Rethinking Why Cancer Doesn't Happen – Part 1

Is DNA fate? Are cell mutations really the cause of cancer? A Fred Hutch skin cancer and stem cell scientist poses other possibilities.

September 5, 2022 By Fred Hutch News Service

Our cancer is written in our DNA. Or is it?

There's no doubt that many tumors can be traced back to damaged DNA. And a lot of cancer research, including the field of precision oncology, has primarily focused on the genetic hardware inside our cells.

But is DNA fate?

"The idea that you get a mutation and you'll get cancer is so ingrained in us because of the way we as scientists have been telling this story, the way physicians have been repeating it," said Fred Hutchinson Cancer Center skin cancer and stem cell scientist Dr. Slobodan Beronja.

Certain inherited mutations in genes like BRCA1 and BRCA2 raise the risk of several cancers, including breast, ovarian and prostate tumors. But a BRCA mutation isn't a cancer guarantee. Between 45% to 85% of BRCA carriers will get cancer — but that means that in 55% to 15% of cases, a BRCA mutation doesn't cause cancer.

"Luckily, we're organized as a living unit. We don't have to completely prevent mutations from occurring, because there are systems keeping you cancer-free despite mutations," Beronja said. "There's something hopeful viewing it in those terms: It's not one and done, there's almost like a built-in forgiveness [in the body]."

Rethinking Cancer

Our bodies work hard to keep cancer-associated mutations from taking over.

We are made up of over 30 trillion cells. Just about every one of them has at least one genetic misspelling in the DNA letters that spell out our genes. Many misspellings hit key genes that control cell growth and survival. But cancer — even in a breast cancer patient who harbors 30

trillion dangerous BRCA mutations — only arises from a handful of cells, perhaps even just one. That's a pretty great ratio of non-cancer to cancer.

"Even people who do get cancer, the majority of them get one cancer in their lifetime. So there's a lot that goes right," said Hutch tumor dormancy expert Dr. Cyrus Ghajar.

Looked at this way, cancer may be evidence that our bodies' strategies to tolerate mutated or cancerous cells have broken down. Perhaps cancer cells are not so much bad players or biological delinquents as mistaken cells that have wandered astray and could be shepherded back into obedience. By studying the body's success stories — the mutated cells that don't turn cancerous, the cancer cells that hibernate instead of activating tumors — researchers can discover how the body keeps mutated cells in line, and how to use these processes to treat or even prevent cancer.

Our Forgiving Bodies

Beronja started his Hutch lab expecting to study how stem cells contribute to cancer. He started with skin stem cells, which produce specialized skin cells and renew themselves to maintain the skin's source of specialized cells. He also began with the apparently self-evident assumption that cancer-driving mutations drive cancer. He reckoned that biological forces that increase the number of self-renewing skin stem cells would raise cancer risk by increasing the number of mutated stem cells that could turn cancerous.

"So this is basically looking at stem cell renewal completely as a passive mechanism that would facilitate more efficient tumorgenicity [cancer development] just because there are more [mutated stem cells]," he said.

Beronja developed a technique that would allow him to track stem cell renewal. It seemed logical that cancer-promoting mutations would encourage the generation of more skin stem cells.

But when he introduced a well-known cancer-driving mutation into skin stem cells early in mouse development, the mice had fewer mutated skin stem cells, which renewed themselves more slowly than normal.

Had the assay failed? Was this a setback for his fledgling lab?

But around the same time, another research group released evidence that made Beronja rethink his results. The scientists had looked at UV-exposed eyelid skin of middle-aged adults, and found that a square inch of normal, non-cancerous skin was riddled with mutations, many of them considered cancer drivers. The number of mutations in normal skin tissue rivaled the number seen in skin tumors, and exceeded the number of mutations seen in other tumor types, like breast cancer.

The findings upended researchers' expectations about how powerfully these mutations could promote cancer.

Ghajar noted that cancer-driving mutations are defined via animal studies. After identifying common cancer-associated mutations in human cancers, researchers introduce them into mice to see if tumors arise. If they do, they're considered cancer drivers.

"But when you find these mutations in people in normal tissue, then what does that mean? It's clearly not a driver," Ghajar said.

Most mutations, it turns out, need a partner in crime — another powerful mutation — to push cells toward cancerous delinquency. The mutation-riddled reality of normal skin tissue prompted Beronja to reevaluate his stem cell-tracking assay. The notion that skin has ways of handling mutations cast his results in a new light.

A Body in Balance

Our 30 trillion cells work in concert. The biological forces that ensure this collaboration also keep cancer at bay, Ghajar said.

"Our organs are set up for function, and that function is inextricably linked to architecture," he said.

Most cells in an organ are differentiated, meaning they perform a specialized function (often in a specific arrangement within the organ) and generally no longer divide to produce new cells. (A notable exception to this would be immune cells; despite having very specialized roles, immune cells are often able to divide and must be able to migrate through our tissues to perform their roles.)

And this differentiated state isn't merely governed by an internal molecular decision-making process within each cell. It's a collective magic.

"If a cancer cell wanders into another organ and survives, it falls under this spell," Ghajar said.

So a healthy organ can stop a cancer cell cold.

"To me, it's always raised the issue, well, what if you damage the microenvironment? Is that sufficient to cause cancer?" Ghajar said. "It has been demonstrated that it is. And that is a really instructive and important lesson. But it's not always sufficient, even in the presence of a mutated cell. And there is something we need to learn from that, too."

Cancer-promoting tissue damage can precede DNA damage.

For example, over 20 years ago, Ghajar's postdoctoral mentor, Dr. Mina Bissell at Lawrence Berkeley National Laboratory, showed that enzymes that break down tissue structure can fuel blood vessel growth, inflammation and, eventually, reactive oxygen molecules that eventually damage DNA. Together, these changes pave the way for tumor growth. To seed a new tumor, a

metastatic cancer cell must find its way into fertile ground.

“The microenvironment, the power of the systemic environment — these are incredibly important and on an organismal level, something we still have so much to uncover, so much to understand,” Ghajar said.

There are times when a tissue needs to lessen its quieting, differentiating spell.

When an organ heals from a wound, the biological forces within it shift from encouraging stasis and differentiation to movement and growth: Blood vessels need to grow, and rather than sitting still, skin cells must crawl across the gap to seal it. Cancer cells behave like this all the time — but unlike normal tissue, they don’t stop. In fact, cancer has been described as a wound that doesn’t heal, Beronja said.

Beronja’s own investigations into how skin stem cells respond to mutations also support the idea that at least in some cases, cancer cells are frantically trying to heal a wound that doesn’t exist.

He found that one mutation seems to act as a phantom wound, triggering individual skin stem cells to multiply themselves in the same way they’re thought to do when a gap in tissue needs closing. But the mutated stem cells found restraint: When the clump of mutated cells grew so wide that the clump’s interior cells were totally surrounded by other mutated cells, the surrounded cells flipped from multiplying to differentiating. Balanced between renewal and differentiation, the clump stopped growing.

Beronja suspects that a normal tissue-maintaining mechanism had kicked in.

“Once you do have the more efficient closing for the epidermal compartment, because you’ve increased the number of stem cells, you need to get rid of them,” he said. Too many skin stem cells will lead to an overgrowth of skin tissue, so after healing, skin needs to get back to its stem cell sweet spot: not too many, not too few.

“You don’t need to kick them out,” Beronja said, “you can get rid of them slowly.”

After they differentiate, former stem cells will behave just like any other specialized skin cell: After spending about two weeks as skin cells that maintain the barrier against the outside world, they’ll get sloughed off. Beronja suspects that evolution has connected the pro-growth signal tripped by the mutation to a fail-safe switch that ensures that skin stem cells return to business as usual when needed.

There are already therapies on the market that target cancer by forcing tumor cells to differentiate and lose their power to grow and spread. (For example, tretinoin, a form of vitamin A, is part of the treatment regimen for acute promyelocytic leukemia.) Beronja’s work suggests discovering how this is controlled in normal tissue could help us find ways to use differentiation to prevent cancer to begin with.

The balance between renewal and differentiation is a recurring theme in the mutation-tolerating mechanisms that Beronja and his team have worked out. He initially thought that cells might respond to dangerous mutations by sacrificing themselves (cell death, or apoptosis) or by figuratively throwing up their hands and taking a permanent hiatus (senescence).

“But neither of those matter. And they don’t matter because neither is consistent with how the tissue should be organized and how it functions,” Beronja said. “The fundamental point of all of this is that the function of skin is to maintain your barrier between the inside and the outside. So basically everything it does is subservient to this simple goal.”

So instead of dying or quitting, skin stem cells choose to keep marching forward.

Specialized skin cells are shed every two weeks, so skin stem cells must continually produce more while also maintaining themselves. And skin is constantly exposed to DNA-damaging UV light. If every stem cell that collected a mutation died off, soon we would have no skin stem cells and, not long after, no skin.

Beronja expects that other tissues with high turnover will also incorporate similar strategies as skin to maintain function in the face of mutations. But other tissues with other needs, he believes, will employ different, so-far undiscovered tolerance mechanisms.

Ghajar’s work on dormant tumor cells also suggests that there are tissue-by-tissue nuances at play in how organs keep tumor cells quiet, likely linked to a specific tissue’s function and needs. He studies breast cancer metastasis, in which cancer cells spread beyond the original tumor site in the breast. He found that tumor cells become ensnared and befuddled right after they’ve crossed the blood vessel wall into a new tissue. But the factors putting them to sleep vary depending on whether the blood vessel is located in the brain, the bone marrow or the skeletal muscle.

His team’s studies in skeletal muscle identified a unique aspect of the tissue that cancer cells can’t overcome, while also highlighting a deep truth about cancer cells and their needs. Dr. Sarah Crist, then a graduate student in Ghajar’s lab, found that tumor cells can barely withstand the unusually high level of reactive oxygen molecules in skeletal muscle. It’s all they can do to survive the stress, let alone grow.

Giving the tumors extra antioxidants helped tumor cells grow in mouse skeletal muscle — but this same antioxidant boost proved detrimental when tumor cells tried to grow in the animals’ lungs.

“What does that tell us? It tells us there’s an optimal level of oxidation and reduction [antioxidation] that a tumor cell needs, and it’s tuned to the tissue that it’s in,” Ghajar said. “It simply can’t tune itself to thrive within the muscle. So the question is how we can take lessons from this and apply them to stop these cells from thriving elsewhere.”

When the Balance Fails

After outlining how our bodies tolerate mutations, the obvious question, Beronja said, is, “How does it fail?”

This is a question he’s just beginning to explore, but Beronja thinks that different mutation-tolerating mechanisms, and differences in how they break down, could be at play in when and where we get cancer.

For example, the two most common skin cancers: Basal cell carcinomas arise mostly on the nose, while squamous cell carcinoma usually crops up along the hairline. Could that be explained by different suppression strategies, possibly including differences in our microbiome, in different regions of skin?

And perhaps the patterns of mutations that we see in tumors are also shaped by our bodies’ flexibility, he said. Perhaps common cancer mutations are common not because they drive cancer, but because that tissue was able to tolerate that mutation and maintain the cells that harbor it.

Beronja also believes that mutation-tolerating mechanisms go a long way to explaining why age is the biggest risk factor for cancer. Over 90% of cancers are diagnosed after age 45.

To Beronja’s mind, this is more than evidence that tumors arise from a mix of mutations that take time to accumulate. He also sees evidence of our bodies’ tumor-preventing mechanisms wearing out. He noticed that many people seem to experience a general physical downturn around age 40.

“That got me thinking about the concept that maybe it’s not necessarily the accumulation of, let’s say, mutations in your cell [causing cancer], but it’s maybe what happens to some sort of a protection mechanism,” he said. “If it’s a competition between your normal and mutated cells, maybe at some point [with age] your normal cells become just not very good at competing, and the mutant cells take over.”

Beronja and his team are working to identify and figure out how to reactivate these protective mechanisms. Whatever it is that causes them to break down, Beronja hopes that reawakening them — helping the body return to its previous state of balance — could be a way to rein in tumors without needing to eradicate every hidden cell.

“If you look at the human body, it’s an amazing construction,” he said. “It’s so efficient at being alive and satisfying the needs of trillions of cells, a multitude of organs. … There’s an organizing principle, which is to maintain function despite persistent challenges.”

Read more about how Hutch scientists are rethinking how cancer doesn’t happen in Part 2 of this two-part series.

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