# Study details on-off switch that promotes or suppresses breast cancer

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Signals can tell cells to act cancerous, surviving, growing and reproducing out of control. And signals can also tell cells with cancerous characteristics to stop growing or to die. In breast cancer, one tricky signal called TGF-beta does both - sometimes promoting tumors and sometimes suppressing them.

A University of Colorado Cancer Center study recently published in the journal *Oncogene* details how tumors may flip the TGF-beta signalling switch, allowing doctors to delete the pathway entirely when it promotes tumors, and leave it intact when it's still working to suppress them.

"Basically, a tumor hijacks an embryonic program and turns it back on," says Heide Ford, PhD, investigator at the CU Cancer Center, associate professor in the CU School of Medicine department of ob/gyn, and the paper's senior author.

Embryos grow quickly and so require cells that proliferate quickly and are able to move to other areas of the embryo. Early in human development, we depend on a transcription factor called SIX1 to create this weed-like growth and nimble movement. Then, as adults, we turn off this SIX1 pathway in most cells - we no longer need explosive growth or movement and so the pathway goes to sleep in our genome.

Many breast cancers wake SIX1, and the *Oncogene* paper details how SIX1 flips the TGF-beta signalling switch from tumor-suppressing or tumor-promoting.

SIX1 creates small molecules called microRNAs that regulate gene activity. In this case, SIX1?s microRNAs attach to and mute the section of TGF-beta that stops cell growth. With TGF-beta silenced, the signal does nothing to stop cell growth, and instead encourages these cells to migrate into new tissues. Turning on SIX1 and its associated microRNAs is like removing the speed governor from a reckless teenager's Mustang convertible.

"High SIX1 or high microRNAs associated with SIX1 are a sign that a breast cancer is using TGF-beta signaling in a tumor-promoting way," Ford says. Patients whose tumors have high SIX1 or associated microRNAs are likely to benefit from "TGF-beta inhibitors" - drugs that turn off the signal - that are currently in clinical trials. Conversely, patients with low SIX1 are best left with TGF-beta signaling intact - in this case, the signal is likely helping these breast cancer patients fight against their tumors.

In the future, Ford hopes to target SIX1 directly.

"Because we don't need it in most adult tissues, if we could target SIX1, we could probably inhibit the tumor on multiple fronts with few side effects," she says.

Stay tuned: now with the SIX1 target in sight, Ford and collaborators at the CU Cancer Center are developing novel drugs to stop this tumor-promoting factor.

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