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Cancer-Causing ‘Frankengene’ Mutation Could Be Target For New Drugs

This gene is fused to many partner genes in different tumors. Now, scientists know it causes cancer — and how they might intervene.

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Sometimes the DNA changes that drive cancer are small, just a few modifications to the molecular letters that make up our genetic code. But sometimes DNA undergoes bigger changes. One such “Frankengene” that’s widely seen is YAP, a growth-promoting gene found fused to another gene in many different cancer types.

In new work published today in the journal Genes & Development, scientists at Fred Hutchinson Cancer Research Center show that YAP gene fusions cause cancer. The team tested the effect of each of four different YAP fusions in mouse brain cells and found that tumors developed in the presence of each fusion. By comparing the different YAP gene fusions, they were able to narrow down the key functions of YAP that trigger cancer and figure out how its gene fusions sidestep molecular controls that normally rein in YAP activity. In lab dishes, drugs that block these common traits slowed growth of cancer cells with YAP fusions.

“YAP gene fusions not only happen to be in cancers, they actually are causal,” said brain cancer researcher Dr. Eric Holland, who directs the Hutch’s Human Biology Division and led the study.

Though YAP gene fusions are rare in any given cancer, they’re found in many different kinds of tumors. And though YAP has may different fusion partners, the fact that they all appear to cause cancer in the same way suggests that the same therapy may work against many different YAP fusions.

“[The idea is] if you have an anti-YAP therapy, it will likely work against these fusions. Even though YAP fusions are a rare part of all of these cancers, if you add them all up, it’s a lot of tumors out there that can potentially be treated,” Holland said.

YAP promotes cellular growth

One of the YAP protein’s main functions is to promote cell growth. In a healthy, growing cell, active

YAP travels to the nucleus, our cells' DNA storehouse, and turns on genes that help the cell grow. When the cell needs to stop growing, it activates molecules that modify YAP to keep it out of the nucleus and break it down into amino acids.

Small mutations in genes that encode the molecules that help turn YAP off are seen in many kinds of cancer. But these kinds of small mutations, known as point mutations, are rarely seen in the YAP gene.

"Point mutations in YAP don't usually occur in cancer because its regulation is complicated and a single mutation would not make YAP constitutively [always] active," Holland said.

Instead, when YAP is mutated in cancer, it's almost always stuck to a different gene. YAP's fusion partner often changes, and the proportion of tumors that carry YAP fusions is generally low in a given cancer type — but the fusions crop up in many cancers across many areas of the body, Holland said.

This means that if YAP gene fusions cause cancer, a YAP-focused therapy would be applicable to people with many different tumor types. But merely amping up normal YAP activity doesn't cause cancer — would grafting it onto other genes do the trick?

YAP gene fusions cause cancer

To determine if YAP gene fusions cause cancer, Dr. Frank Szulzewsky, the postdoctoral fellow in Holland's lab who spearheaded the project, examined whether four different YAP gene fusions could cause brain tumors.

YAP gene fusions are found in about 25%-30% of ependymomas, a rare type of central nervous system cancer. Only 60%-65% of people with this cancer survive for at least five years after diagnosis. These tumors often have few other mutations, but it wasn't known for sure that the YAP gene fusions were the critical genetic drivers of tumor formation and progression. Understanding this is key to understanding whether YAP may be an effective treatment target in these cancers.

Szulzewsky found that brain tumors formed in the presence of each YAP gene fusion, and that genetically blocking the activity of the fusions prevented tumor development, suggesting that YAP gene fusions do indeed cause cancer.

But YAP has many potential functions within the cell, and only some of those contribute to cancer development. The fact that YAP is found fused to several different partners provided the researchers with an opportunity.

"We have enough fusions to really figure out the parts that matter, the important parts of YAP's function," Holland said. "Because [the gene fusions] have to maintain certain functions of YAP and lose other things [in order to promote cancer]."

When Szulzewsky compared the different gene fusions, he saw shared characteristics: Each gene fusion produced a fusion protein that was always "on" — able to get into the nucleus and work

with molecular partners to turn growth-promoting genes on. And, they couldn't be turned off — each fusion had lost the section of YAP that cells use to flag it to be broken down and taken out of circulation.

Working with systems biologist and Hutch Human Biology colleague Dr. Taran Gujral, Szulzewsky tested the effect of experimental compounds that block YAP protein activity on the growth of tumor cells harboring YAP gene fusions. Treatment with these compounds, he found, slowed the growth of these cancer cells in lab dishes.

Because many molecular players involved in regulating YAP activity have been implicated in cancer, scientists have begun testing the effectiveness of anti-YAP drugs in patients with cancer. One of the experimental drugs Szulzewksy tested, called verteporfin, is currently being tested against breast cancer in clinical trials. The current work suggests that tumors carrying YAP fusions, like many ependymomas, may also be susceptible to similar compounds.

Pursuing anti-YAP drugs

The team is continuing to pursue potential new drugs with anti-YAP activity. They're also widening their net to see if any of the other genes turned on by YAP could be therapeutic targets, Holland said. With Gujral, they're also seeking drugs that could synergize with anti-YAP drugs to be even more beneficial.

Funded by the Ivy Foundation, a nonprofit dedicated to finding treatments for brain cancer, the team is also collaborating with the National Institutes of Health, which will help bring any promising drugs that Holland's team finds to clinical trials.

"There are several examples of tumors with gene fusions responding to targeted therapy against the fusion partners, while tumor without the fusions do not. In this study we may have found another instance, and identified the tumors that would respond to drugs targeting Yap activity," Holland said.

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