An emerging view of evolution is informing cancer research

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Parag Mallick is working with colleagues to develop a model of how cancer cells behave in order to discover what triggers their sudden transformations, from quiet and comparatively harmless tumor cells into peripatetic, metastatic cells that invade other tissues. Credit: Norbert von der Groeben

Cancer cells can be as cooperative as a flock of birds, making individual

decisions yet somehow acting in unison. A Stanford researcher is using this insight to make a computer model of cancer.

Sitting in his office, at the Canary Center at Stanford for Cancer Early Detection, Parag Mallick, PhD, played a video on a computer: It showed a flock of birds wheeling in a blue sky. An assistant professor of radiology, Mallick said the way birds in flight move like a single, giant, living thing is key to an emerging view of the way cancer cells behave.

Such group behavior, whether in birds, fish or cells, arises from simple rules governing the behavior of each individual.

In a flock of birds, the rules might include how each bird always flies in the same direction as nearby birds and always stays close, though not too close, to them. But the coordinated, dancelike behavior of flocks can't be predicted by studying one bird at a time. Complex behaviors that only emerge in groups are called "emergent properties." For example, no single molecule has a temperature, but groups of them do.

What triggers metastasis?

At the Canary Center, Mallick and other researchers are building on such insights to develop a computer model of cancer. Working with a team that includes the center's director, Sam Gambhir, MD, PhD, professor of radiology; computer scientist Christopher Ré, PhD; and interns from local high schools, Mallick is looking at how cancer cells behave in order to discover what triggers their sudden transformations, or state changes, from quiet and comparatively harmless tumor cells into peripatetic, metastatic cells that migrate all over the body, invading and altering other tissues.

Just as hundreds of birds can suddenly take flight together and head off in one direction, swooping and turning in unison, tumor cells can

perform similar feats.

When cancer cells transition to metastatic behavior, it can happen quite suddenly, said Mallick. Non-metastatic tumor cells might sit quietly inside a tumor with a clear boundary. But when metastasis starts, the same cells become lethal; they aggressively break through the wall of the tumor and launch themselves out into the rest of the body. "Cancer cells will spontaneously start to move in one direction," he said. But what makes cancer cells suddenly get the travel itch? And more generally, added Mallick, "What are the origins of such state changes? How do you describe them? How do we model them? What's governing their behavior?"

Of course, the behavior of cancer cells, like that of healthy cells, is hugely complex. For example, cells might behave in a cancerous way for reasons that are deep in their genes, or the change could be driven by signals from the environment. And metastatic cells might circulate in the blood for long periods before beginning to colonize other parts of the body.

Yet we do know that no single governor gives a top-down order to all the cells; instead, just like a flock of birds taking wing, the cells all begin moving at once, responding to one another.

Building a model

In an attempt to detect, predict and prevent such transitions, Mallick and his colleagues are building a massive computer model of cancer that includes every level of organization, starting from molecular processes and the behavior of individual cells to the growth of whole tumors and their metastasis, as well as immune responses throughout the body. "We're working on coalescing all of that information into what, in our mind, is the first-ever truly multiscale data set," he said.

Mallick's forte is finding ways to connect all these different levels of organization. One connection is the sudden transition from the independent behavior of cancer cells to group behavior. Another might be a nutrient gradient across a tumor that connects the effects of nutrients on individual cells with those on the whole tumor.

"If you are modeling water," he said, "there's a particular sort of math that you use to describe the behavior of single atoms, and a very different sort of math for describing the flow of rivers." For a multiscale model of water, you would need a way for those two models to connect.

Putting the pieces together means accepting that the very theory of how cancer works is evolving.

An evolving theory of cancer

Decades of work had researchers convinced that cancer resulted from genetic mutations in individual cells. The theory was that a carcinogen, such as asbestos or cigarette smoke, induced mutations in a cell's DNA that eventually caused it to become cancerous. That bad cell multiplied and spread.

But it has turned out that most of the things that cause cancer, including tobacco smoke and asbestos, don't cause mutations. Rather than modifying the genes themselves, smoke and asbestos alter the activity of genes through a collection of processes called epigenetics.

Epigenetics consists of tiny modifications—either to the DNA itself or to proteins called histones that wrap around the DNA and change the activity of the genes. For example, if you spend every weekend gardening, changes in the activity of genes in the skin cells of your hands will produce callouses.

Our callouses might seem very ordinary to us; they come and go depending on what we've been up to recently. But what if the genes whose activity changes to produce them could mutate so that our callouses became permanent? What if some babies were born with calloused hands?

Amazingly, modern evolutionary biologists are moving to the view that that's exactly how wild plants and animals often evolve.

It all starts with the phenotype, which is every single trait of an organism or cell other than the genome itself. The phenotype includes the actual enzymes encoded by genes, myriad metabolic pathways, the shape of a nose or the hands, a vast repertoire of behavior and even memories of an equation or a loved one.

We already know that the same genes can produce alternate phenotypes, depending on just how the genes are expressed. That phenotypic plasticity delivers different castes of ants, all from the same genotype; hands that look different from our feet, even though they have the same genotype; and identical twins of different heights and personalities. All these changes arise from the way the immediate environments of cells, or of organs, or of whole individuals interact with genes. The differences in gene activity are mediated by an array of hormones, transcription factors and other mechanisms.

'Genes are followers, not leaders'

Evolutionary biologist Mary Jane West-Eberhard, PhD, one of the leaders of the movement to reframe evolution, has laid out the experimental evidence showing that the plasticity of an organism's characteristics, or phenotype, foreshadows its evolution. In essence, you can start with an epigenetic variant—think calloused hands—and later that particular trait can become permanently fixed in the genes.

Famously, West-Eberhard said, "Genes are followers, not leaders, in evolution." Now that same idea is invading the theory of cancer. It seems that cancer cells, too, can first begin to change through temporary epigenetic changes, instead of by means of mutations in the DNA.

In cancer biology, the role of epigenetics is gaining acceptance, but it's still meeting resistance from researchers who may have spent a lifetime with the idea that cancer cells are primarily the result of individual mutations, said Alexander Anderson, PhD, chair of integrated mathematical oncology at the Moffitt Cancer Center, in Tampa, Florida. "There's still definitely an old-school crowd who think if we just sequence deep enough, we'll solve all the problems."

A recent article in The New Yorker about epigenetics by Siddhartha Mukherjee, MD, DPhil, triggered a storm of complaints from molecular biologists who felt that standard genetics had been ignored. But while it's possible to quibble about whether Mukherjee, an assistant professor of medicine at Columbia University, should have put his discussion of epigenetics in context, there's no question that epigenetics is deeply altering our understanding of both evolution and cancer. "There's a feeling in the field that we have to start thinking more holistically," said Anderson. And the key to that, he said, is math.

A systems approach

Mallick, said Anderson, is one of a few researchers with a strong understanding of both cancer biology and the mathematics needed to build a model of cancer based on a systems approach.

Said Mallick, "We just had a paper accepted where we found that when you treated cells with a chemotherapeutic drug over long periods of time, you could make cells that were 40 times more drug-resistant. Yet the cells had no genetic alterations." Instead, all the changes were

epigenetic. "If you treated the cells with the drug, they were like, 'Oh, OK, let me change my histones,'" he said. "It's a crazy thought."

While the mechanisms for changes may be modifications to the histone proteins or the DNA, the driver of change is the environment. It is now well-established that epigenetic changes play a role in both cancer initiation and progression. The same processes may also determine if cells are cancerous or healthy, metastatic or not.

Cancer, explained renowned developmental biologist Scott Gilbert, PhD, of Swarthmore College, can result not only from bad cells but from a bad cellular environment.

For cancer cells, said Mallick, that means where the cells live in a tumor, how close they are to nutrient-rich blood vessels, the behavior of nearby cells and where the cells are in the body. Each of these situations can induce a range of epigenetic reactions that can impact, for example, how resistant or sensitive the cells are to chemotherapy drugs or how likely the cells are to begin to metastasize.

A tumor comprises an array of ecological niches, each of which can induce a different kind of behavior or phenotype in the cancer cells that live there, said Anderson. But just as a tropical rainforest functions similarly whether it's on one continent or another, different kinds of tumors share common rules that govern their overall behavior and the phenotypes of individual cells in different parts of the tumor.

Animals and other organisms can pass epigenetically mediated traits to multiple generations without any change in the genes themselves. And at least some of these phenotypic traits can become permanently fixed in the genome, as demonstrated in lab studies. It makes sense then that cancer cells could do the same.

Mallick said the epigenetic changes that incite tumor cells to resist deadly drugs are passed on to daughter cells. Although no one has witnessed it happen, it's pretty clear that the right mutation could turn the trait for drug resistance from plastic to permanent, making the trait part of the cancer cells' permanent genetic repertoire.

As Gilbert said, "You start off with an epigenetically induced phenotype. And then if any mutations occur that allow this to be fixed into the genome, it goes for it."

Markerville

This new way of understanding evolution is the theoretical engine that drives Mallick's research. Viewing cancer as a dynamically evolving adaptive system, his team's big focus is the giant model of cancer behavior that integrates all the different levels. "Our entire purpose in life is to build a virtual model of cancer," said Mallick.

The ultimate goal of the model is to explain cancer, but the model also has immediate medical uses. For instance, Mallick is using the model as a tool to help identify markers of important transitions in the life of populations of cells—to cancer, to drug resistance or to metastasis. Such markers are essential to developing tests for diagnosing cancer and for investigating how patients respond to treatment over the course of their disease.

Mallick and his colleagues are on the verge of launching a publicly accessible, interactive database and model of cancer called Markerville. "It includes both a model of cancer and a collection of data we've pulled from the literature about each protein," he said. Markerville will tell users everything known about a particular protein and also how it might be expected to serve as a marker in a given cancer. "Our goal is to build a computer program that you could come to with any protein and say,

'OK, I'm interested in this protein and I'm looking at this cancer. Do you think it has potential to be a good biomarker?'"

Our understanding of cancer biology has taken off in recent years, but it's not yet clear where it's leading researchers. Just as it's difficult to see which way the individual birds in a flock will turn from moment to moment, it's difficult to predict which discoveries will transform our understanding of cancer. But changes in the understanding of both basic evolutionary biology and systems biology are helping researchers see things in new ways.

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