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Research Briefs

Feb 16, 2017

Making the Stand-Ins Stand Out In Cancer

In a systematic, large-scale effort, scientists from Brigham and Women's Hospital (BWH) and Harvard Medical School (HMS) have revealed how some genes that fuel cancer — so-called "cancer drivers" — work together, and can even stand in for each another. The work, which appears in the journal Genes & Development, sheds light on the complex molecular network that underlies cancer growth and illuminates some previously unknown mechanisms. Importantly, the research also provides inroads into understanding how some tumors outwit drug treatment.

"If we want to have a high resolution view of how cancers grow, then it's important to understand how many different types of cancer drivers there are," said senior author Stephen J. Elledge, PhD, the Gregor Mendel Professor of Genetics at Brigham and Women's Hospital and Harvard Medical School. "That is to say, 'Do they all do the same things? Can one driver substitute for another?' These are the kinds of questions that haven't really been asked in a systematic way."

Over the last decade, the scientific community has invested considerable effort and resources into scouring the DNA of tumors for telltale signatures that can suggest which genes drive cancer growth. That work has yielded a long list of cancer driver genes — roughly 600 of them in total — that researchers must now sift through to figure out their biological roles and how they contribute to tumor formation.

Elledge and his colleagues decided to tackle this problem systematically, and as a starting point, focused on an important signaling cascade in multiple types of cancer — the epithelial growth factor receptor (EGFR) pathway. Notably, as many as 30 percent of patients with non-small cell lung cancer harbor EGFR mutations in their tumors. Although drugs that inhibit the EGFR pathway can help a significant fraction of these patients, not all patients with EGFR mutations respond to these drugs. And even those who do respond often relapse, as tumors eventually evolve ways to resist EGFR inhibitors.

To begin to unravel how the differential characteristics of cancer drivers might contribute to these challenges, first author Sida Liao, a graduate student in Elledge's laboratory, harnessed a suite of approaches that can increase or decrease gene function. Liao and his colleagues analyzed over 600 genes implicated as cancer drivers to determine whether altering these genes' activities could substitute for EGFR signals. Remarkably, they uncovered scores of genes — some that had been previously identified for their ability to fill in for EGFR, and several that had not.

"EGFR is one of the most intensively studied signaling systems, so it is pretty amazing that we could walk in and learn something new right away," said Elledge.

Among the researchers' novel findings is a gene called PBRM1, which functions as part of a larger, multi-protein complex. That complex, known in scientific parlance as SWI/SNF, acts a sort of widget, which helps accomplish different molecular tasks in different contexts. Precisely how it works in lung cancer cells remains to be elucidated, but it appears to enable EGFR-activated signals to be maintained even in the face of EGFR inhibition.

Another intriguing find is the CIC gene. Few studies have so far examined its role in humans, yet its counterpart in fruit flies has been more intensively studied and offers some tantalizing clues. Based on their own follow-up experiments, the BWH team proposes that CIC triggers a cascade of molecular events that help reinstate downstream genes typically controlled by EFGR signaling

Elledge and his colleagues plan to extend these initial results, and also apply their approach to other key signaling pathways in cancer. "Certainly, people have examined cancer drivers individually, but not in this sort of large-scale, systematic way," said Elledge. "The approach can really teach us some new things about how cancers grow and escape treatment."

The work was supported by funds from the Ludwig Foundation. S. Elledge is also an investigator of the Howard Hughes Medical Institute.

Paper cited: Liao S. "A genetic interaction analysis identifies cancer drivers that modify EGFR dependency." Genes & Development doi: 10.1101/gad.291948.116. [Epub ahead of print]n MID:28167502

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