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MicroRNA makes triple-negative breast cancer homesick

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Epithelial cells are homebodies – they like to attach to things and becoming detached initiates a form of cell suicide known as anoikis (literally "homeless" in Latin). But in order for cancer cells to metastasize they have to leave their homes and to survive while traveling they must resist anoikis – like a third-grader at sleep-away camp. Cancer cells do this by taking a page from the neuron playbook. Neurons are by nature unbound – they grow and link to each other and not to a substrate. Neurons have a protein called TrkB that allows them to survive anoikis; healthy epithelial cells don't have TrkB and so are susceptible to anoikis.

Carcinoma cells are epithelial cells gone bad and have learned to act like neurons, inappropriately activating TrkB signaling to escape anoikis. They do it by a mutation that nixes production of a microRNA called miR-200c.

When researchers at the University of Colorado Cancer Center reintroduced miR-200c to aggressive, triple-negative breast cancer cells, these cells regained sensitivity to anoikis and self-destructed.

"The reason this is attractive is that we're restoring something that healthy cells make normally. We foresee that miR-200c therapy will be a lot less toxic than chemotherapeutic drugs," says Jennifer Richer, PhD, co-director of the CU Cancer Center Tissue Processing and Procurement Core and senior author of two papers on miR-200c, one published today in the journal *PLOS ONE* and another published October 16 in the journal Molecular Cancer Therapeutics.

In the PLOS ONE paper, Richer and colleagues including first author Erin Howe, PhD, cultured triple-negative breast cancer cells in forced suspension – detached from a substrate. This most aggressive form of breast cancer didn't care – it had learned to be anoikis-resistant. But then the group reintroduced miR-200c, which had been lost in these cells. MicroRNAs regulate genes, turning them on or off, and sure enough in this case, the group saw that miR-200c directly turned off the neuronal protein TrkB. With miR-200c added, TrkB turned off the cells died of homesickness.

In the Molecular Cancer Therapeutics paper with Diana Cittelly, PhD as first author, the group showed that reintroducing miR-200c to ovarian cancer cells in animal models not only restarted anoikis, but also sensitized these cells to the widely used chemotherapy paclitaxel. This preclinical work takes the important first steps toward a human clinical trial of miR-200c, likely in combination with existing chemotherapies.

"But you can't just introduce microRNAs into the bloodstream," Richer says, "because they end up trapped in the liver." Richer points out that for this reason the only existing clinical trial of microRNA-based therapy is for hepatitis C – which, of course, targets the liver. The other option is applying microRNA directly to tumor cells, "Which seems very possible in the case of metastatic ovarian cancer, which tends to metastasize in the peritoneal cavity and is often directly targeted in this cavity by chemotherapy in the clinic," Richer says.

Unbound cancer cells that are immune to anoikis are most dangerous – they can travel away from their home to invade other tissues. Unbound cancer cells sensitized to anoikis by the reintroduction of miR-200c aren't dangerous at all. They're dead.

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