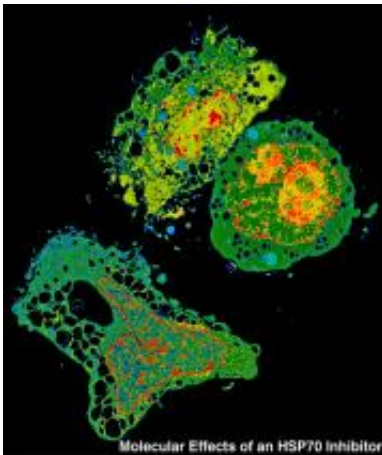


Inhibitor of Heat Shock Protein is a Potential Anticancer Drug, Study Finds

October 29 2009



Accumulation of holes, called vacuoles, inside a cell, which are associated with protein aggregation and disrupted regulation of normal protein degradation processes following exposure of cells to the HSP70 inhibitor. Credit: Donna George, PhD, University of Pennsylvania School of Medicine

(PhysOrg.com) -- Like yoga for office drones, cells do have coping strategies for stress. Heat, lack of nutrients, oxygen radicals - all can wreak havoc on the delicate internal components of a cell, potentially damaging it beyond repair. Proteins called HSPs (heat shock proteins) allow cells to survive stress-induced damage. Scientists have long studied how HSPs work in order to harness their therapeutic potential.

Donna George, PhD, Associate Professor of Genetics, and Julie Leu,

PhD, Assistant Professor of Genetics, both at the University of Pennsylvania School of Medicine, in collaboration with the lab of Maureen Murphy, PhD at Fox Chase Cancer Center, identified a small molecule that inhibits the heat shock protein HSP70. They also showed that the HSP inhibitor could stop tumor formation and significantly extend survival of mice. They describe their findings in this month's issue of *Molecular Cell*.

HSP70 is an intracellular quality control officer, refolding misfolded proteins and preventing protein aggregation, which among other disorders, is associated with [neurodegenerative diseases](#). HSP70 also ferries proteins to their proper intracellular locations. Tumor cells, which face an abundance of cellular stresses, typically overexpress HSP70, making it a potentially interesting anticancer target.

The cancer microenvironment exposes [malignant cells](#) to a variety of stressful conditions that promote [protein misfolding](#). HSP70 helps [cancer cells](#) deal with this stress. Unlike normal cells, which typically express little, if any, of HSP70, cancer cells contain high levels of this protein all of the time. Indeed, HSP70 has been termed a cancer-critical survival factor, since cancer cells probably require the actions of this protein to survive the protein-altering adverse conditions. The inhibitor, called PES, interferes with the HSP70 activities that the cancer cell needs to survive, so by targeting HSP70, one can target the cancer cell.

The investigators showed that PES interacts with HSP70 by blocking its stress-relieving functions. It also induces HSP70-dependent cell death by disrupting the cell's ability to remove damaged components. Paradoxically for a compound first identified for blocking the cell-death pathway of apoptosis, PES does kill cells, but by a different mechanism.

PES seems to be specifically targeting HSP70, a protein that is differentially expressed in normal versus cancerous cells, and “one that

the cancer cell seems to require to survive” says George. “It's still early days - we don't know what it will do in a human. But, the exciting part is that this is a pathway and a protein target that clearly is important for cancer cells.”

Given the extreme heterogeneity of cancer cells, simultaneously disabling networks of signaling pathways may be important. Indeed, PES was more or less equally effective in every type of cancer cell tested, she says, “which is unusual and supports the idea that it is targeting a protein that is required for the functioning of multiple pathways.”

To figure out just what PES was doing Leu chemically tagged it to see what proteins it interacted with. They were surprised and excited to have pulled out HSP70.

Next, the team investigated the consequences of PES binding. Like many proteins, HSP70 doesn't act alone; it functions through a cadre of interacting proteins, which augment its activity. So, the team systematically scanned these proteins, to see if PES blocked their interactions with HSP70. “We found several known HSP70-interacting proteins that were no longer interacting properly when the cells were exposed to the small molecule,” Leu notes.

Among those were proteins that help HSP70 refold misfolded proteins and proteins that abet its [protein](#) trafficking functions.

When they then studied the effect that loss of those functions had on the cell, the team discovered that PES blocks the cell's ability to get rid of the proteins damaged by cellular stress in a process called autophagy, a process in which cells were basically eating themselves to death. In mice, Murphy and her students Julia Pimkina and Amanda Frank found that PES could inhibit tumor formation and significantly extend survival.

“That was one of the highlights from our perspective, because PES has potential to be developed as a therapeutic,” says Murphy.

PES should also be a boon to researchers trying to untangle the biology of HSP70, say the researchers. Other HSP70 inhibitors exist but they are neither generally available, nor sufficiently specific. It also provides a novel platform for anticancer therapeutics, either directly as a treatment, or as a starting point for further development.

Provided by University of Pennsylvania School of Medicine ([news](#) : [web](#))

Citation: Inhibitor of Heat Shock Protein is a Potential Anticancer Drug, Study Finds (2009, October 29) retrieved 19 April 2024 from <https://medicalxpress.com/news/2009-10-inhibitor-protein-potential-anticancer-drug.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--