Breast cancer research gets a mechanical boost

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One of the most puzzling questions in breast cancer research is why some tumors stay put, while rogue cells from others break free and spread to surrounding tissues, the first step toward creating a more lethal disease. Although researchers have found some signs in mutated genes or telltale proteins on the cell's surface, those discoveries don't tell the whole story.

Curiously, one path to unraveling this mystery may lie in a field not usually associated with cancer research: mechanical engineering.

"Over the last 20 years or so there's been increasing evidence that mechanical properties of breast tissue play a key role in promoting breast cancer progression," said Ovijit Chaudhuri, an assistant professor of mechanical engineering, and a member of both Stanford ChEM-H and Stanford Bio-X.

Working with researchers across campus, Chaudhuri's group is now studying the interplay between mechanical properties, such as the stiffness of breast tissue, and why some tumor cells spread to other tissues. By understanding that interplay better, he said, they may – one day – be able to develop better treatments for the women most at risk and ease the often-painful burden for the many others who currently undergo treatment but are less at risk.

Force on the smallest scale

Although it might sound strange for a mechanical engineer like Chaudhuri to study breast cancer – or anything to do with biology for that matter – there is certainly precedent: More than 10 years ago, researchers showed that stem cells respond dramatically differently based on what they were grown on. On a stiffer surface, for example, stem cells mature into bone; on a soft one, they often form neurons, the building blocks of the brain.

That experiment and others like it encouraged more interest in what is now called mechanobiology, the study of how mechanical properties and forces, often at the molecular level, affect everything from what genes a cell turns on and the shape and structure of an entire animal to the chemical processes underlying disease.

A stiff enemy

As with stem cells that behave differently on surfaces with different mechanical properties, stiffer breast tissue seems to encourage tumor growth, invasion and spreading, but the details of that process – as well as the processes of cancer invasion and tumor growth – remain unclear.

Chaudhuri and his lab are taking several different approaches to clarifying how the tissue's stiffness influences the tumor cells. One group in his lab is culturing mammary cells – the kind most likely to become cancerous – inside of a type of material called a hydrogel. These hydrogels were designed to present biochemical signals similar to those that would be received by mammary cells in tissues. By tuning the hydrogel stiffness, the lab can then examine how enhanced stiffness promotes the formation and growth of tumors in mammary cells.

Another group is trying to understand how cancer cells escape past the basement membrane that surrounds breast tissue when they first begin to spread – something they suspect requires the cells to actually push and pull on the membrane. A typical cancer cell is hundreds of times larger than the membrane's pores, if not larger, and although it's clear that cells get through, it's not clear how. Chaudhuri said that this "would be like a dog trying to get through the tiny hole in the mesh on a screen door." One theory is that cancer cells use enzymes called proteases to cut their way through, yet drugs that target proteases often don't stop cancer's spread, suggesting there's more going on than just enzymes.

"What we think is happening is that part of it is force, so cancer cells are physically pushing and pulling and prying open a hole to crawl through," Chaudhuri said. "What we're trying to study is, What does this process look like?"

Finally, the team is also looking at how tumors themselves grow, given that the surrounding tissue becomes increasingly stiff over time. How tumors make space to grow remains an open question, Chaudhuri said.

An end game for breast cancer?

Tackling those problems, Chaudhuri said, would not be possible without the knowledge and insights of researchers outside of mechanical engineering. Although at its core the lab focuses on mechanical systems and tools – creating gels with tunable stiffness is just one example – it counts among its members mechanical engineers, biologists, bioengineers and chemical engineers, and the group collaborates closely with faculty from biology and chemistry as well as the School of Medicine. The long-term goal, he said, is treating – and perhaps preventing – breast cancer.

"A lot of our focus is on understanding the fundamental interactions between cells and the extracellular matrix underlying processes such as breast cancer progression," Chaudhuri said. In five or 10 years, he said, he hopes that turns into improved treatments for breast cancer, but in the long term, the real hope is to prevent breast cancer from happening in the first place, not just to treat it. "This is pretty far off, but I think that should be the ultimate goal."

Provided by Stanford University

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