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Cancer clue in cellular machinery

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EDIT CONNECT

Florida State University

TALLAHASSEE, Fla.—Buried deep within the intricate machinery of the human cell could lie a key to treating a range of deadly cancers, according to a team of scientists at Florida State University (FSU). In a new study, researchers discovered a critical missing step in the production of proteasomes—tiny structures in a cell that dispose of protein waste—and found that carefully targeted manipulation of this step could prove an effective recourse for the treatment of cancer; their findings were published in the journal *Cell Reports*.

"Proteasomes are kind of like the cell's recycling center for proteins," said study co-author Dr. Robert Tomko, an assistant professor of biomedical sciences in FSU's College of Medicine. "Typically, proteins inside the cell are produced to fulfill a certain function, and once that function is fulfilled, they are no longer needed and need to be removed."

In particular, it was the stage of the assembly process that involves cellular chaperones' release of a fully completed proteasome that interested Tomko and his team. Before their study, the signaling mechanisms responsible for triggering the release of assembled proteasomes was a mystery, according to FSU, limiting scientists' understanding of the critical final phase of proteasome assembly.

Tomko's group found that the answer to this puzzle has to do with a feat of "molecular contortion" in which, once a proteasome is nearly finished assembling, it temporarily changes its shape, making room for the chaperone protein as the proteasome's final building blocks are linked together. When assembly is complete, the proteasome suddenly snaps back into its original shape, crowding out the chaperone protein and eventually popping it entirely free.

"This finding explains how this seemingly impossible process happens, and importantly, it suggests that by controlling it, we could regulate proteasome assembly to help treat certain types of cancers," Tomko noted.

The reason? Cancer cells, just like healthy cells, rely on proteasomes to collect and dispense with toxic proteins. Because cancer cells produce large amounts of damaged proteins, they compensate by overproducing proteasome assembly chaperones.

In addition, the specific chaperone protein Tomko and his team studied, called gankyrin, is an oncogene—a piece of genetic material that is present at elevated levels in some tumors and has been shown to promote cancer growth.

Tomko said that if scientists can devise a way of interfering with the "popping off" of gankyrin chaperone proteins from assembling proteasomes, they may be able to mitigate the cancer-causing effects of gankyrin while also condemning harmful cancer cells to death by their own toxic proteins.

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