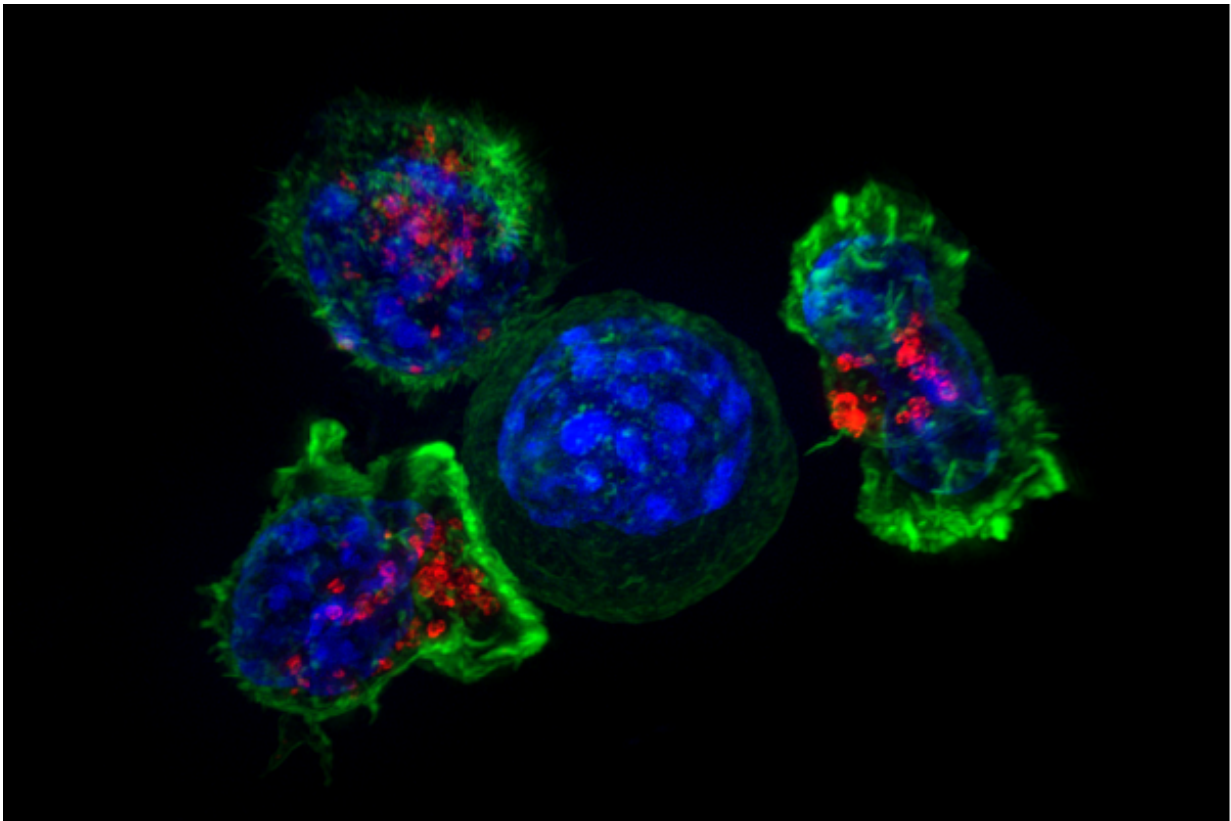


Childhood cancer hijacks cellular quality control system to fuel growth

July 20 2016, by Leigh Beeson



Killer T cells surround a cancer cell. Credit: NIH

A serious childhood cancer takes advantage of a quality control mechanism that usually protects cells from stress-induced damage to propel tumor growth, according to a new study led by researchers at UC

San Francisco and the University of Pittsburgh. By blocking that mechanism, the scientists were able to kill cells derived from patients with rhabdomyosarcoma (RMS), a rare muscle-tissue cancer that affects a few hundred children in the U.S. each year.

The study, to be published online during the week of July 18, 2016 in the Early Edition of *Proceedings of the National Academy of Sciences*, showed that RMS [cells](#) have a unique dependence on a cellular "chaperone" protein called HSP70 (heat-shock protein 70), which helps cells to properly fold badly formed proteins. By co-opting HSP70, RMS prevents the cell death that would usually occur when badly folded proteins accumulate in cells, said corresponding author Trever Bivona, MD, PhD, associate professor of medicine and of cellular and molecular pharmacology at UCSF, and a member of the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC).

The findings offer a potential new therapeutic pathway to fighting RMS, which is generally treatable in younger patients but can be fatal if diagnosed in older children after the disease has metastasized. In all cases the chemotherapy and radiation treatments that are the current standard of care can have significant long-term side effects.

The study was made possible by the Collaborative Innovation Award program of the Howard Hughes Medical Institute (HHMI), which provides funds for diverse, interdisciplinary scientific teams, each headed by an HHMI investigator, to pursue potentially transformative research projects. In 2012, HHMI investigator Jonathan Weissman, PhD, professor of cellular and molecular pharmacology at UCSF, received one of only six Collaboration Innovation Awards to pursue research on the role of protein quality-control systems in [cancer](#).

Weissman, an authority on protein folding, assembled an illustrious team for the project. Among others, UCSF's Peter Walter, PhD, winner of the

2014 Albert Lasker Basic Medical Research Award for his seminal work on a cellular quality control system called the Unfolded Protein Response (UPR), and protein-folding expert Jeffrey L. Brodsky, PhD, professor and Avinoff Chair of Biological Sciences at the University of Pittsburgh, were enlisted, along with UCSF physician-scientists Bivona, a cell biologist who also treats [lung cancer patients](#), and Amit J. Sabnis, MD, a Damon Runyon-Sohn Pediatric Cancer Fellow, who cares for children with cancer at UCSF Benioff Children's Hospital in San Francisco.

In a further example of the research team's range, UCSF's Jason Gestwicki, PhD, who studies misfolded proteins in neurodegenerative disorders such as Alzheimer's disease, also contributed expertise to the work.

"It's a pretty unique project," Bivona said. "It wasn't the basic scientists going off in one direction and the clinical scientists going off in another—it really was an integrated, concerted forward movement of both sides of the table."

Chaperones like HSP70 are produced in response to cellular stress, and protect cells from damage caused by poorly folded proteins. But when chaperones can't adequately deal with cellular stress, the accumulation of unfolded proteins normally triggers the UPR, which activates additional protective pathways. If these fail, the UPR sends signals that cause the entire cell to be destroyed. For reasons that are not completely understood, Bivona said, HSP70 is present at high levels in some [cancer cells](#), which helps damaged cells survive when they may otherwise be destroyed by the UPR, leading to tumor growth.

Many cancers are caused by "fusion genes," two genes that merge and produce a defective, fused protein product that is likely to activate cell-protective mechanisms. The research group assembled over a dozen

cancer cell lines that carried fusion genes, representing lung cancer, RMS, and another type of sarcoma, and administered a recently developed chemical compound called MAL3-101, which is known to inhibit HSP70's actions.

They found that RMS was unusually vulnerable to MAL3-101 treatment—the compound killed more RMS cells than those from any other cancer type. More surprisingly, it even killed RMS cells that did not carry [fusion genes](#).

Further experiments showed that the RMS cells were indeed killed via the UPR: after HSP70's actions were blocked, [unfolded proteins](#) built up in the cell, which ultimately activated a UPR-related protein called CHOP, which prompts faulty cells to commit suicide.

Though the dominant approach to fighting cancer is to kill cells by targeting cellular pathways affected by "driver mutations" such as fused genes, the MAL3-101 results indicated that it might be possible to stem cancer growth by targeting protective mechanisms like HSP70 directly.

This approach may have particular importance for pediatric patients, said Sabnis, co-first author of the new study with Christopher J. Guerrerio, PhD, research assistant professor in Brodsky's lab at the University of Pittsburgh, because childhood cancers tend to have many fewer mutations than those seen in adults.

"This study really identified a whole new area of cancer cell biology," Sabnis, assistant professor of pediatrics, said. "It shows that HSP70 dependence is a very specific vulnerability for RMS cells and can serve as a therapeutic target. These findings change the paradigm for thinking about how to develop new drugs in these sorts of diseases, because we don't necessarily need to look for mutations—there are other ways to find targets."

And because compounds like MAL3-101 affect different mechanisms than those targeted by chemotherapy and radiation, HSP70 inhibitors could potentially be used in conjunction with those treatments, a combined approach Sabnis said has proven effective in battles against other deadly diseases such as tuberculosis and HIV.

"For the patients, the promise is that it's a new approach to therapy," Sabnis said. "It's something that works completely differently from everything else that we're currently using."

More information: *Proceedings of the National Academy of Sciences*, www.pnas.org/lookup/doi/10.1073/pnas.1603883113

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