Destructive enzyme shows a benevolent side

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New research shows that a recently discovered enzyme that destroys the messenger RNA (mRNA) for some proteins can also help to protect the mRNA during times of stress. The response might help cancer cells survive chemotherapy and radiation therapy.

The study examined a recently discovered enzyme called PMR1. That enzyme attaches to certain mRNA molecules and remains there like a hand grenade with its pin in place.

These mRNAs carry the information for making highly potent proteins, proteins that cells must stop making suddenly. When that 'stop' command arrives, the pin is pulled and the enzyme destroys the mRNA, quickly halting production of that protein.

This new study found, however, that under stress conditions, the same enzyme – while attached to the mRNA – helps form temporary shelters within the cell called stress granules. There, the mRNA can be protected so that production of the protein can quickly resume whenever the stress ends, perhaps insuring that the cell survives.

Stress granules are short-lived aggregates of mRNA and proteins, and they accumulate when cells are subjected to conditions such as starvation, low oxygen (which can occur within large tumors), chemotherapy or radiation therapy.

The study, led by researchers at Ohio State University's Comprehensive Cancer Center, is published in the December issue of the journal

Molecular and Cellular Biology.

"The stress response protects cells from these conditions by sequestering mRNAs for those proteins not specifically involved in the stress response itself," says principal investigator 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."

Schoenberg first discovered the PMR1 enzyme in 1995, and his lab has been actively studying it since that time.

For this study, Schoenberg and a group of colleagues wanted to learn if the enzyme also destroys its mRNA during periods of stress.

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

The investigators found that during stress, the enzyme interacts directly with another protein called TIA-1, a key protein involved in assembling stress granules. This interaction draws the enzyme-mRNA 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 degrading enzyme PMR1 is there in the stress granules with its target mRNA."

Schoenberg and his colleagues will next study the other proteins within stress granules to try to learn how PMR1-mRNA complex is preserved.

Source: Ohio State University