Blocking 'scaffold' protein inhibits cancer growth, study finds

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(Medical Xpress)—Researchers at the Stanford University School of Medicine have devised an entirely novel way to block biological signaling pathways that, when overactive, lead to many types of cancers. They've done so by disrupting the function of a mediator, or scaffold, protein that brings together key members of the pathway and promotes their interaction to stimulate cell growth and division.

Blocking the function of the scaffold protein, or even removing it entirely, impeded the development of chemically induced skin cancers in laboratory mice and extended the life span of mice with established pancreatic tumors, the researchers say. It also significantly slowed the growth in laboratory culture of human melanoma cells that had become resistant to a new, targeted cancer treatment called vemurafenib (marketed as Zelboraf).

The versatility of the technique, as well as its apparent ability to tackle drug-resistant cancers, indicates that targeting scaffold proteins may lead to a new class of cancer therapies in humans.

"This could be a new type of tool for clinicians," said Paul Khavari, MD, PhD, the Carl J. Herzog Professor and chair of the Department of Dermatology. "It's as if the cancer-causing proteins are convening around a conference table to implement tumor-forming discussions. This new approach takes away the table so those cancer-promoting actions never happen. By doing so, this blocks growth of even cancer cells that have already become resistant to other targeted treatments."

Khavari, who is also a member of the Stanford Cancer Institute and chief of the dermatology service at the Veterans Affairs Palo Alto Health Care System, is the senior author of the study, which was published online April 21 in *Nature Medicine*. Former graduate student Katherine Jameson, PhD, and postdoctoral scholar Pawel Mazur, PhD, share lead authorship.

Unlike traditional chemotherapy and most radiation treatments, targeted cancer treatments are meant to kill only cancer cells and leave others unscathed. They generally do so by inhibiting specific signaling relays that are abnormally active in cancer cells, by tagging cancer cells with antibodies that recognize certain molecular configurations found only on the surface of diseased cells, or by blocking cancer cell-stimulated growth of new blood vessels to tumor sites.

When successful, targeted treatments reduce the overall toxicity to the patient compared with chemotherapy, and also can be more effective. Current examples of targeted therapies include some well-known drugs: Herceptin, Gleevec, Retuxan and Avastin, to name a few. On paper, it's a sure-fire win-win—when it works.

Unfortunately, the pinpoint specificity of such treatments can make it easier for a rapidly mutating cancer cell to develop resistance. As a result, many patients who at first respond successfully to treatment can face the heartbreak of a relapse within months or a few years.

Researchers haven't given up hope, though. Many believe that a simultaneous combination of two or more treatments targeted to the same pathway could overwhelm the cancer cells' evasive abilities.

One such pathway involves a class of proteins called MAP kinases, or MAPKs, essential to convey signals from outside of the cell into the nucleus. Over 30 percent of human cancers rely on overactivation of this

pathway to drive tumor cell growth.

Although researchers have successfully designed some cancer therapies targeted to this pathway, including the recently approved melanoma drug vemurafenib, it's been difficult to identify protein participants that aren't also essential to the growth and function of normal cells. That's where the scaffold proteins come in.

"We were hoping to find something that was required for cancer, but not necessary for most normal physiological activities," said Khavari. "We didn't want to shut down something that the body needs to be healthy. When we started looking at scaffold proteins in the MAPK pathway, we found one, called IQGAP1, that can be knocked out in laboratory mice without the lethal side effects seen of targeting the MAPKs themselves."

Because IQGAP1, which binds many members of the MAPK pathway, had been previously implicated in cancer development, the Stanford team decided to take a closer look at the mice in a disease context. They found that mice that had been genetically engineered to lack the IQGAP1 gene were resistant to the development of chemically induced skin cancers—because the pathway functions far less efficiently without the physical coordination provided by the scaffold protein.

Curious about a possible role in humans, the researchers investigated IQGAP1 expression levels in naturally occurring skin cancers. They found that the protein was strongly expressed in nearly one half of the patient-derived tumors. In a mouse model of human pancreatic cancer, levels of IQGAP1 are elevated in pre-cancerous and cancerous cells.

Further research suggested that IQGAP1's association with MAPKs might be responsible for its cancer-stimulating ability. The researchers devised a small protein molecule to block this interaction and tested its effect both on human cancer cells grown in culture as well as in mice

with pancreatic tumors.

Not only did the molecule significantly inhibit the growth of human breast, colorectal and melanoma cancer cells in culture, it also blocked the growth of human breast and melanoma tumors implanted into mice. It also significantly increased the life span of mice predisposed to lethal pancreatic cancers, even when administered after the development of a noticeable tumor mass.

Finally, the researchers tested the effect of the small blocking peptide on the growth of vemurafenib-resistant human melanoma cancer cells in culture. They found that it significantly slowed the cells' growth, indicating that it works in a novel way on the cancer cells.

"This may be a general strategy for many types of human cancers," said Khavari. "We're hopeful that further studies will identify other scaffold-protein interactions that may be susceptible to this approach. Once we know that, we anticipate having a whole new set of targets for drug development."

More information: IQGAP1 scaffold-kinase interaction blockade selectively targets RAS-MAP kinase–driven tumors, DOI: 10.1038/nm.3165

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