Seeking a unique treatment for lobular breast cancer

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Though the two main histological types of breast cancer—lobular and ductal—are treated with the same hormonal therapies, women with lobular breast cancer often have recurrence or metastasis of the disease several years after their initial treatment.

In an attempt to find out why the long-term outcomes are poorer for patients with lobular breast cancer—which affects some 40,000 women a year—University of Colorado Cancer Center member Matthew Sikora, Ph.D., began looking at the role of the protein MDC1 in tumor cells.

"This is a protein that's normally involved in DNA repair, but it seems to have some new function in lobular cancer cells," Sikora says. "It's now required for estrogen receptor activity."

MDC1 and estrogen

Ductal cancer and lobular cancer cells both use the hormone estrogen to grow, Sikora explains, and the antiestrogen drug tamoxifen typically blocks estrogen in the tumor cell, thwarting that growth. In a paper published in May in the journal Molecular Cancer Research, however, Sikora and his fellow researchers from the CU School of Medicine examined how in lobular cancer cells, the MDC1 protein allows cells to use tamoxifen as a weak estrogen, causing them to keep growing, albeit at a lesser rate.

"We think this MDC1 protein may be what influences how lobular cells respond to estrogen in the first place," Sikora says. "Back in the 1980s, when women got hormone replacement therapy and there was an uptick in breast cancer risk, most of that was lobular. It's this idea that these cells are just seeing anything that is estrogen-like differently. Not only is MDC1 possibly promoting this resistance to tamoxifen because of how it changes the way estrogen receptors work, but it may be playing a role in how estrogen works in the tumor cell."

Looking for new treatments

Because lobular tumors often metastasize to the abdomen, GI tract, and

ovaries, they can be harder to detect, Sikora says. This makes it all the more imperative to figure out a novel way to treat this type of tumor. Based on his initial research, Sikora is now looking at what other proteins work with MDC1 to promote tumor growth—and novel ways to stop that growth from happening.

"The way MDC1 normally works in DNA repair is like a scaffold. It sits on damaged sites and then recruits in other repair proteins," he says. "It's plausible that it would do something similar for estrogen receptor—instead of repair proteins, it might bring in partners that open and close DNA to let genes turn on and off. We have to figure out if there are other partners involved, if there's a bigger complex that makes that process possible."

With funding from the American Cancer Society, Sikora and his research partners will spend the next few years identifying those partners and how to combat them. They also plan to explore how the role of MDC1 in DNA repair changes in lobular cancer cells, and how that might reveal other vulnerabilities. Ultimately, he hopes the research will lead to better treatment for lobular cancer patients—treatment that reduces the risk of metastases and recurrences years down the road.

"Right now, even though patients are differentially diagnosed with either lobular or ductal breast cancer, there are few different therapy decisions, despite what we're learning about how outcomes are different," Sikora says. "For a patient with lobular cancer, ideally we could identify, using gene-expression signatures, whether this estrogen receptor-MDC1 partnership is active in the tumor. Then we can treat them accordingly. That's the long-term goal."

More information: Joseph L. Sottnik et al, Mediator of DNA Damage Checkpoint 1 (MDC1) Is a Novel Estrogen Receptor Coregulator in Invasive Lobular Carcinoma of the Breast, *Molecular Cancer Research*

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