In the fight against breast cancer, researchers identify malignancy hibernation as the next battleground

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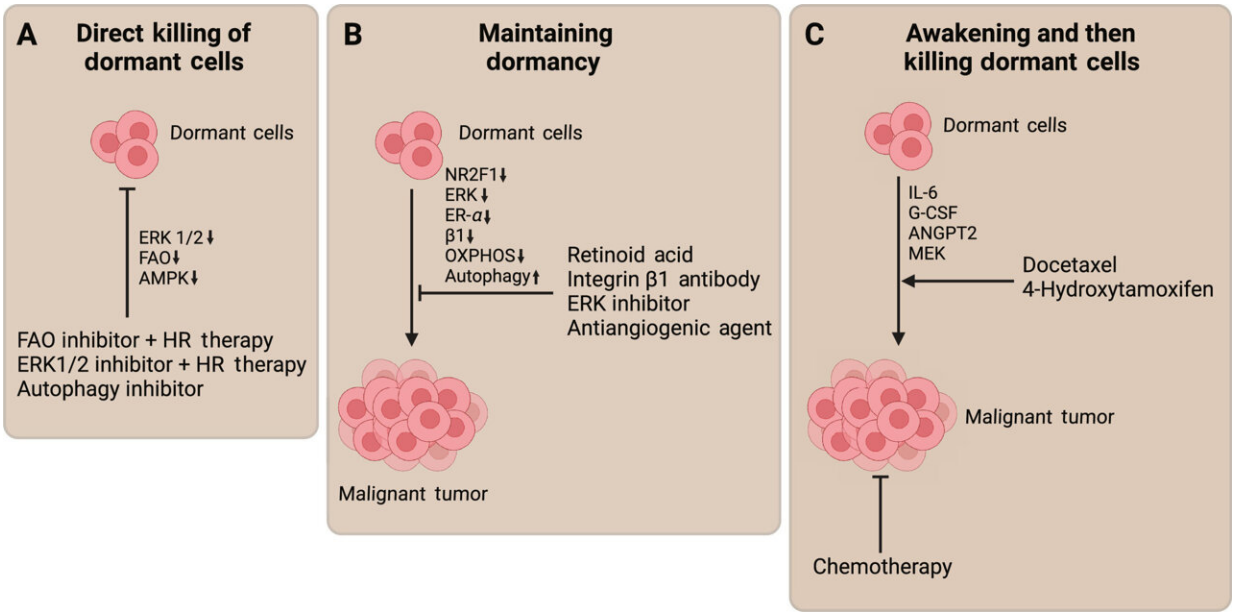

Treatment approaches for breast cancer dormancy. Plausible therapeutic pathway targets to (A) directly kill, (B) maintain, or (C) activate and then kill dormant tumor cells. Figure created in BioRender. Credit: *Science Advances* (2024). DOI: 10.1126/sciadv.adl0165

There is a surprising dearth of research about how breast cancer cells can go dormant, spread and then resurface years or even decades later, according to a new review of in vitro breast cancer studies conducted by

researchers at the University of Massachusetts Amherst.

"[Our review found that] less than 1% of all these studies that combine cells with designer environments look at dormancy," says Shelly Peyton, Provost Professor of Chemical Engineering. "It's not enough. We just don't understand what's happening— and it's killing patients."

Breast cancer dormancy is a phenomenon in which breast cancer cells metastasize—or spread to different tissue sites throughout the body (typically the liver, lungs, brain, or bones)—but don't grow.

"They're not detectable or symptomatic tumors," Peyton explains. "A patient will have their primary tumor removed and appear to be disease-free for months, years, even decades. And for reasons we don't understand, something changes about the environment that causes those cells to start regrowing, and then you have a deadly metastasis."

Patients with metastatic breast cancer have a 30% five-year survival rate, compared to a 99% survival rate for localized breast cancer. "Early detection is key, particularly in the Western world," says Peyton. "You can have lumpectomies, radiation, small surgeries. And women can survive. It's when that cancer has spread that it becomes much harder to treat."

This relapse in distant organs impacts 40% of early-stage breast cancer patients, and breast cancer dormancy is a contributing factor. But while metastasis has known biomarkers, dormant cancer cells are very hard to identify.

The Peyton Lab at UMass Amherst. Credit: Ben Barnhart

"When you have a single dormant breast cancer cell that's hiding in a distant tissue, it's really hard to detect that," says Nate Richbourg, lead author on the paper and postdoctoral researcher in the Peyton Lab. "And you don't want to do an invasive biopsy or prescribe toxic chemotherapy for something that might not be a problem."

With these challenges in mind, the review, published in Science Advances, aimed to identify gaps in the research, particularly focusing on in vitro studies, or research using benchtop-model environments instead of animal models or humans. In vitro studies allow for the precise control of the environment, which Peyton's research group says

may play a deciding role in whether a cell remains dormant or reactivates into a deadly metastatic tumor.

"What can we control in these artificial environments that will give us insight into how breast cancer dormancy happens, and what we can do to treat it as well?" Richbourg asks, describing the importance of in vitro modeling. "When we create this artificial dormancy, we can see how many of those cells could turn back into proliferating and potentially deadly cells."

Their review highlights just how complex the role of the environment is. "If you have a [breast cancer] cell somewhere in the bone marrow, you're going to have other cells there, the physical factors in your environment, and the biochemical factors," Richbourg gives as an example.

"We try to use reductive models to separate the thing that is influencing this behavior. But what we're seeing is that everything works together to create this breast cancer dormancy effect. The better we can create models that capture all that nuance, the better we're going to be able to understand it."

For Peyton, their work is also a call to action. "The paper is calling out to the field that we need to do more," she says. This includes being more creative with the materials that already exist and developing new materials; identifying ways to model the decades-long progression of dormancy that is impossible to recreate in a single study; and expanding the diversity of cell lines used for research (Richbourg points out that many of the studies they reviewed used the same cell line, MDA-MB-231, derived from one 40-to-50-year-old white woman).

Finally, the researchers have an eye for the ultimate goal: better treatments to save patients. "We see that that there are some clinical

trials that are happening that are derived from some of those in vitro models," says Ninette Irakoze, graduate student in the Peyton Lab. "The paper gives hope that, with more development of these in vitro models, eventually we could find treatments to eradicate dormant cancer."

More information: Nathan R. Richbourg et al, Outlook and opportunities for engineered environments of breast cancer dormancy, *Science Advances* (2024). DOI: 10.1126/sciadv.adl0165

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