Sheltering Of Messages May Help Cancer Cells Defeat Therapy

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New research has discovered that cells protect rather than destroy the message molecules needed to make certain proteins during periods of stress. The response might help cancer cells survive chemotherapy and radiation therapy.

The study examined a recently discovered protein called PMR1. The protein attaches to message molecules that leave the cell nucleus during the making of proteins. Under certain conditions, the PMR1 destroys those messages, and the protein is not made.

This study found, however, that under stress conditions, this protein does not destroy the message. Instead, both become incorporated into bodies called stress granules. There, the message is preserved, perhaps helping the cell to survive.

Stress granules are short-lived complexes of message molecules – also called messenger RNA (mRNA) – and proteins. The granules accumulate when cells are subjected to conditions such as starvation, low oxygen (which occurs within large tumors), chemotherapy or radiation therapy. The mRNAs within the granules are either marked for destruction or for preservation.

The study, led by cancer researchers at the Ohio State University Medical Center , is published in the Dec. issue of the journal *Molecular and Cellular Biology*.

“The stress response protects cells from these conditions by sequestering mRNAs for proteins not specifically involved in the stress response itself,” says Daniel R. Schoenberg, professor of molecular and cellular biochemistry and a researcher with Ohio State's Comprehensive Cancer Center.

“By understanding how PMR1 and similar enzymes are incorporated into stress granules and inactivated, we may be able to learn how to block this protective mechanism and make it harder for cancer cells to survive cancer therapies.”

The protein PMR1 is an enzyme discovered in 2002 by Schoenberg. It becomes joined to certain mRNAs and under certain conditions quickly destroys them.

For this study, Schoenberg and a group of colleagues wanted to learn what happens to PMR1 and its message during periods of stress. They wanted to learn if the PMR1 destroys its mRNA or whether the mRNA is incorporated into stress granules.

To answer the question, the researchers used cultured cells to which they'd added active and mutant forms of PMR1. They stressed the cells using the chemical arsenite, a relative of arsenic.

The investigators found that PMR1 interacts directly with a protein called TIA-1, a key protein involved in assembling stress granules. This interaction draws the PMR1-messsage complex into stress granules.

But the researchers were unable to detect any sign that the message was destroyed.

“The fact that we don't see an acceleration of mRNA decay suggests that something in the stress response protects these mRNAs from being

degraded, even though the degradative enzyme PMR1 is there in the stress granules with its target mRNA."

Next, Schoenberg and his colleagues will study the other proteins within stress granules to try to learn how the PMR1-message complex are preserved.

Source: Ohio State University