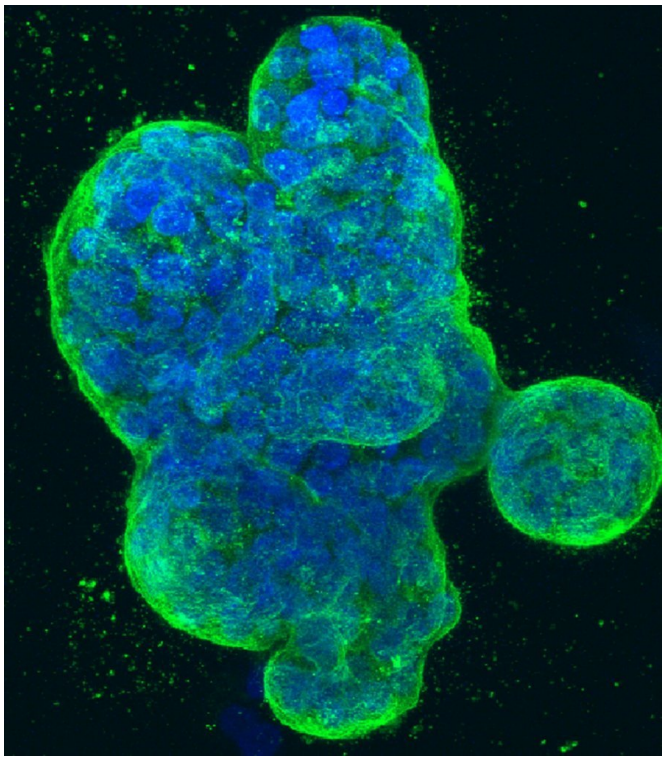
# Splicing factor to blame in triple negative breast cancer

26 November 2019



Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. Image created in 2014 by Tom Misteli, Ph.D., and Karen Meaburn, Ph.D. at the NIH IRP.

If your DNA is a cookbook, a single gene is a recipe. But it's a flexible recipe that if edited one way can make a pie; edited another way can make a cake. And that difference can mean cancer, as a team of researchers who looked at those gene editors writes in the 26 November issue of *Cell Reports*.

Those gene editors are known as splicing factors. When a gene is read out and copied, splicing factors choose where to cut and past the text so that it will give the right recipe to the cell for that moment in time.

"A gene can code for a protein that causes cell death, or a protein that prevents it, depending on the editing," says breast cancer researcher Olga Anczukow, a molecular biologist who holds joint affiliations at the Jackson Laboratory for Genomic Medicine (JAX) and UConn Health .

Anczukow and colleagues at UConn Health, JAX, and Cold Spring Harbor Laboratory were curious whether splicing factors could be responsible for the way some breast cancers grow and spread through the body. If a splicing factor was giving the cell the wrong recipe, it could cause the cell to behave badly, growing out of control or migrating through the body to cause cancers elsewhere, in what's called metastasis.

They looked at cells from breast cancers, and found that only a few splicing factors seemed connected to the cell's cancerous behavior. In particular, three splicing factors gave the cells the same wrong recipe, enhancing the cell's ability to grow and to migrate. Among these, a splicing factor called TRA2B seemed particularly enriched in triple negative breast cancers. Triple negatives are the worst breast cancers: they have the highest rates of metastasis, worst prognosis, and no targeted treatments.

The researchers blocked TRA2B expression in cells, in tiny tumors in a petri dish, and in mice. In all three situations, cells lacking TRA2B were unable to metastasize.

Identifying TRA2B was exciting. Finding a way to block it could provide a treatment for this most dreaded form of breast cancer. The researchers hope to learn more about how the splicing factors become dysregulated, and eventually develop a drug to target them.

Targeting splicing defects has become a reality with

the approval of Spinraza, a first of its kind drug that corrects abnormal splicing. Spinraza was developed by Adrian Krainer from Cold Spring Harbor Laboratory, co-author on this study, and is the first FDA-approved drug to treat children with spinal muscular atrophy. Researchers hope that in the future this type of drug can be used to treat other diseases with splicing defects, including cancer.

Provided by University of Connecticut

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