A Deeper Look at Tumor Heterogeneity

The sheer complexity of genetic variability within individual tumors raises huge challenges—and opportunities

For many cancer researchers, the large amount of genetic variability in tumors is a troubling topic. However, the topic has been widely debated throughout the field since March, when the *New England Journal of Medicine* published the results of a study that carried out deep sequencing of metastatic renal-cell carcinomas and demonstrated that most mutations do not occur throughout an individual tumor (N Engl J Med 2012;366:883–92).

Although this work is not the first to reveal lack of uniformity in tumors, researchers who didn't participate in the study give it credit for sharpening our picture of cancer's genetic variety.

"It's one of the first studies that shows tumors are heterogeneous in a comprehensive way," says Kornelia Polyak, MD, PhD, professor of medicine at Harvard Medical School and a breast cancer geneticist at Dana-Farber Cancer Institute in Boston, MA.

"We knew what to expect, but not the exact extent," adds Darryl Shibata, MD, professor of pathology at the University of Southern California in Los Angeles.

In the study, Charles Swanton, MD, PhD, group leader of the translational cancer therapeutics laboratory of the Cancer Research UK London Research Institute, along with his colleagues analyzed biopsy samples from 4 patients.

Instead of a clone descended from a single renegade cell, each tumor displayed a diverse, diverging cell population that the researchers could depict with an evolutionary tree. About two thirds of the mutations that Swanton and colleagues detected weren't present in all sequenced parts of the tumors.

When the researchers looked more closely at 1 patient's tumor, they discovered that even so-called driver genes necessary for oncogenesis weren't always mutated in the same way. Only 1 of 4 driver genes for this type of cancer, *VHL*, exhibited the same mutation throughout the tumor. One of the other drivers, *SETD2*, appeared in 3 mutated forms that were confined to different regions of the tumor or the metastases. "We were certainly surprised that heterogeneity outweighed ubiquitous cancer events," says Swanton.

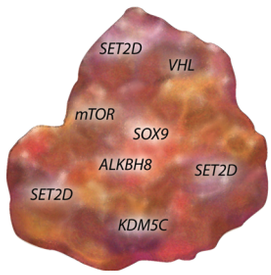
A similar pattern of diversity emerged when the team derived a "prognostic signature," based on expression of 110 genes, from the same patient's tumor. Depending on where a sample came from in the tumor, it could suggest a good or a poor prognosis.

That disparity "smacks you in the face," says Carlo Maley, PhD, associate professor of surgery and director of the Center for Evolution and Cancer at the University of California, San Francisco.

"What we're seeing is stark proof that there's genetic diversity that can be regional" in tumors, comments John Dick, PhD, professor of molecular genetics at the University of Toronto.

These findings heightened concerns that tumor heterogeneity will impede the march to personalized medicine, which tailors treatment to a tumor's genetic defects, because a single biopsy of a heterogeneous tumor might not give doctors sufficient information about mutations driving the tumor.

However, researchers say that widespread tumor diversity won't deal a fatal blow to this approach. "We don't want this to stall personalized medicine—and it may not," says Lillian Siu, MD, professor of medicine at the University of Toronto.



Examining tumor tissue from patients with metastatic renal-cell carcinoma, researchers found that about two thirds of the mutations weren't present in all sequenced parts of the tumors. In 1 tumor, even so-called driver genes necessary for oncogenesis weren't always mutated in the same way.

TRACKING TRUNK MUTATIONS

Scientists might be able to locate early mutations—those that are on the trunk of the tumor's evolutionary tree—that are universal and could still help guide treatment choices, Siu points out.

Swanton agrees, saying that he expects that more deep sequencing of tumors will help uncover these trunk mutations.

Frank Furnari, PhD, a faculty member at the Ludwig Institute for Cancer Research at the University of California, San Diego (UCSD), and associate professor of pathology at UCSD, adds that researchers could test whether targeting the trunk mutation revealed by Swanton and colleagues—in the gene *VHL*—is effective. *VHL* controls the transcription factor HIF-1α, and drugs that block certain transcriptional targets of HIF-1α, such as VEGF receptor and PDGF receptor, are already available.

Better understanding of tumor heterogeneity also will offer insight into the difficulties of treating cancer.

"The good part about all of this work is that it goes a long way toward explaining why recurrence is so high," says Dick. These myriad mutations are fodder for the evolution of drug resistance, and tumors are constantly evolving.

This heterogeneity might explain, for instance, why excising a primary tumor itself sometimes improves the survival of patients with metastases, says Swanton. Surgery "might be removing an evolutionary sink of diversity," he suggests.

Similarly, Shibata says, drugs that reduce heterogeneity—even if they don't eliminate the tumor—might be beneficial, leaving the tumor more vulnerable to other drugs.

Although heterogeneity will complicate efforts to investigate tumors and devise treatments, researchers say they are ready for the challenge.

"The heterogeneity and mutability of tumors are higher than we feared," says Maley, "but we now have the assays to measure it and see the fundamental dynamics that are driving it."

"Some people consider this as scary and daunting," says Polyak. "The way I look at it is that we now have a real opportunity to understand cancer in greater depth." —*Mitchell Leslie* ■

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.