Skin tumors develop specific mutations to resist drug, researchers say

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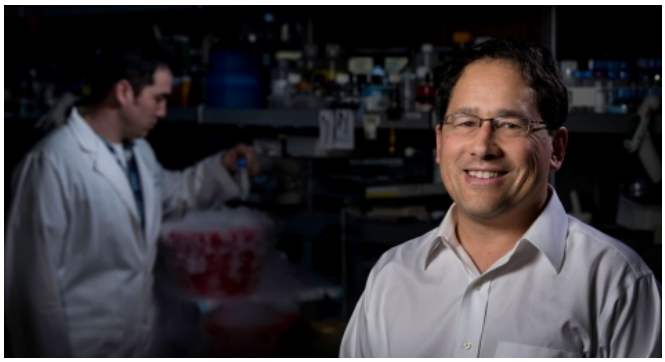

Anthony Oro and his team have identified mutations in cancer cells that make them resistant to a common drug therapy. Credit: Steve Fisch

Among people with advanced basal cell carcinomas who see their skin cancers shrink or disappear in response to a common drug therapy, about 20 percent will relapse within months as the cancer cells become resistant to the treatment. The situation is frustrating to both patients and their physicians.

Now, researchers at the Stanford University School of Medicine have identified specific mutations in the cancer cells that confer resistance to the drug, vismodegib, which is sold under the brand name Erivedge. They've also shown that another class of drug, called a Gli antagonist, may be able to successfully tackle even vismodegib-resistant cancers. The finding could hasten the use of Gli antagonists in the clinic, they said.

"This research sheds new light on mechanisms of how tumors evolve to develop drug resistance, and has already helped us with personalized cancer genetics and therapy for our patients," said Anthony Oro, MD, PhD, professor of dermatology. "It is now possible for us to identify those people who may benefit from a combination therapy even before they begin treatment."

A paper describing the research findings was published March 9 in *Cancer Cell*. Oro; Jean Tang, MD, PhD, associate professor of dermatology; and Anne Chang, MD, assistant professor of dermatology, share senior authorship. Postdoctoral scholar Scott Atwood, PhD, and Kavita Sarin, MD, PhD, assistant professor of dermatology, share lead authorship.

Approximately 2 million new cases of basal cell carcinoma are diagnosed each year in the United States, making it the most common cancer in the country. About half of patients with advanced basal cell carcinomas will respond to vismodegib, which belongs to a class of drug compounds called Smoothened inhibitors. About 20 percent of these responders will go on to quickly develop resistance to the drug.

Basal cell carcinomas are uniquely dependent on the inappropriate activation of a cellular signaling cascade called the Hedgehog pathway. Blocking signaling along this pathway will stop the growth and spread of the cancer cells. The Hedgehog pathway plays a critical role in normal development. It's also been found to be abnormally active in many other cancers, including pancreatic, colon, lung and breast cancers, as well as in a type of brain cancer called medulloblastoma.

Domino effect

Signaling cascades like the Hedgehog pathway can be imagined as a line of upright dominos on the floor. Tapping one domino on the end causes a chain reaction down the line until all the dominos are toppled. In this way, signals from outside the cell are transmitted into the cell by the sequential activation of specific proteins until a particular action is accomplished.

Vismodegib binds to and inactivates Smoothened,

or Smo, a key protein in the Hedgehog pathway. In the domino analogy, Smo is one of the first tiles in the signaling chain. In 2012, vismodegib became the first Smo inhibitor approved by the Food and Drug Administration to treat advanced and metastatic basal cell carcinoma.

Smo is one of many members of a class of proteins called G-protein-coupled receptors. These receptors sit on the surface of the cell and translate external signals across the cell membrane to control cellular processes like growth and division. However, it's possible for the protein to develop mutations that allow it to escape the inhibitors.

The researchers examined gene expression patterns in 44 vismodegib-resistant tumors from 15 patients. (Every tumor can have a distinct genetic profile.) They found that the Hedgehog pathway remained active in the resistant tumors, despite ongoing treatment with vismodegib. This indicated that the cancer cells were not switching to other cancer-associated pathways in response to therapy but were instead figuring out a way to continue to transmit the signal.

Evasive action

Oro and his colleagues then sequenced the cells' exomes, or regions in the genome that encode protein-making instructions. They found mutations in 15 of the 29 proteins in the Hedgehog pathway. Of these, Smo was the protein most often affected: It was mutated in six of the 14 tumor samples, suggesting that mutations in the protein are one of the primary ways that basal cell cancers overcome vismodegib treatment.

Upon further investigation, the researchers found two main classes of mutations in Smo that were associated with vismodegib resistance. One class included mutations in the region of the protein to which the inhibitor binds. Four mutations in this region stopped vismodegib from binding to Smo.

The second class of mutations was somewhat unexpected. "We found that there are particular amino acid residues that bind together to hold the protein in an inactive conformation," said Oro. "These are like little springs. When these amino acids are mutated, the Smo protein becomes what's called constitutively active, or always 'on' regardless of what signals it receives from upstream in the pathway." The researchers found four mutations in this region of the protein in the resistant tumors.

Finally, the researchers grew both vismodegib-resistant and -susceptible cells in the laboratory. They found that tumors with either class of mutations in the protein grew more quickly in the presence of vismodegib than did cells with unmutated Smo proteins. Furthermore, treating the cells with inhibitors that target a portion of the pathway downstream of Smo blocked the activation of the pathway even in cells with the mutations. These inhibitors, called Gli antagonists, could be an effective way to treat vismodegib-resistant tumors, the researchers said.

Plans for personalized therapies

Oro and his colleagues are now using information about mutations in Smo as a way to guide therapy decisions for their patients.

"We've just started a personalized genomics clinic at the Stanford Cancer Institute," said Oro. "Our expectation is that patients will come in, have their tumors sequenced and subsequently receive the best treatment for their types of cancer. Eventually we would like to do this for many types of skin cancers, including melanomas and squamous cell carcinomas."

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