Plus

An evolving view of cancer

It may not always start with a mutation

By Jennie Dusheck
Photograph by Timothy Archibald

Last spring, *The New Yorker* published a piece on epigenetics and cancer that triggered a storm of complaints from molecular biologists, who called the article "misleading" and even "horribly damaging."


Photo of Parag Mallick

The article's author, Siddhartha Mukherjee, MD, DPhil, an assistant professor of medicine at Columbia University, issued a rebuttal. But even after the dust settled, many seemed to agree that Mukherjee had ignored traditional genetics and that his description of epigenetics — how cells regulate the activity of genes — was too streamlined to satisfy the biologists.

Yet it likely wasn't just Mukherjee's approach that triggered the anger. Cancer researchers are beginning to embrace a new paradigm: that how cancer cells behave and evolve is a response to their environment, not just to genetic mutations. That paradigm is meeting significant resistance from researchers who have spent a lifetime with the idea that cancer cells result from mutations.

"There's definitely an old-school crowd who think if we just sequence deep enough, we'll solve all the problems," says Alexander Anderson, PhD, chair of integrated mathematical oncology at the Moffitt Cancer Center, in Tampa, Florida. Epigenetics, he says, is transforming our concept of cancer biology.

Beyond mutation

For decades, researchers have accepted the idea that cancer results from genetic mutations in individual cells. And indeed if you look at tumor cells, they differ generically from healthy cells nearby — sometimes dramatically so. The theory has been that a carcinogen, such as asbestos or cigarette smoke, induces mutations in a cell's DNA that eventually cause it to become cancerous. That bad cell and its descendants multiply faster than healthy cells and take over.

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

Epigenetics consists, among other things, 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. (Like Mukherjee, we are leaving a lot out.)

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 — everything but the genes. The phenotype includes the 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, organs or 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 callused hands — and later that particular trait can become permanently fixed in the genes. In fact, ostrich chicks do just that, hatching with callouses that help protect their young chests from the hot, rocky ground.

Famously, West-Eberhard, staff scientist emerita at the Smithsonian Tropical Research Institute, said, "Genes are followers, not leaders, in evolution."

Now that same idea of genes as followers 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.

A systems approach

"There's a feeling in the field that we have to start thinking more holistically," Anderson says. And the key to that, he says, is math.

One of a few researchers with a strong understanding of both cancer biology and the mathematics needed to build a new model of cancer based on a systems approach, says Moffitt Cancer Center's Anderson, is Stanford assistant professor of radiology Parag Mallick, PhD.

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Mallick, who works at the Canary Center at Stanford for Cancer Early Detection, describes a paper he and his colleagues published in May 2016 in *Genome Medicine*: "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 says. "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. Cancer, explains 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, says Mallick, whether the environment is good or bad depends on where the cells live in a tumor, how close they are to nutrient-rich blood vessels, how many immune cells they have been in contact with, the phenotypes 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, says Anderson. But just as a tropical rainforest functions similarly whether it's on one continent or another, all tumors share some common rules that govern their behavior and even 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. Lab studies demonstrate that some of those phenotypic traits can become permanently fixed in the genome. It makes sense that cancer cells could do the same.

Mallick says the epigenetic changes that help tumor cells 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 says, "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."

A mathematical model of cancer

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 is focused on developing a giant model of cancer behavior that integrates all the different levels. "Our entire purpose in life is to build a virtual model of cancer," says Mallick.

Sitting in his office, Mallick plays a video on a computer. It shows a flock of birds wheeling in a blue sky. Mallick says the way flocks of birds move — forming dense clouds, then moving here and there, all together like a single being — is key to an emerging view of the way cancer cells behave.

'Our entire purpose in life is to build a virtual model of cancer.'

Such group behavior, whether in birds, fish or cells, arises from simple rules governing the behavior of each individual. In a flock of birds, for example, 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 the others. But the behavior of flocks can't be predicted by studying one bird at a time. Complex behaviors that emerge only in groups are called "emergent properties." For example, no single molecule has a temperature, but groups of them do.

What triggers metastasis?

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. Working with a nationwide team, funded by the National Cancer Institute's Physical Sciences in Oncology Initiative and by the Defense Advanced Research Project Agency and including the Canary Center's director, Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology; computer scientist Christopher Ré, PhD, and interns from local high schools, Mallick is looking at how cancer cells behave. The team aims to discover what triggers their sudden transformations, or stem changes, from quiet and comparatively harmless tumor cells into peripatetic, metastatic cells that migrate all over the body, invading and altering other tissues.

When cancer cells transition to metastatic behavior, it can happen quite suddenly, says Mallick. Nonmetastatic tumor cells might sit quietly inside a tumor with a clear boundary. But when metastasis starts, they 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 says. But what makes cancer cells suddenly get the travel itch? And more generally, adds 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 the model

In an attempt to detect, predict and prevent such transitions, Mallick and his colleagues' massive computer model of cancer will include 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 says.

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 says, "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 to connect.

The ultimate goal of the model is to explain cancer, but it 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.

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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