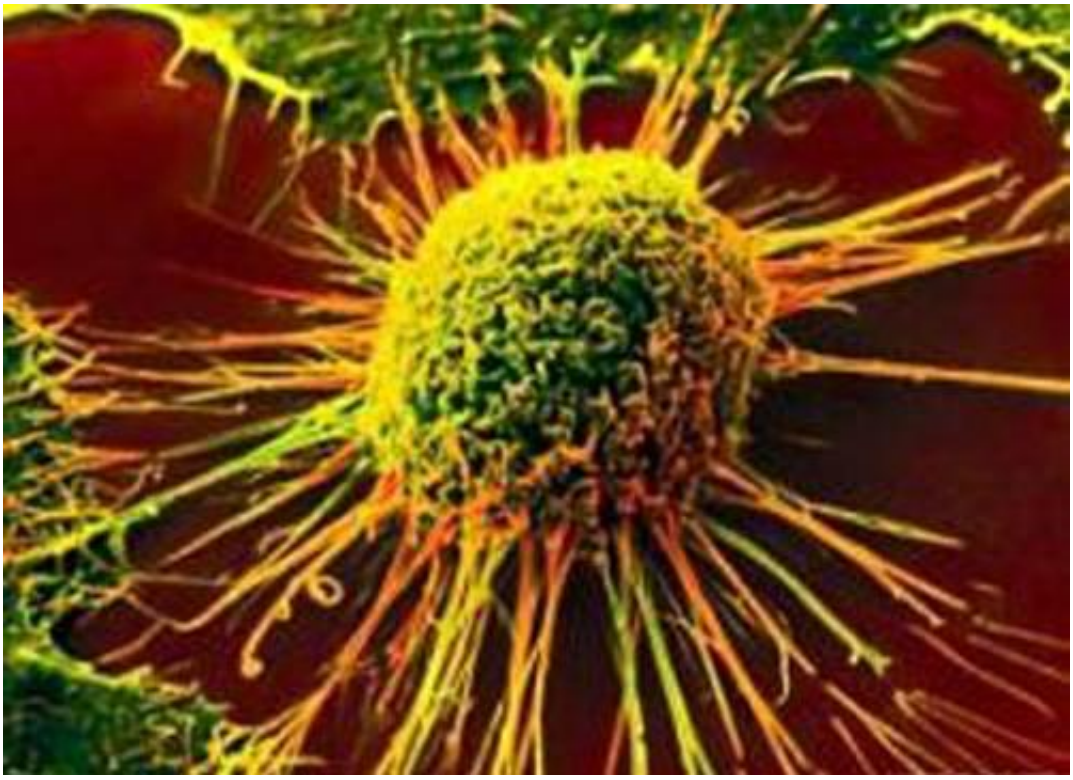
MedicalXpress

Study shows why some targeted cancer drugs lose effectiveness

February 9 2015



A protein called YAP, which drives the growth of organs during development and regulates their size in adulthood, plays a key role in the emergence of resistance to targeted cancer therapies, according to a new study led by UC San Francisco researchers.

By precisely identifying the mechanism by which elevated levels of YAP promote the survival of cancer cells, the new work points the way to combination therapies that may overcome resistance to individual targeted drugs, the scientists said.

Though cancer drugs aimed at specific genetic mutations have had some success in recent years, most patients who have a good initial response eventually develop resistance to these therapies, most likely because cancer cells engage alternative survival mechanisms that lie outside the biological pathways targeted by the drugs.

Though oncologists have the option of switching to a different targeted drug after resistance takes hold, many cancer researchers believe that a better strategy would be to forestall cancer cells' eventual escape routes by using customized combinations of targeted drugs at the outset of therapy.

"Instead of trying to figure out why patients have developed resistance after it has emerged, we need to decipher what survival tactic tumor cells will be most dependent on when they are challenged with targeted therapy," said the senior author of the study, Trever Bivona, MD, PhD, UCSF assistant professor of medicine and a member of the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC). "We want to learn how to wipe out that alternative survival pathway at the beginning of therapy—to pull the rug out from under those cells right away."

In the new research, published in the Feb. 9, 2015 online issue of *Nature Genetics*, an international team of scientists led by Bivona used a gene-silencing tool called short-hairpin RNAs (shRNAs) to tamp down the activity, one-by-one, of more than 5,000 proteins in lung cancer cells that carried cancer-causing mutations in a gene called BRAF. By simultaneously treating the cells with the cancer drug vemurafenib (Zelboraf), which specifically targets faulty BRAF proteins, the

researchers were able to determine whether the drug was more effective when the action of other particular proteins was blocked.

These experiments quickly and decisively fingered YAP in vemurafenib resistance, as all six YAP-directed shRNAs employed by the scientists significantly enhanced the drug's effectiveness at killing BRAF-mutant cancer cells. The researchers saw similar results with trametinib (Mekinist), which targets a BRAF-activated protein called MEK. Working with other types of cancer cells carrying BRAF mutations, including cells from human melanoma, colon, and thyroid cancers, the researchers again found that suppressing YAP enhanced the effectiveness of both vemurafenib and trametinib.

The collective lab-dish results held up in experiments with animal models in which cells from melanoma and colon cancer were injected under the skin of mice and formed tumors: vemurafenib and trametinib were far more effective in treating these tumors when YAP had been suppressed.

The researchers then turned to cells carrying mutations in another important cancer-driving gene, called RAS. Cancers with these mutations are particularly problematic, because the RAS protein is widely considered to be "undruggable"— no effective targeted therapies have been developed for tumors expressing mutant RAS. Like BRAF, the RAS protein also activates MEK, but MEK-targeted therapies have not been particularly effective in patients with RAS-mutant tumors.

After YAP suppression, however, the MEK inhibitor trametinib was highly effective when tested in RAS-mutant lung cancer, melanoma, and pancreatic cancer cells, and also against RAS-mutant lung tumors implanted in animals.

To ensure that these findings were clinically relevant, the authors

examined human tumor samples and found that YAP was highly expressed in BRAF- and RAS-mutant lung cancer and melanoma before patients had received any treatment. Moreover, patients whose tumors had higher YAP levels were more likely to have had an incomplete response when treated with a BRAF and/or MEK inhibitor. Finally, YAP levels rose in tumors when patients developed resistance to those therapies.

The researchers found that YAP exerts its effects across a wide variety of cancer types via a single mechanism involving a protein called BCL-xL, which sends out signals that prevent cells from self-destructing. High YAP levels in cancer cells keep BCL-xL activated, overwhelming the ability of targeted drugs to successfully kill off the cells.

Therefore, when vemurafenib or trametinib treatment was combined with inhibitors of BCL-xL, the drugs were much more effective than when either was given alone, indicating that a combined therapy targeting both the MEK and YAP pathways may be effective in overcoming resistance to targeted therapies for many BRAF- and RAS-mutant tumors.

Bivona emphasized that YAP's role in organ development was first discovered in the fruit fly Drosophila, and he sees the research as a testament to the importance of basic biological research to improving human health. "YAP was the number-one hit in our screening process, but it wasn't much of a leap to think it might be promoting resistance to targeted therapy, because it had been shown to promote organ growth and cell proliferation in other organisms and systems," he said. "So this work stood on the shoulders of very good, purely basic science."

Because BCL-xL has widespread roles in the body, however, BCL-xL inhibitors may prove too toxic to be practical, Bivona said, adding that he and colleagues are exploring partnerships with pharmaceutical

companies to develop compounds that target YAP directly.

"This is the first paper to establish that YAP is a bona fide mechanism of resistance to RAF and MEK inhibition," Bivona said, "and it's exciting to contemplate and plan what we may be able to do with this knowledge to help cancer patients by improving their precision treatment."

More information: The Hippo effector YAP promotes resistance to RAF- and MEK-targeted cancer therapies, *Nature Genetics*, DOI: 10.1038/ng.3218

Provided by University of California, San Francisco