New study opens door to multipronged attack against skin common cancer

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Hailed as a major step forward in the effort to develop targeted cancer therapies, a recently approved drug for the most common type of skin cancer has been a mixed blessing for patients. Although the initial response is usually dramatic, the tumors often recur as the cancer becomes resistant to treatment.

Now researchers at the Stanford University School of Medicine have identified a second way to block the activity of the signaling cascade, called the Hedgehog pathway, that is abnormally active in these cancers. The researchers hope the new approach may not only one day help patients with tumors that have become resistant to the first drug, vismodegib (marketed as Erivedge), but may also provide a novel combination therapy for newly diagnosed tumors that may be more effective than either treatment alone.

"These new, highly targeted therapies work really well," said dermatology professor Anthony Oro, MD, PhD, who was one of several Stanford researchers involved in the multiyear effort that brought vismodegib to market in 2012. "But this type of treatment is a race against evolution. Within a year, many of the tumors recur when the cancers become resistant to the inhibitor."

The effect on patients, particularly those with a severe condition called Gorlin syndrome, is a heartbreaking yo-yo as the tumors that cover most of their bodies disappear within weeks, but often recur in force.

But Oro and his colleagues' discovery of another, previously unknown component of the Hedgehog pathway—a component vital to its cancer-causing ability—could address this problem. Blocking the activity of this protein, called aPKC, can stop the growth in mice of transplanted skin tumors and tumor cells resistant to vismodegib. The finding, which will be published Feb. 28 in *Nature*, may pave the way to a future in which cancers are treated with more than one specifically targeted drug.

"Although these tumors evolve in response to targeted drug treatment, we believe there's a limited number of ways they can escape these therapies," said Oro. "If we were able to hit them at the time of diagnosis with drugs that target more than one step in the pathway, they may be less able to evade treatment. We've identified a new target in the Hedgehog pathway and we've developed an inhibitor of this target that we hope will work in human cancers."

Oro, who is the senior author of the study, was also one of several authors on a series of three papers in the New England Journal of Medicine last June describing the effectiveness of vismodegib in treating the most common type of skin cancer, basal cell carcinoma. Postdoctoral scholar Scott Atwood, PhD, is the lead author of the current study.

Taken together, the recent studies illustrate the nature of the constant battle among physicians and the rapidly growing and changing cancer cells they strive to eradicate. Targeted treatments that focus on unique vulnerabilities exhibited by specific types of cancers can be highly effective. They can also minimize the unpleasant side effects of less-specific treatments that kill many other non-cancerous cells. But their very specificity encourages and drives the tumor cells to evolve resistance in a way that might not be possible against a more broad-based therapeutic approach. Many researchers believe that a multipronged attack targeted at more than one point in critical cancer-causing pathways could be an effective way to combat resistance.

"Our goal is to provide precision cancer care at the time of diagnosis," said Atwood. "We're working toward developing better, more specific single and combination therapies to reduce the chance of

resistance through tumor evolution."

The Hedgehog pathway is critical to many aspects of embryo development in animals as diverse as fruit flies and humans. When abnormally activated, it can cause uncontrolled cell growth. The pathway was first linked to human cancer about 16 years ago by researchers, including Stanford professor of developmental biology Matthew Scott, PhD. Since that time, researchers around the world, including a large group at Stanford, have worked to learn more about the pathway and how to inhibit it.

That work led to the development of vismodegib, which blocks a protein called Smoothened, or Smo, that acts near the beginning of the Hedgehog pathway. Smo sits in the cell membrane and sends signals into the interior of the cell. When activated, it initiates a biological cascade of signaling molecules that culminates in the cell's nucleus at a protein called Gli, which governs gene expression.

Oro and Atwood discovered another, previously unknown protein player in the Hedgehog pathway called aPKC. This protein perpetuates Gli's ability to transcribe, or activate, certain genes by giving it a specific molecular tag (a process called phosphorylation). The phosphorylated Gli in turn goads aPKC to higher levels of activity in what's known as a positive feedback loop.

The researchers studied human skin cancer cells removed from patients and grown in a laboratory dish. They also used a model in which basal cell carcinomas were transplanted onto mice. They looked at levels of aPKC activity and gene expression profiles in the tumors.

"We've found that aPKC is highly active in human basal cell carcinomas that have become resistant to vismodegib," said Atwood. "This positive feedback with aPKC allows tumors to grow really well even in the presence of vismodegib."

When the researchers used an aPKC inhibitor to treat mice bearing transplanted tumors or tumor cells resistant to Smo inhibitors, the growth of the cancer cells was suppressed and the tumors shrank.

The researchers are now working to optimize the selection and design of the aPKC inhibitor. They are also interested in exploring its effect in other cancers in which the Hedgehog pathway is implicated.

"There are a host of Hedgehog-dependent cancers," said Oro, "and we have many researchers and clinicians here at Stanford poised to conduct clinical trials of these types of therapies. It's very exciting."

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