

How Triple-Negative Breast Cancer Cells Metastasize

Research led by Heide Ford at University of Colorado points to the role of the EYA3 protein in priming distant sites for cancer's spread.

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Newly published research led by [Heide Ford](#), PhD, associate director of basic research at the [University of Colorado Cancer Center](#), sheds new light on how triple-negative [breast cancer](#) cells evade immune surveillance to spread to other sites in the body.

In a paper that [came out in May](#) in the journal Science Advances, Ford and her co-investigators show that a family of proteins called the “Eyes absent” (EYA) proteins can help to prime distant sites for metastasis after becoming dysregulated in cancer cells, suppressing the presence of natural killer cells in sites such as the lungs.

“We published a paper a few years ago on a protein called EYA3, which is a known transcriptional cofactor,” Ford says. “We showed that this transcription factor, through a phosphatase activity — which occurs through an interaction with another protein — could affect the transcription and stability of the MYC oncogene, allowing for tumor growth by suppressing the function of CD8+ T-cells. For this paper, my postdoctoral fellow, Sheera Rosenbaum, together with our MD-PhD student, Connor Hughes, found that the same protein also induces metastasis, and it dramatically induces metastasis in a way that’s separate from its function to affect primary tumor growth.”

Reducing natural killer cells

Examining lung cells in an animal model of breast cancer, the researchers found that the population of cytotoxic natural killer cells — white blood cells that act quickly to kill invading cells — was reduced when the breast tumors expressed EYA3 and increased when EYA3 was removed.

“We showed that what’s being secreted by the tumor is educating the secondary site,” Ford says. “It was clear that in this model, the natural killer cells are important, and that through regulating the signaling pathway, that regulates the natural killer cell response to the secondary site, enabling the cells to grow out.”

Targeting EYA

Ford is working with other collaborators, including CU Cancer Center member [Rui Zhao](#), PhD, a co-author on the Science Advances paper, on ways to target and inhibit EYA3 without increasing treatment toxicity. An effective drug for this purpose, she says, could potentially inhibit or treat breast cancer metastasis in the lungs and other distant sites in the body.

“There are people out there who think that inhibiting metastasis is not worthwhile, because once you try to go after metastasis, the horse is out of the barn, and it’s too late,” Ford says. “But I would disagree with that, because there’s a lot of data now that show that metastases at one site actually seed metastases at secondary sites. So, anything we can do to inhibit metastasis would be critical for the patient.

“We’d love to find something that would inhibit not only the process of metastasis — the ability of cells to move — but also to outgrow at the secondary site,” she continues. “The natural killer cells are the first responders to the tumor cells hitting the secondary site, then T cells and other immune cells come in. The longer-term response is probably not as dependent on natural killer cells, so any therapy would need to be multifaceted. Harnessing the immune system on multiple levels is going to be important.”

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