New clues on the cellular 'garbage disposal'

Cancer cells rarely cooperate with the drugs that science devises to kill them. They're constantly evolving, often developing resistance or finding escape routes to stay one step ahead of the treatment.

For example, a popular target for chemotherapy in the treatment of many human cancers is the proteasome, a protein complex found in nearly all cells, from microorganisms to humans. Proteasomes are assembled within cells and function like a garbage disposal to remove damaged or unneeded proteins.

Cancer cells often must find ways to evade molecular signals that tell them they shouldn't be growing, or that they should commit cell suicide. They often evade these signals by using the proteasome to destroy the proteins carrying the signal. The cancerous cells are then able to divide unchecked.

Understanding how our cells — healthy or otherwise — build new structures (such as proteasomes), then, is useful in understanding how to deal with defective cells, such as cancer cells.

That's one of the things Robert J. Tomko Jr., assistant professor of biomedical sciences at the College of Medicine, is doing. He is first corresponding author of a paper published in the journal *Cell* that presents a major step forward in understanding the mechanisms by which cells build proteasomes.

"Our study describes how the 'tail' of a single protein subunit acts as a trigger in the assembly process when proteasomes are being built within the cell," Tomko said. "This tail acts like a key that inserts into a lock, triggering a reorganization of the assembling proteasome from a structure similar to a closed fist into one more like an open hand."

From there, the under-construction proteasome fits into the palm of the open hand to complete assembly.

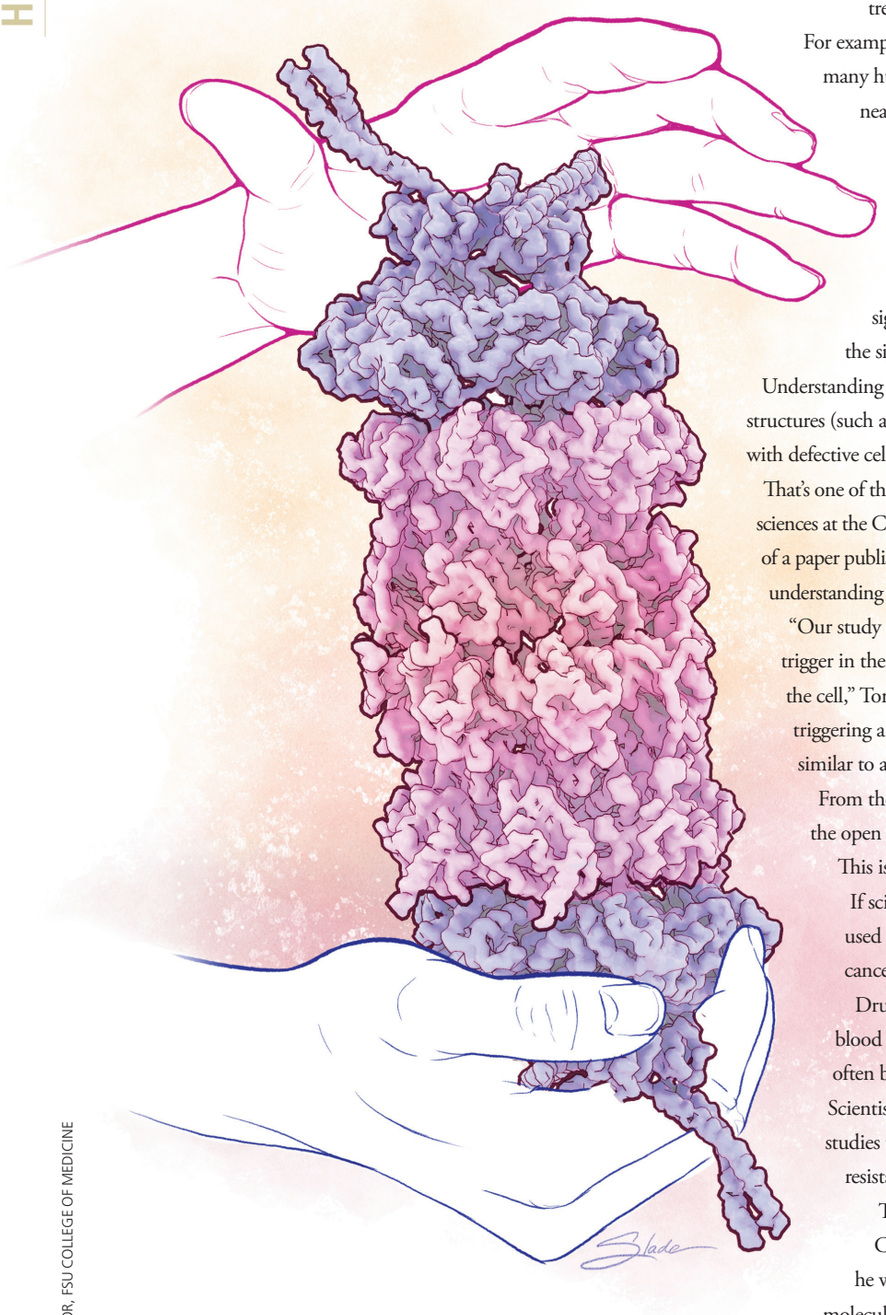
This is where the discovery might be particularly useful.

If scientists can stop the "tail" from opening the lock, it could be used to prevent cancer from growing new proteasomes that allow cancers to grow unchecked.

Drugs that target the proteasome are extremely effective in several blood cancers, but resistance is emerging. These resistant cancer cells often build new or slightly different proteasomes to gain resistance. Scientists could use the knowledge of assembly gained from these studies to prevent new proteasome assembly, thereby reversing resistance to drugs that target the proteasome.

Tomko began working on the science as an American Cancer Society Postdoctoral Fellow at Yale University, where he worked with senior author Mark Hochstrasser, professor of molecular biophysics and biochemistry.

He completed his work and wrote the paper after joining the FSU College of Medicine in January.



JODI SLADE/MEDICAL ILLUSTRATOR, FSU COLLEGE OF MEDICINE

A "lid," which looks similar to an open hand, grasps the proteasome and allows it to perform its function, disposing of other proteins. The lid is prevented from grasping the proteasome prematurely by assuming a shape like a closed fist. A subunit identified in Tomko's research attaches to the lid, opening it and allowing it to activate the proteasome. This information provides clues to developing new anticancer drugs that trap the proteasome in an inactive state.

"The experimental approach is a tour de force combining cutting edge technologies to resolve a question that could otherwise not be addressed," one scientist wrote in the peer review process before the paper was accepted for publication. "The insights may become useful in developing novel pharmaceutical approaches to inhibit proteasome activity."

Understanding cancer at the molecular level is one of the focal points of the College of Medicine's research program, and served to attract Tomko and other recent additions to the Department of Biomedical Sciences.

Tomko's work is a prime example of why molecular mechanisms are so important in advancing our understanding of diseases such as cancer. The cell is constantly building large structures out of smaller protein parts to perform different required tasks, and the more we know about how that works, the more effectively physicians can act when problems occur.

Tomko likens a cell building a proteasome to a human building a car. As with any complicated assembly, there are different ways to put the pieces together, but only a few pathways are likely to generate a working product.

Robert J. Tomko Jr.

Building the outside of an engine first, for example, could block access to install inner components needed for that engine to actually work.

"Thus, some mechanisms must be in place to make sure that all of the pieces go together in the right way, in the right order," Tomko said.

And with his team's discovery, scientists now have a better understanding of the order and manner in which cells build proteasomes.

"We feel strongly," Hochstrasser said, "that this work breaks both important new conceptual ground in our understanding of how assembly of large protein complexes occurs in vivo and methodological ground in studying protein assembly."

A protein with promise

Sometimes you wonder whether researchers who spend their careers peering into microscopic cells lose their sense of wonder. Then again, sometimes all you have to do is ask.

"Evolution has done such a good job of producing molecules to perform these exquisitely, highly regulated chemical reactions," Daniel Kaplan said recently when asked about scientific wonder. "It's just a big bucket of chemistry in a cell, and it's very precisely regulated and orchestrated."

Every orchestra needs a conductor, and Kaplan's lab has identified another one of them. This latest discovery not only sheds light on cell division but also could lead to improved cancer therapy.

The key, says Kaplan, a Department of Biomedical Sciences researcher, is a protein called Treslin.

"It can target cancer cells," he said. "Most chemotherapy also targets rapidly dividing normal cells, but this seems to have promise for not doing that. Drug companies are going to be excited."

Before cells can divide, their DNA must be copied. In addition, the strands of the DNA's famous double helix must be unwound, via a protein called helicase. One strand needs to be inside the helicase ring, the other outside. As Kaplan's lab reported last year in the *Journal of Biological Chemistry*, a kinase — that is, a protein that chemically modifies other proteins — called Cdc7 opens up the helicase ring to let one strand out.

But not until this summer, in a paper published in *Proceedings of the National Academy of Sciences*, did Kaplan and Research Faculty Irina Bruck figure out that Treslin was also a key ingredient — in two ways.

Treslin not only stimulates the chemical modification of the helicase, thereby activating it, but also assembles the helicase in preparation for cell division. Since cancer is the unregulated division of cells, knowing how to stop the division process is crucial to halting cancer.

"We think this is really important," Kaplan said, "because now we can take this purified Treslin and the helicase, put them in a tube and watch the chemical modification occur. Then we can add small molecule inhibitors to see if we can inhibit that. That should stop activation of the helicase. That should stop the cancer cells from dividing. You kill cancer cells but not normal cells."

Florida State has filed a provisional patent. Meanwhile, the Kaplan lab keeps probing the mysteries of that "big bucket of chemistry in a cell."

Daniel Kaplan

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