tumor development.

"This requirement for both receptors explains why mice engineered to have only LRP6 are resistant to Wnt-mediated tumors," Alexander says. "We think that the Wnt ligand normally responsible for maintaining mammary stem cells falls into the group of ligands that is dependent on both LRPs."

Alexander theorizes further that the dual-action signaling may occur through some pathway that is completely different than the traditional so-called canonical pathway.

To see clearly how LRP5 and LRP6 act singly and together, the team employed a novel technique called IFAST, which works even when natural receptor concentrations are low. The technique was developed by CCC researcher Dr. David Beebe, a UW professor of biomedical engineering.

The technique showed that LRP5 and LRP6 are linked structurally in a single signaling complex, called a heterodimer. Nobody has been able to make such an observation until now.

The dual-requirement for LRP5 and LRP6 was also observed in live mice that had the first stages of tumor growth, which depends on early ductal stem cell activity.

Pharmaceutical companies that produce breast-cancer drugs have focused most of their efforts on the Frizzled receptor and the more traditional canonical signaling pathway it uses. But that may change in the near future, Alexander says.

"Having a different Wnt receptor complex and signaling pathway is something drug companies would be interested in," she says.

Provided by University of Wisconsin-Madison