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Overabundance of protein expands breast cancer stem cells

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An essential protein for normal stem cell renewal also promotes the growth of breast cancer stem cells when it's overproduced in those cells, researchers at The University of Texas MD Anderson Cancer Center report in the February edition of *Cancer Cell*.

In mouse and lab experiments, the team also discovered that two drugs block the cascade of molecular events that they describe in the paper, thwarting formation of breast tumor-initiating cells.

"Overexpression of the EZH2 protein has been linked to breast cancer progression, but the molecular details of that connection were unknown," said senior author Mien-Chie Hung, Ph.D., professor and chair of MD Anderson's Department of Molecular and Cellular Oncology.

"Tumor-initiating cancer cells that arise from the primary cancer stem cells also are thought to drive cancer progression," Hung said. "This research connects EZH2 to the growth of breast tumor-initiating cells."

EZH2 blocks DNA damage repair

The molecular chain of events that improves self-renewal, survival and growth of these breast cancer stem cells can be initiated by oxygen-starved portions of a tumor, Hung said. This hypoxia stimulates a protein that in turn causes overexpression of EZH2.

Abundant EZH2, the team showed, dampens production of an important protein involved in DNA damage repair. Unrepaired chromosomal damage then amplifies production of RAF1, which unleashes a molecular cascade that promotes expansion of breast tumor-initiating cells and cancer progression.

Two drugs slash breast cancer stem cell population

The team tested five anti-cancer drugs against a culture of breast cancer cells and in tumor samples of human breast cancer in a mouse model. Sorafenib, a RAF inhibitor also known as Nexavar, eliminated more cancer stem cells and blocked tumor formation better than the other four.

Sorafenib inhibits multiple targets, so the researchers also tested an experimental drug called AZD6244, which specifically inhibits the MEK-ERK kinase cascade launched by RAF1. They found the drug eliminates EZH2-promoted breast cancer stem cells and blocks the formation of precancerous mammospheres.

"The drugs' inhibition of the breast tumor-initiating cells reveals a previously unidentified therapeutic effect for RAF1-ERK inhibitors to prevent breast cancer progression," Hung said. AZD6244 is being tested in multiple clinical trials, he noted, and it will be interesting to see whether the cancer-stem-cell-killing ability will be induced in those trials.

Hunting down a dangerous pathway

Breast cancer stem cells can be sorted from other primary cancer cells by the presence of the surface protein CD44 and low or absent CD24 in tumor cells.

The researchers found that high expression of EZH2 in breast cancer stem cells reduced the levels of the tumor suppressor RAD1 and correlated with high-grade tumors in a sample of 168 human breast cancer tumors. It also increased the number of tumor-initiating cells in culture.

EZH2 also is heavily expressed, and RAD1 diminished, by lack of oxygen in the tumor's environment, which causes activation of the HIF1a(alpha) protein. HIF1a(alpha), the researchers found, activates the EZH2 gene by binding to the gene's promoter region.

With RAD1 unable to repair damage, amplified RAF1 triggers the MEK-ERK-ß-Catenin pathway, a well-known cancer promoting molecular pathway. The team showed EZH1 enhances this signaling pathway, which they found correlates with breast cancer progression.

In December, Hung and colleagues published a paper in *Nature Cell Biology* showing that the enzyme CDK1 shuts down EZH2.

Provided by University of Texas M. D. Anderson Cancer Center

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