MedicalXpress

Study reveals startlingly different tissue sensitivities to cancer-driving genes

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New research led by Harvard Medical School and Brigham and Women's Hospital has unmasked hundreds of cancer-driving genes and revealed that different tissue types have shockingly variable sensitivities to those genes.

The findings, published online in *Cell* on March 22, promise to improve scientists' understanding of normal and malignant cell proliferation.

They also help explain why individual cancer drivers appear in some tumors and not others and could inspire more tissue-specific strategies for cancer treatment.

"Genes that regulate pancreatic cancer make pancreatic cells proliferate but not breast cells, and vice versa," said the study's senior author, Stephen Elledge, professor of medicine at Brigham and Women's and the Gregor Mendel Professor of Genetics and of Medicine at Harvard Medical School. "The degree to which we see different cells respond to different genes is unprecedented."

Hidden players

Although a certain amount of cell growth and division, or proliferation, is essential for maintaining health, cancer steps on the gas pedal so cells proliferate with abandon.

Some genes drive harmful proliferation because they've been mutated. Other genes remain intact but still fuel tumor growth because they've been turned on too high or been duplicated.

Scientists have had a hard time identifying these overactive genes because they don't get flagged by genetic sequencing. Elledge's lab, along with colleagues at the Dana-Farber Cancer Institute and Baylor College of Medicine, devised another way to find them.

The researchers built a library of 30,000 individually bar-coded genes, representing about 80 percent of the genome. They took a collection of cells and put one gene into each of them. Instead of using 30,000 separate lab dishes, they let the cells grow in the same container. After a few days, the cells had proliferated at different rates. The researchers then used the bar codes to determine which genes drove growth.

The team ran the experiment on cells from three types of noncancerous tissue: breast cells, pancreatic cells and connective-tissue cells called fibroblasts.

A full 10 percent of the genes tested turned out to regulate proliferation. Some had already been linked to cancer by DNA sequencing studies, but many more had not.

About 250 of the genes that hadn't been previously associated with normal or abnormal cell proliferation can be found in tumors where large segments of DNA are repeatedly amplified or deleted, "suggesting they help drive cancer," said Elledge.

More different than alike

Even more startling were the distinctive ways in which each tissue type responded to the same gene activity.

"We didn't realize how profoundly different the tissues would be," said Elledge. "The closest two were 90 percent different."

Genes that drove proliferation in one tissue often had no effect, or even suppressed proliferation, in another.

"That was shocking to me," said Elledge. "One family of genes made breast cells grow as fast as the greatest oncogene and did nothing in these other cells."

Analyses of gene expression in cancerous tissue reinforced the researchers' findings. They discovered that the genes that drove proliferation only in breast tissue matched patterns of gene activity seen in certain breast cancers. Similarly, genes that drove proliferation only in pancreatic tissue matched those seen in pancreatic tumors known as

adenocarcinomas.

The results suggest that tissue type plays a larger role than previously appreciated in cancer genetics and should be taken into greater account when devising treatments that aim to curb cell proliferation, Elledge said.

The insight could explain why drugs that target the same proliferation driver sometimes work in some cancers but not others.

"This work sounds a note of caution to those who wish to develop therapies for all tissue types based on one driver mutation," Elledge said. "Just because a proliferation-targeting drug works in one tissue doesn't mean it will work elsewhere."

A broader atlas

How many more proliferation-driving genes lurk in the rest of the body's tissues? Do tissue types respond in unique ways to hallmarks of cancer other than proliferation?

The researchers have made their tool available so that the scientific community can investigate these and other questions.

"There are so many cancers and so few treatments; we're still building our tool kit of therapies," said Elledge. "This work suggests it's worth paying attention to this whole new set of genes."

Provided by Harvard Medical School

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