Putting a target on breast cancer that spreads to the brain

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Breast cancer patients whose cancer spreads to the brain may soon have new treatment options, thanks to research led by CU Cancer Center member Diana Cittelly, Ph.D.

Cittelly's research, published this week in *Clinical Cancer Research*, a journal of the American Association for Cancer Research, looks specifically at the role of interleukin 13 receptor alpha 2 (IL13Ra2), a protein that is found in increased rates in cancer cells that metastasize to other locations in the body—particularly the brain and the lungs.

"We found that patients expressing high levels of IL13Ra2 in their brain metastases have worse survival than those expressing low levels of IL13Ra2, but we could not see this correlation when examining the primary tumors. That was important because it suggested that there is adaptation of the cancer cells when they spread to the brain, and we could eventually target it," Cittelly says. "We were able to identify a role for this receptor as a tool in promoting the proliferation and outgrowth of metastasis in the brain."

Brain metastases from breast cancer develop in 15% to 50% of metastatic breast cancer patients, depending on breast cancer subtype. Current treatment options for brain metastases—including surgery, radiation, chemotherapy, and targeted therapies—have limited success and could worsen neurological function. As 80% of women with brain metastases from breast cancer die within a year of their diagnosis, Cittelly and her team were hoping to find a way to target cancer cells after they have spread to the brain. Working on cells in the lab, they identified IL13Ra2 as a likely target for treatment, particularly as the protein has shown vulnerability to CAR T-cell treatment in clinical trials on brain tumors.

"We know that in breast cancer, particularly, there is an increased risk of brain metastasis in younger women, as well as those that have HER-2

positive breast cancers, or a subset of triple-negative breast cancer," Cittelly says. "We still don't know exactly what subpopulations of cancer cells can actually grow in the brain, but our studies specifically suggest that there are some interactions with the brain that lead to the upregulation of the IL13Ra2 receptor as a tool to promote the proliferation in that environment."

The researchers' next step is to initiate a collaboration with CAR T-cell experts to further understand how CAR T-cell therapy can be targeted to IL13Ra2. Eventually, Cittelly hopes to see clinical trials for patients with breast cancer that has metastasized to the brain, as they are currently left out of clinical trials.

"Patients with brain metastases are often considered terminal, and they are excluded from the majority of clinical trials," she says. "Having something that could be used for that very specific population will be great.

"Then, in the clinical scenario, when people are already presenting with a brain metastasis, we could potentially target IL13Ra2 to decrease the outgrowth of those metastases and decrease the progression," she says. "If we can target that protein, we can improve the outcomes of these patients."

More information: R. Alejandro Marquez-Ortiz et al, IL13Rα2 promotes proliferation and outgrowth of breast cancer brain metastases, *Clinical Cancer Research* (2021). DOI: 10.1158/1078-0432.CCR-21-0361

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