Tumor-mimicking platform shows promise for breast cancer research, treatment

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UNL engineer Srivatsan Kidambi and colleagues have unveiled a synthetic platform that mimics the cellular-level progression of breast cancer tumors. The researchers used the new platform to determine a source of the body's resistance to a common breast cancer drug.

By simulating the growth of cancerous tumors, a new synthetic platform

developed at the University of Nebraska-Lincoln could accelerate the testing of breast cancer treatments—and has already revealed a potential source of the body's resistance to a therapeutic drug.

As detailed in two recent studies, UNL engineer Srivatsan Kidambi and colleagues used a polymer-based film to assemble cell cultures without the need of adhesive proteins required by other methods.

The innovation has allowed the researchers to better mimic various stages of tumor progression by more precisely controlling how cancerous and normal tissue cells interact, Kidambi said.

"Tumor cells were (once) believed to be the ones that controlled everything, but now it seems as though they are more like queen bees," said Kidambi, assistant professor of chemical and biomolecular engineering. "They recruit the cells inside the body to do their dirty work for them.

"We want to (coordinate) spatial organization of the cells so that we can really have a scientific way of understanding how they are going to behave. The number of cells in one stage of tumor is different in another, because the recruitment keeps happening. Cancer is a dynamic process, and that dynamism gets lost when you randomly throw cells together."

To demonstrate the platform's versatility, the researchers examined how patient-derived cancer cells from two stages of tumor interacted with two types of stromal cells that form connective tissues in the body.

The authors found a substantial increase in proteins linked to the development and proliferation of breast cancer tumors. They also measured a rise in microRNA molecules believed to disrupt the genes that keep cell reproduction in check. According to Kidambi, the findings

suggest that the platform effectively imitates the cellular activity occurring within clinical tissue samples of cancer patients.

Kidambi said the new platform could further the cause of precision medicine by allowing clinicians to quickly test pharmaceutical drug combinations on cancer cells drawn from individual patients.

"The good thing about this is that we could know whether a drug works within a couple of days," he said. "Given a few weeks, we could potentially know which drug regimen works best, compared with waiting for six months before you know whether one works in a particular patient. Cancer patients (often) don't have the luxury of that time."

The researchers then used their platform to explore why many later-stage breast cancer patients show physiological resistance to a drug called Herceptin. A lab-grown antibody, the drug is used to treat a type of breast cancer that represents approximately 25 percent of diagnosed cases.

Prior research suggests that an enzyme called Src may trigger resistance by permanently activating a protein that otherwise acts as a responsible steward of cell growth. Kidambi hypothesized that Src might itself be activated—and trigger resistance to Herceptin—when breast cancer cells make physical contact with a type of stem cell found throughout the body.

To test the hypothesis, the researchers assembled breast cancer cells adjacent to the stem cells before introducing Herceptin. Kidambi and his colleagues found that the drug failed to limit the activation of the resistance-triggering enzyme, with the cancer cells reproducing and migrating as they normally would. They discovered the opposite when the cancer cells were left by themselves or cultured with stem cells using other traditional methods.

The findings hint that the stem cells could represent a target for researchers looking to combat this common physiological resistance, Kidambi said. They also offer an early glimpse at how the new platform might advance the medical field's understanding of the mechanisms and dynamics that contribute to tumor progression, he said.

"The tumor microenvironment is much more complex than single tumor cells," said Kidambi, who has a courtesy appointment with the University of Nebraska Medical Center. "Our whole effort … is focused on recreating the environment of these bodily tissues.

"People haven't really focused as much on that, mostly because they thought that the environment of the tissue cells didn't mediate much of the biology. Now that's changing. There's a paradigm shift (under way)."

More information: Amita Daverey et al. Breast Cancer/Stromal Cells Coculture on Polyelectrolyte Films Emulates Tumor Stages and miRNA Profiles of Clinical Samples, *Langmuir* (2015). DOI: 10.1021/acs.langmuir.5b02227

Stephen L. Hayward et al. Ionic Driven Embedment of Hyaluronic Acid Coated Liposomes in Polyelectrolyte Multilayer Films for Local Therapeutic Delivery, *Scientific Reports* (2015). DOI: 10.1038/srep14683

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