Mammary Gland Mysteries, Solved

The way cells behave depends on more than just their genes, it also depends on what else they can sense around them.

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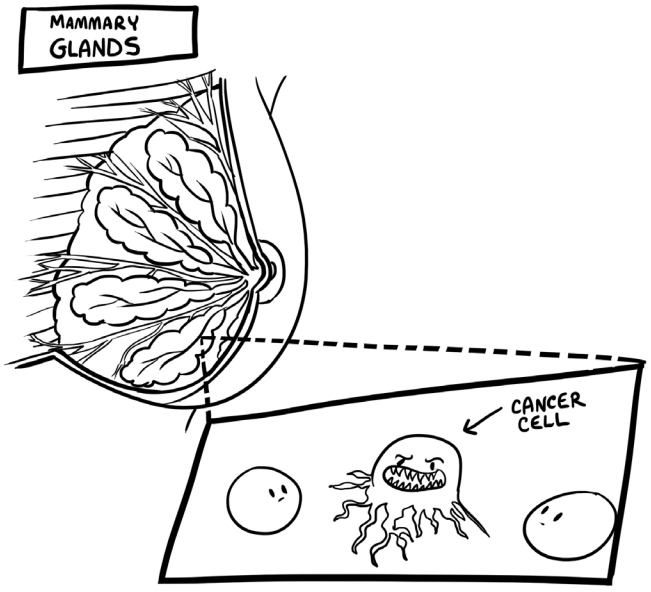
Breasts are beautiful organs. No, not in the sexualized sense, but because underneath the skin, **mammary** ducts and lobes form a stunning, radially branching array. Human mammary glands look strikingly similar to daisies, where each of the many lobes is a petal, all attached to the central nipple by ducts that can channel milk for nursing. Sometimes, though, this spectacular architecture goes awry.



In Canada, approximately 27,000 women and 200 men are diagnosed with breast cancer in 2019, with transgender people experiencing intermediate risk. When breast cancer forms, cells in a mammary duct or lobule (raspberry-shaped bundles of cells that make up the lobes) begin growing too fast, marring the exquisite, daisy-like architecture and forming a lumpy tumor instead. Tragically, over 5,000 Canadians and 600,000 people worldwide die from this disease annually, and rates are on the rise.

Dr. Mina Bissell, a professor of biological and systems engineering at the University of California Berkeley, spent much of her career studying breast cancer, including how and why these tumors form. In the 1980s, she discovered that the **extracellular matrix**, the structural scaffolding that surrounds cells in tissues, has a profound influence on how cells behave, including whether mammary cells become cancerous.

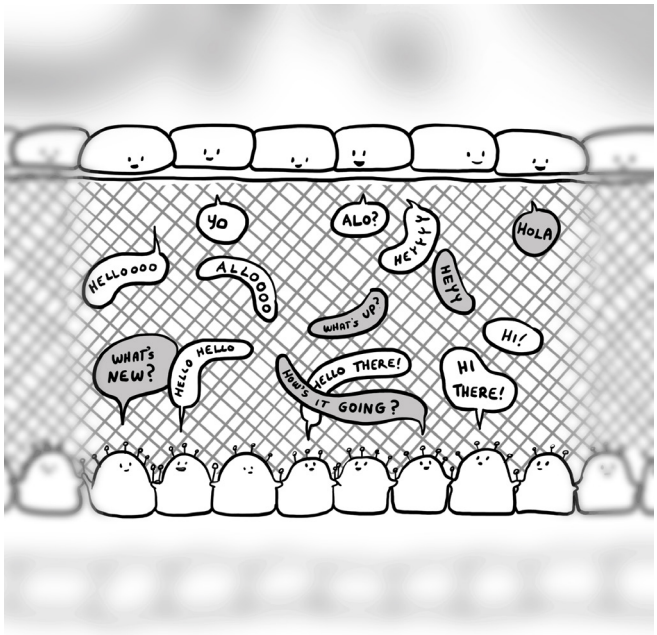
"Originally, I wanted to study glucose metabolism," says Bissell, "but I had a fellowship from the American Cancer Society, and wanted to move to California." Although Bissell did not have her sights set on a career studying breast cancer, she quickly adapted to this competitive field. In the 1970s, she focused her research on the mammary gland, but her discoveries apply to almost all the cells in our bodies.

At the time, there was a long standing belief that a *single* **oncogene** – a mutated gene that can lead to

Extracellular Matrix: *A molecular cobweb connecting cells within tissues. It is primarily made up of large, protein fibers (like collagen and fibrinogen) as well as long chains of sugars (forming a type of molecule called polysaccharides, meaning 'many sugars'). Once thought to function purely as a structural support for cells, we now know it is extraordinarily complex, controlling cell growth, communication, movement, and differentiation.*

rapid cell growth – in a *single* cell was sufficient to cause cancer. However, Bissell wasn't convinced – she reasoned that because we have so many cells in our bodies, between 10 and 70 trillion, that if the belief were true, we should have far more cancer than we do. "This did not make sense to me," Bissell says in her 2012 TED Global talk. Doing the math, "you would be a lump of cancer – you would have cancer all over you – and you're not. Why not?"

She had a hunch that it had something to do with the extracellular matrix, but at first, her colleagues didn't take her seriously. At the time, people thought that components of the matrix were like bricks, and her peers thought she was crazy for suggesting that they could have more complex functions, like being linked to cancer cell growth.



She wasn't dissuaded by the skepticism. After all, an idea wouldn't be radical if it wasn't met with some resistance. Initially, her curiosity piqued when she noticed that cells from mammary glands never grew quite right in the laboratory, and started wondering why. "If you took cells from your skin, mammary glands, tendon, or bone and you put them in culture," says Bissell, "they basically forgot where they came from."

In a flat petri dish, the mammary cells didn't form their normal raspberry-shaped lobules like they do in real tissue, and they didn't secrete milk, which should be their hallmark job. Bissell set out to establish a better culturing system for her experiments, and uncovered something big.

While experimenting with growing the cells in different ways, she found that if she cultured them in a substance that we now call **Matrigel** – a protein jelly that gives the cells an artificial scaffold, letting them grow in 3D space instead of on a flat surface – the mammary cells did something new. They started growing in bundles that looked more like raspberries. They even began secreting milk and producing their own scaffolding proteins around the cell bundles, just like they do in real tissue.

The mammary cells were receiving some kind of signal just by being suspended in a protein jelly, which mimics the context they would normally have in our bodies. This was the clearest demonstration yet that the way cells behave can be dramatically altered by the context, or **microenvironment**, in which they grow.

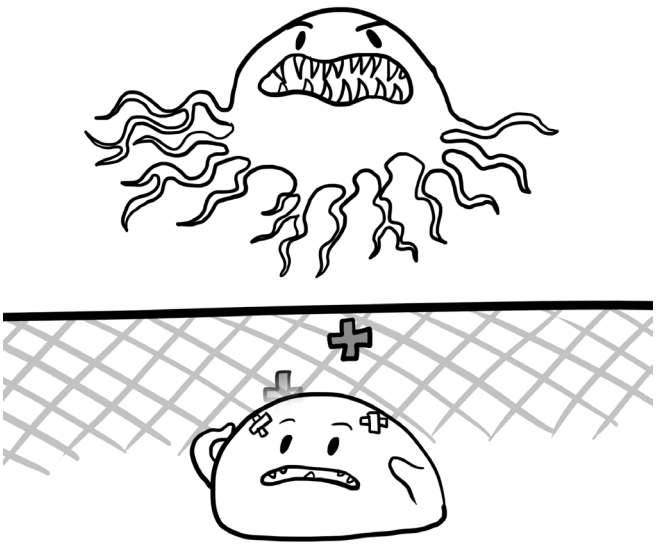
And as Bissell points out, context is everything. "I could see that the culture environment changed the way the cells behaved," she says. "I used to talk about this in the late 70s and early 80s, but people just couldn't appreciate it. I think I was one of very few people who understood that this was intrinsically important."

The cancerous cells also grew in the 3D gel. But instead of looking like raspberries, they looked more like overly mature heads of cauliflower.

Bissell grew up in Iran and, at just 17 years old, she moved to the United States on her own to go to Bryn Mawr – a distinguished women's college (the Ivy League schools did not accept women at the time). During her first year in the bacterial genetics PhD program at Harvard Medical School, she became pregnant with her first child. While her advisor assumed she would drop out, giving up on her education never crossed her mind. After finishing her PhD, she switched disciplines to cancer research, had a second child, and went on to make ground-breaking discoveries. Today, she has won some of the most prestigious awards in science, including the 2020 Gairdner International Award, recognizing her outstanding contributions to cancer research and cell biology.

For some reason, they were not able to properly organize. Cancer cells have so many things wrong with them, it was hard to know exactly why they formed this ugly, disorganized shape. But Bissell had an idea of what it could be.

Scientists have known since the 1960s that cells can communicate with each other using chemical messages, and that this communication goes haywire in cancerous cells. What if cells also communicate with the extracellular matrix, the connective scaffold, that holds our tissues together? Given the results of her Matrigel experiment, it sure looked like they might. Maybe the cancerous cells were not communicating with the logical chatter of normal cells – perhaps instead, they were babbling nonsense.



What if the cancer cells could be calmed down by muting some of this babble between them and their matrix? That's exactly what Bissell tested: She cut off the cells' line of communication by blocking specific receptors on the surface of the tumor cells, which normally allow them to receive signals from the extracellular matrix. Within days, the tumor cells reorganized, transforming into plump little raspberry bundles once again. The cancer was reverted. "It was absolutely incredible," Bissell recalls.

Bissell and her colleagues started their experiments over thirty years ago. Now, their research has led to the development of a new breast cancer therapy, which is currently entering clinical trials. Using this same principle of blocking the tumor cells' receptors (with what are called **inhibitory antibodies**), they hope they can shrink tumors in actual patients, with reduced toxicity compared to conventional treatments. But the impact of this work extends far beyond breast cancer.

The lobules of cells that Bissell grew in Matrigel were some of the first modern examples of what researchers now refer to as **organoids** – artificially cultured cell masses that resemble components of organs. Figuring out how to grow mammary cells in 3D space facilitated a whole new field of organoid research, turning cultured cells into more realistic tissues.

Today, scientists can do far more than grow mammary lobules. They can culture heart organoids that really beat, miniature brains with firing neurons, skin organoids complete with hairs, and many others that resemble simplified versions of the pancreas, lung, liver, and more.

Growing these tiny organoids in the laboratory allows researchers to conduct advanced drug testing before moving to clinical trials, saving time, money, and risk to patients. They make it possible to study infectious diseases, like Zika, meningitis, or COVID-19, in a more realistic context. Organoids can even be grown from a patient's own cells, allowing doctors to test if people with rare conditions will respond to a new drug, or if a chemotherapy-resistant tumor will respond to other treatments.

Organoids are not only useful for drug testing – they can also help rebuild parts of your body. One

of the motivations for developing heart organoids was to be able to make laboratory-grown surgical replacements – patches of heart muscle, for example – to repair weak, damaged, or defective tissue. One day, researchers hope to be able to be able to grow larger structures, possibly even whole hearts, for implantation. And it all began with wondering why mammary cells "forgot where they came from" when they were put in a dish.

Science depends on this kind of basic curiosity. Without it, Bissell may never have questioned the entrenched belief that one cell's mutation was enough to cause cancer. She followed her hunch that there was more to the story – that the way cells communicate with their 3D environments was important too – and her discoveries have unapologetically shifted our understanding of multicellular life. "Don't be arrogant," Bissell reminds us, reflecting on the skepticism she received early in her career. "Arrogance kills curiosity."