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Researchers find stem cell marker controls 2 key cancer pathways

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Researchers at Georgetown University Medical Center have discovered that a gene associated with human breast stem cells can stimulate development of mammary cells by activating two critical cancer pathways. They say this finding, reported at the annual meeting of the American Association for Cancer Research (AACR), provides new evidence that breast cancer can arise from stem cells and that targeting this gene might provide a new way to treat cancers of the breast as well as other tumor types.

“This is the first time any role has been attributed to this gene, and it turns out to be one that is surprisingly powerful,” says the study’s lead author, Xiaoyang Wang, Ph.D., Postdoctoral Fellow at Georgetown’s Lombardi Comprehensive Cancer Center.

Specifically, Wang and the researchers show for the first time that this gene, Musashi1 (Msi1), switches on Wnt and Notch cell signaling. Both of these pathways help control stem cell growth, and are known to be critically important to the development of many cancers.

Msi1 was named after a famous 17th century Japanese swordsman, Miyamoto Musashi, by Japanese researcher Hideyuki Okano, Ph.D., who identified it in fruit flies in 1994. Okano currently collaborates with the Georgetown scientists.

Recent studies have shown Msi1 to be a marker of human stem cells in general because it has been found in human breast, colon, brain, skin,

and other cells, says Robert Glazer, Ph.D., a professor of Oncology and Pharmacology and the study's senior author.

So Glazer and Wang decided to probe the gene's function. "Msi1 is known to be a marker of stem cells, but no one knows what it does. We wanted to see if it had a function in the mammary gland," Glazer says.

They were especially interested in whether Msi1 is associated with cancer development because recent studies have suggested that stem cells may be the causative root of some cancers – a notion that is vigorously debated among cancer researchers.

"It is really critical to understand if stem cells are involved in cancer development because a lot of therapies used to treat cancer don't target stem cells," he says. "That may explain why tumors come back."

In laboratory experiments, the scientists found that, in mammary cell development, Msi1 drives mammary cells along different lineages – in other words, it can decide what type of cell develops in the breast, be it muscle cells or cells that line milk ducts, etc.

In cancer, the Wnt and Notch pathways are often activated, and the researchers found that Msi1 is expressed in particularly aggressive tumors. The researchers then tested whether Msi1 regulates these pathways in mammary cells and found that it did.

The researchers then studied how Msi1 drives the Wnt and Notch pathways found that when Msi1 was over-expressed, there was an increased secretion of a growth factor known as proliferin, and reduced secretion of the Wnt pathway inhibitor, Dickkopf-3. Additionally, Msi1 programmed the expression of a number of genes that have a concerted effect on the cell cycle, Wang says.

“We believe that while Msi1 may contribute to cell proliferation, it is not the single gene that controls cancer development,” Glazer says.

“This work suggests, but does not prove, that stem cells drive breast cancer formation,” he says. “Msi1 might make a good therapeutic target, and we are currently testing ways to interfere with its function in cells to see if it disrupts cancer cell proliferation.”

Source: Georgetown University