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Saving tumor suppressors from the shredder

Novartis opens up a path of research to protect proteins that guard against cancer.

By Eric Bender | Apr 24, 2017

Tumor suppressor proteins do exactly what their name suggests—they put the brakes on uncontrolled cell division or instruct damaged cells to kill themselves. In cancer, unfortunately, these proteins often disappear. In many cases, they are ripped apart in molecular shredding machines known as proteasomes.

Cancer researchers have long studied the proteasome, and drugs that inhibit its blades have proven effective in multiple myeloma and mantle cell lymphoma. However, the proteasome is crucial for many normal protein-recycling operations, so its inhibition can bring serious side effects that limit their use.

But what if a drug could be more selective? Scientists at the Novartis Institutes for BioMedical Research (NIBR) are one step closer to discovering such a treatment. They have identified a compound that keeps some proteins—including many tumor suppressors—out of the proteasome while allowing other proteins to enter.

While this is promising news, there is still much work to be done. To help advance the science, Novartis has engaged the broader research community and made the compound available to academic scientists for testing. So far nearly two dozen have requested it. This is part of the company's broader effort to increase collaboration with external investigators.

"We offered our compound to academic researchers because we need help answering many questions before we can test this type of molecule in patients," says Jörg Eder, an executive director at NIBR and co-corresponding author on a paper describing the research in *Nature Communications*.

For example, the team wants to find out which patients might benefit from such a compound.

"I was excited that Novartis researchers created such a wonderful tool that we and the rest of the field could use," says Raymond Deshaies, professor of biology at Caltech. "We have obtained the compound from Novartis and perhaps the experiments we plan to do will yield some insight into how this tool might be used in a therapeutic context." At the very least, he says, the compound will help his team to explore unanswered questions about which proteins end up in the proteasome and how they get there.

Stopping a deadly game of tag

The proteasome acts on proteins that are tagged with chains of "ubiquitin" molecules, explains Anita Schlierf, a NIBR molecular biologist and co-lead author on the Nature Communications paper. When the proteasome recognizes such a chain, it gobbles up the protein and rips it apart.

Proteins called E3 ligases, which are present in about 600 varieties in human cells, attach the ubiquitin tags read by the proteasome. The team wondered if they could disrupt the E3 ligases that tag tumor suppressors for destruction while allowing the other E3 ligases to go about their business.

But how could the researchers accomplish this task?

They zeroed in on a protein complex called the COP9 signalosome (CSN), which helps the largest subfamily

of the E3 ligases tag proteins. CSN levels rise in many tumors. Perhaps the E3 ligases that are dependent on CSN actually tag a disproportionate number of tumor suppressors. That would make CSN a promising therapeutic target.

The NIBR scientists decided to test this hypothesis, and began searching for a compound that blocks a key CSN protein. Other labs had attempted this feat and failed. Undeterred, the NIBR team set up a complicated experiment, assembling many different proteins in a dish and screening thousands of compounds for the desired activity. One series of compounds stood out. Together with her colleagues, Eva Altmann, a NIBR chemist and another co-lead author on the paper, synthesized hundreds of derivatives to finally identify the first highly selective and potent CSN inhibitor.

Compound interest

The compound showed promise in lab models of cancer. For example, it stabilized tumors in mice given grafts of human cells with an aggressive blood cancer. The animals didn't seem to suffer any side effects, an improvement over approved proteasome inhibitors.

"We learned that the compound works in mice, although not yet to the extent we had hoped to see, since we would prefer to see tumor regression," Altmann says. The scientists will continue to advance their compound designs before any can be tested in patients.

Francois Claret, an associate professor of cancer medicine at the University of Texas MD Anderson Cancer Center, plans to use the compound in his lab. According to Claret, the research community recognized the key CSN protein—which he discovered as a postdoc—as an attractive therapeutic target years ago. "However, it was almost impossible to validate it without a clinically viable inhibitor," he says. "I am glad that Novartis saw this opportunity and took on the challenge."

As the NIBR team extends its studies of how CSN-inhibitors may protect proteins from the shredder, many academic labs around the world are launching their own efforts. "I have 20 requests on my table as of today for this compound, which is really amazing," says Altmann. "This can only be a win-win situation for all."

Main image caption: An office shredder rips apart a tumor suppressor protein. Original iStock image adapted by Dwayne Quimby. Proteasome shown in social media posts by Thomas Splettstoesser.

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