

# Cellular recycling complexes may hold key to chemotherapy resistance

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Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Altering the protein recycling complexes in human cells, including cancer cells, allows the cells to resist treatment with a class of drugs known as proteasome inhibitors, according to Whitehead Institute scientists.

"This is why some cancers can be so difficult to treat with chemotherapy, because the [cells](#) can be in different states—some sensitive to treatment and some resistant to treatment, all in the same tumor," says Sandro Santagata, a former visiting scientist in the lab of Whitehead Member Susan Lindquist. Santagata is now Assistant Professor of Pathology at Brigham and Women's Hospital and Harvard Medical School.

The key to this treatment resistance lies in the proteasome, a highly regulated complex in the cell that degrades excess and misfolded proteins. The main type of proteasome in humans is the 26S proteasome, which is composed of a catalytic barrel (the 20S core complex) with lids on either end (19S regulatory complex). The 19S complex recognizes proteins tagged for degradation, unfolds them, and feeds them into the 20S complex, where they are broken down into peptides to be recycled into new proteins.

Regulating and removing proteins is vital for all cells, but [cancer cells](#) are highly dependent on their protein production machinery to fuel their proliferation. The chemotherapy drug bortezomib (marketed by Millennium Pharmaceuticals under the brand name Velcade) takes advantage of this reliance and targets the proteasome's function. In certain blood cancers, including myeloma and mantle cell lymphoma, bortezomib is very effective, at least initially. Yet most cancers maintain a pre-existing resistance to such proteasome inhibitors.

To understand how cancer cells could have an established tolerance, Santagata and Peter Tsvetkov, a postdoctoral researcher in the Lindquist

lab, analyzed the genes that allow cells to survive exposure to proteasome inhibitors at toxic levels. According to their work, resistance is conferred by a reduction in the 19S complex's expression. This alters the ratio of the 26S proteasome to an alternative proteasome composed solely of a 20S complex. The scientists' work is described in this week's issue of the journal *eLife*.

"We think this may be a fitness tradeoff mechanism in tumors that enables these cells to proliferate in normal conditions a bit more slowly, but when they encounter a concentration of proteasome inhibitors that would be toxic to the rest of the cancer cells, these cells are able to survive," says Tsvetkov, who is also a lead author of the *eLife* paper.

"It is exciting that this mechanism is conserved from yeast to humans—organisms that are separated by more than 1 billion years of evolution," says Lindquist, who is also a Howard Hughes Medical Institute investigator and a professor of biology at MIT. "Targeting something that is fundamental and not just a peculiarity of a particular cell type holds greater promise."

According to Tsvetkov, [normal cells](#) may use this mechanism to deal with naturally occurring protein stresses, including protein aggregation. He explains that cells could potentially lower their 19S subunit levels through a wide variety of epigenetic mechanisms, including microRNAs, transcription regulation, and histone modifications.

"We propose that this mechanism allows the same cell—normal or malignant—to shift between a sensitive state and a resistant state without any permanent changes in their DNA, such as genetic mutations," says Santagata.

Santagata and Tsvetkov want to target this resistant state. Adds Tsvetkov: "We know a mechanism of resistance now. Let's find something that

kills the [resistant cells](#)."

**More information:** "Compromising the 19S proteasome complex protects cells from reduced flux through the proteasome" *eLife*, August 25, 2015.

Provided by Whitehead Institute for Biomedical Research

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