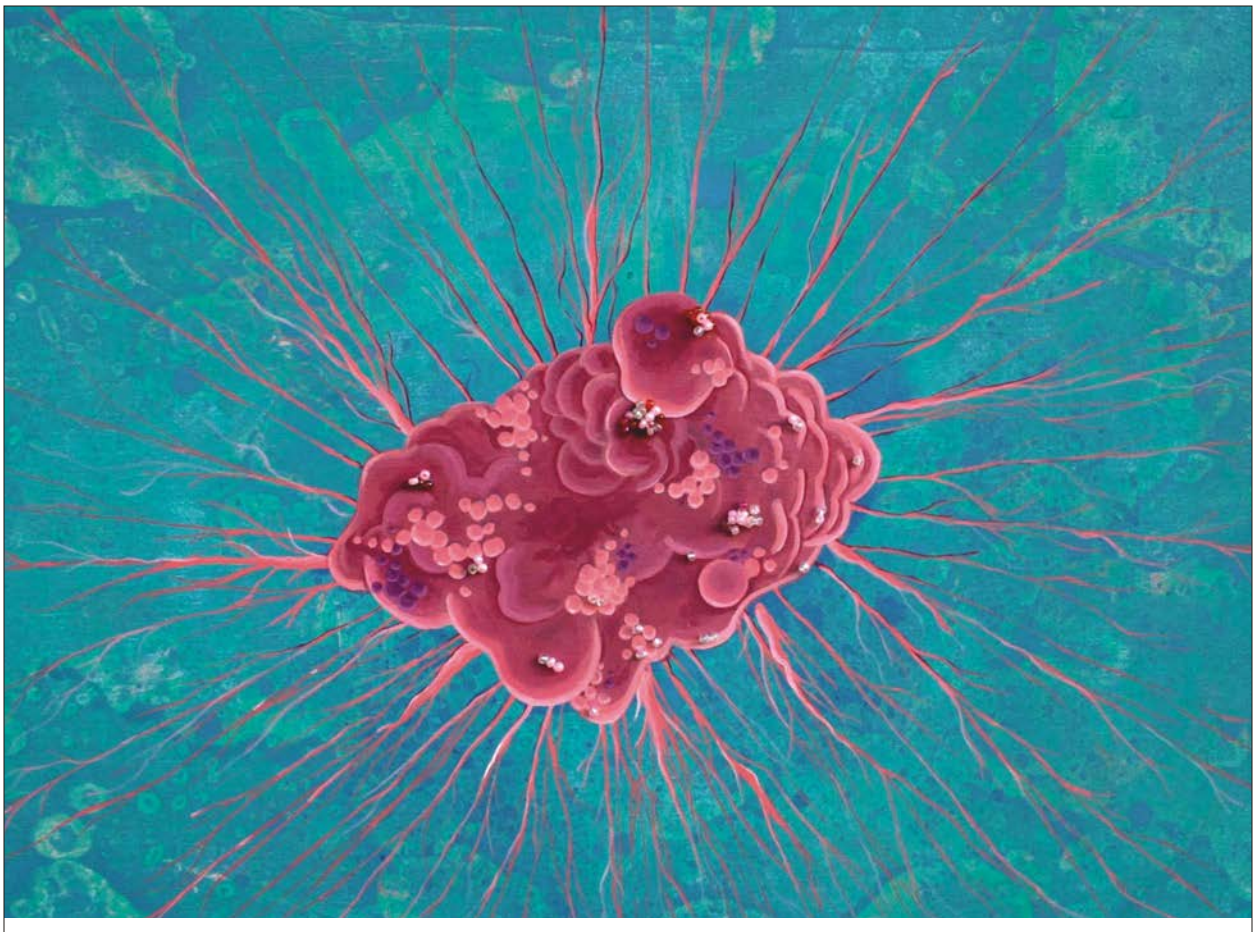

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Discovery Halts Breast Cancer Stem Cells

Breast cancer stem cells (CSCs), the aggressive cells thought to be resistant to current anti-cancer therapies and which promote metastasis, are stimulated by estrogen via a pathway that mirrors normal stem cell development. Disrupting the pathway, researchers were able to halt the expansion of breast CSCs, a finding that suggests a new drug therapy target.

The study, done in mice, is published in the Proceedings of the National Academy of Sciences (PNAS) Early Edition this week.

"A critical aspect of our work was to discover that estrogen could promote breast cancer growth by modulating the proportion of breast CSCs. Since CSCs were not directly sensitive to estrogen, it wasn't clear, how estrogen could affect their numbers? However, we found that hormone-sensitive cancer cells can communicate with CSCs to regulate their numbers. By disrupting the interaction between cancer cell populations we were able to prevent tumor growth," said Charlotte Kuperwasser, PhD, Associate Professor in the Anatomy and Cellular Biology and Radiation Oncology Departments at Tufts University School of Medicine, and Member of the Genetics and Cell, molecular & Developmental Biology Program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

"Interestingly, this signaling pathway involves many of the same players that control normal stem cell biology, raising a more general possibility that CSCs in other tumors might be regulated by the mechanisms guiding normal development," said Kuperwasser.

Kuperwasser and colleagues from MIT and Harvard used a mouse model to examine the behavior of cancerous human breast tissue with a method that mimics the human body more closely than standard mouse models. The researchers first examined estrogen's effect on breast CSC growth, finding that estrogen caused breast CSC numbers to increase by nearly 800 percent. Since few breast CSCs contain estrogen receptors, the researchers suspected that estrogen's actions were through a signaling mechanism from nearby cells that express the receptors.

"When nearby cells were exposed to estrogen, they secreted 14 times more FGF9, a signaling protein that drives CSC proliferation. When we blocked the FGF pathway with a small molecule inhibitor, we saw loss of CSC growth, tumorspheres generation, and even tumor formation. We then linked FGF signaling to the Tbx3 signaling axis, which is also important for embryonic mammary gland development," said first author Christine Fillmore, PhD, a 2009 graduate of the genetics program at the Sackler School and currently a Research Fellow in Genetics at Children's Hospital Boston.

"These results show that interfering with this signaling pathway is a promising strategy for targeting breast CSCs. We are hopeful that the improved understanding of the mechanisms that promote breast CSCs will lead to the development of drugs that can be used to halt CSC proliferation," said Kuperwasser.

Kuperwasser also leads a laboratory at the Molecular Oncology Research Institute (MORI) at Tufts Medical Center, which is dedicated to the exploration of the molecular

mechanisms of cancer and the translation of findings into the clinic.

Additional authors on the study include Piyush Gupta, PhD, formerly of the Broad Institute, and now a member of the Whitehead Institute for Biomedical Research as well as an Assistant Professor of Biology at MIT; Jenny Rudnick, a graduate student in the Cell, Molecular & Developmental Biology Program at the Sackler School and member of the Kuperwasser lab at MORI; Silvia Caballero, formerly a participant in the Post-baccalaureate Research Education Program at the Sackler School, and now at Cornell University; Patricia Keller, PhD, a Postdoctoral Fellow in the Department of Anatomy and Cellular Biology at TUSM and member of Kuperwasser's Lab at MORI; and Eric Lander, PhD, Founding director of the Broad Institute, Professor of Biology at MIT, and Professor of Systems Biology at Harvard Medical School.

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Editor's Note: This article is not intended to provide medical advice, diagnosis or treatment.