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Novel membrane gel from UCSB offers new tool for breast cancer research

In 2020, right when Jane Baude was starting her Ph.D. research at UC Santa Barbara, she learned that a critical component of her experiment — the gel needed to grow and test mammary epithelial cells — wouldn't be available for nearly a year because of pandemic-related production issues. So, she and her adviser, professor Ryan Stowers, decided to pivot: Baude would engineer her own gel to study cells.

Now Baude, Stowers and their colleagues have created an algae-based gel in the lab as a platform for studying mammary epithelial cells, which form milk-producing ducts and glands in healthy breast tissue and can transform into cancer cells. "Not only did we create something that can mimic commercially made gels, but we were able to use what we've made to our advantage to learn more about the cells and the material," Baude said.

In research published in the journal Science Advances, the team demonstrates that their gel successfully supports the development of normal mammary gland tissue and can be modified to direct how cells grow. By adjusting the mechanical and biochemical properties of the gel, researchers can learn more about how cells in the body are shaped by their physical environment.

Looking at the relationship between cells and their physical environment may offer new insights into how cancer develops. Historically, cancer research has focused on how mutations initiate a cascade of signals that drive tumor growth, Stowers explained.

“The environment the cell grows in is just as important as its genetics,” he said. “You can put the same cells in different environments and they might behave like normal cells, or they might behave like invasive malignant cells, just by changing the context that they’re growing in.”

Their new gel environment can provide a new understanding of how the “neighborhoods” that cells inhabit in the body send cells down developmental pathways that lead toward cancer, said Stowers, who has joint appointments in the departments of mechanical engineering and bioengineering.

“Basement membranes” direct epithelial cells

In your body, the neighborhood where epithelial cells live is called the basement membrane. “All the epithelial cells in your body are surrounded by this very thin mesh of proteins that anchors cells in place, providing support while also playing an important role in cell signaling,” Stowers said.

As a result, researchers who study epithelial cells in the lab need an equivalent basement membrane to understand how these cells act in their environment. Most commercially produced reconstituted basement-membrane products made for studying breast cancer and breast tissue are extracted from mouse tumors.

While traditional gels are widely used, “Everybody knows they’re not perfect,” said Stowers, who has done previous work with algae-based gels.

As he and Baude began to work, he recalled, “We thought, why don’t we try to overcome some of these limitations? If we’re going to go through the effort of designing a new gel, we can try to start from scratch and engineer some tunability and modularity into the synthetic system that we’re trying to develop.”

Stiff basement membranes linked to tumors

Cells respond to the physical properties of what surrounds them, whether in the lab or in the body. Being able to adjust the properties of a membrane in the lab, helps researchers see how cells react to different environments. “Cells are particularly mechanosensitive, so they can feel the difference between a soft gel and a hard gel, for example,” said Stowers, who focuses his research on how cells interact with the mechanical properties of their environment.

Those interactions can play a role in cancer. Recent research has linked stiffer surrounding environments to tumor development. “Oftentimes, when people feel a stiff lump, they go get it checked out, knowing intuitively that this hard mass, this stiff lump, is potentially bad,” Stowers explained. “The mammary gland is one of the softer tissues in the body, but a malignant tumor actually increases in stiffness as disease progresses.”

New gel adds precision, flexibility

To develop the synthetic basement membrane, Baude used a previously studied algae-based gel and tested combinations of short peptide sequences until it matched the capabilities of Matrigel, a commercially available gel for studying mammary cells. She and her colleagues also varied the crosslinking and length of polymer chains in the gel to modify its stiffness and how quickly it responds to applied force.

“We found a combination of mechanical and biochemical cues that work well,” she said. “Some of the changes we were able to make in the gel help us pick apart how different kinds of matrices contribute to cell development.” Additional modifications also allowed the researchers to mimic a matrix that makes cells more likely to become cancerous.

In the right conditions, cells placed in the gels were able to make their own basement membranes, Stowers said, “But when we supply the wrong cues, they start making other proteins and don’t develop in the right fashion.”

Stowers and his colleagues are interested in exploring the extent to which they can control the initial conditions of the gel to shape cell development, including the possibility of using the gel to grow complex tissues and organs from patient cells.

“We’re hopeful,” he said, “that by applying an engineering approach to developmental biology, we can uncover insights into how to guide the formation of complex, functional engineered tissues."

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