# Scientists identify gene that controls aggressiveness in breast cancer cells

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In a discovery that sheds new light on the aggressiveness of certain breast cancers, Whitehead Institute researchers have identified a transcription factor, known as ZEB1, that is capable of converting non-aggressive basal-type cancer cells into highly malignant, tumor-forming cancer stem cells (CSCs). Intriguingly, luminal breast cancer cells, which are associated with a much better clinical prognosis, carry this gene in a state in which it seems to be permanently shut down.

The researchers, whose findings are published this week in the journal *Cell*, report that the ZEB1 gene is held in a poised state in basal non-CSCs, such that it can readily respond to environmental cues that consequently drive those non-CSCs into the dangerous CSC state. Basal-type breast carcinoma is a highly aggressive form of breast cancer. According to a 2011 epidemiological study, the 5-year survival rate for patients with basal breast cancer is 76%, compared with a roughly 90% 5-year survival rate among patients with other forms of breast cancer.

"We may have found a root source, maybe the root source, of what ultimately determines the destiny of breast cancer cells—their future benign or aggressive clinical behavior," says Whitehead Founding Member Robert Weinberg, who is also a professor of biology at MIT and Director of the MIT/Ludwig Center for Molecular Oncology.

Transcription factors are genes that control the expression of other genes, and therefore have a significant impact on cell activities. In the case of ZEB1, it has an important role in the so-called epithelial-to-

mesenchymal transition (EMT), during which epithelial cells acquire the traits of mesenchymal cells. Unlike the tightly-packed epithelial cells that stick to one another, mesenchymal cells are loose and free to move around a tissue. Previous work in the Weinberg lab showed that adult cancer cells passing through an EMT are able to self-renew and to seed new tumors with high efficiency, hallmark traits of CSCs.

Other earlier work led by Christine Chaffer, a postdoctoral researcher in the Weinberg lab, demonstrated that cancer cells are able to spontaneously become CSCs. Now Chaffer and Nemanja Marjanovic have pinpointed ZEB1, a key player in the EMT, as a gene critical for this conversion in breast cancer cells.

Breast cancers are categorized into at least five different subgroups based on their molecular profiles. More broadly these groups can be subdivided into the less aggressive 'luminal' subgroup or more aggressive 'basal' subgroup. The aggressive basal-type breast cancers often metastasize, seeding new tumors in distant parts of the body. Patients with basal breast cancer generally have a poorer prognosis than those with the less aggressive luminal-type breast cancer.

Chaffer and Marjanovic, a former research assistant in the Weinberg lab, studied non-CSCs from luminal- and basal-type cancers and determined that cells from basal cancers are able to switch relatively easily into CSC state, unlike luminal breast cancer cells, which tend to remain in the non-CSC state.

The scientists determined that the difference in ZEB1's effects is due to the way the gene is marked in the two types of cancers. In luminal breast cancer cells, the ZEB1 gene is occupied with modifications that shut it down. But in basal breast cancer cells, ZEB1's state is more tenuous, with repressing and activating markers coexisting on the gene. When these cells are exposed to certain signals, including those from TGFß, the

repressive marks are removed and ZEB1 is expressed, thereby converting the basal non-CSCs into CSCs.

So what does this new insight mean for treating basal breast cancer?

"Well, we know that these basal breast cancer cells are very plastic and we need to incorporate that kind of thinking into treatment regimes," says Chaffer. "As well as targeting cancer stem cells, we also need to think about how we can prevent the non-cancer stem cells from continually replenishing the pool of cancer stem cells. For example, adjuvant therapies that inhibit this type of cell plasticity may be a very effective way to keep metastasis at bay."

Marjnaovic agrees but cautions that the model may not be applicable for every cancer.

"This is an example of how adaptable cancer cells can be,," says Marjanovic, who is currently a research assistant at the Broad Institute. "We have yet to determine if ZEB1 plays a similar role in all cancer types, but the idea that cancer cells reside in a poised state that enables them to adapt to changing environments may be a mechanism used by many cancers to increase their aggressiveness."

**More information:** "Poised chromatin at the ZEB1 promoter enables breast cancer cell plasticity and enhances tumorigenicity" *Cell*, July 3, 2013.

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