To cap or not to cap: Scientists find new RNA phenomenon that challenges dogma

August 27 2012, by Emily Caldwell

Some RNA molecules spend time in a restful state akin to hibernation rather than automatically carrying out their established job of delivering protein-building instructions in cells, new research suggests.

And instead of being a fluke or a mistake, the research suggests that this restful period appears to be a programmed step for RNA produced by certain types of genes, including some that control cell division and decide where proteins will work in a cell to sustain the cell's life.

This could mean that protein production in cells is not as clear-cut as biology textbooks suggest, scientists say.

"This could mean there are more variations to the proteins in our bodies than we realize; it means that RNAs can be stored and reactivated and we don't know what biological process that affects - it could influence embryonic development, or neurological activity, or even cancer," said Daniel Schoenberg, professor of molecular and cellular biochemistry at Ohio State University and lead author of the study.

Schoenberg and colleagues discovered this phenomenon by tracing the origins of a cap-like structure on messenger RNA (mRNA) that is known to coordinate most of this RNA molecule's short life. Messenger RNA is manufactured in a cell's nucleus and each mRNA contains the instructions needed to produce a specific protein that a cell needs to live.

Until now, scientists have believed that once an mRNA is no longer

needed to make protein, the cap comes off and the molecule is degraded, its job complete. But Schoenberg's lab discovered in 2009 that some mRNAs that were thought to be degraded were instead still present in the cell, but they were missing part of their sequence and had caps placed back on the newly formed ends. Because these mRNAs were in the cytoplasm, the changes had to happen there rather than inside the nucleus.

In this new study, the researchers were looking for further evidence of these apparent rogue mRNAs, but instead they found that a completely unexpected biological process occurs before some proteins are even a glimmer in a gene's eye: The uncapping and recapping of mRNAs outside the nucleus results from a cap recycling operation in the cell cytoplasm. This process appeared to enable certain RNAs to pause, without being degraded, before launching protein production.

"What this discovery tells us is a complete fundamental reworking of the relationship between a gene, messenger RNA and a protein. It's more complicated than we realize," Schoenberg said.

The research is published online in the open-access journal *Cell Reports*.

That fragments of mRNA could exist at all in the cell's main body was first reported by other scientists in 1992. Years later, Schoenberg asked a postdoctoral researcher in his lab to revisit these unexpected RNA fragments and confirm they exist. The postdoc's experiments showed that these mRNA, thought to be the dregs left over from their degradation, had caps on them - suggesting they still had the potential to function in protein production. Schoenberg, also director of Ohio State's Center for RNA Biology, has been investigating this cytoplasmic capping operation ever since.

In 2009, he and colleagues reported the discovery of two enzymes in the

cell's main body that would enable mRNA capping to occur completely outside the nucleus and in the cytoplasm instead.

In the current studies, Schoenberg sought to determine the physiological significance of this capping operation. The researchers engineered a way to block cytoplasmic capping in cells in the lab and then looked at changes in more than 55,000 RNAs.

This interference with cytoplasmic capping revealed that two different types of pathways could exist in the cells - some mRNAs remained stable without their caps, while others without caps were rapidly destroyed. This finding indicated that mRNAs can lose their caps in the cytoplasm and at some point get recapped. With further experimentation, the researchers determined that only some mRNAs lost their caps in the cell body.

"It's not all of any particular message that's uncapped, just a portion of a message," Schoenberg said. "We wanted to show that we have uncapped RNAs in the cell and they are not degraded. It means they're stored that way."

This finding offered hints that there is a higher order to this phenomenon, and that some mRNAs purposefully rest in an uncapped state without being degraded by enzymes within the cell whose job is to remove them. It also suggested that as the capping circumstances change inside the cell body, signals from genes might undergo change that allows for two or more proteins, one being shorter than the other, to be made from the same mRNA.

"We have always thought that one gene would give an mRNA for one kind of protein. But what we have found makes us wonder if multiple proteins could be made from each of the messenger RNAs that undergo decapping and recapping in the cytoplasm," Schoenberg said.

The researchers used bioinformatics technology to determine which genes were manufacturing mRNAs that could exist in this uncapped and recapped state in the cytoplasm. These genes included those that control some of the most basic elements of cell survival: They determine the location of proteins and RNAs within the cell and, perhaps most significantly, the mitotic cell cycle - part of the process of cell division.

"It wasn't random. It was very specific," Schoenberg said. "There are specific families of mRNAs that are regulated in this way, and that has ramifications for how proteins are expressed and regulated."

As an example, he cited how neurons communicate messages across vast distances to other nerve cells. It is known that mRNAs are deliberately kept in a silent state while they travel from, for example, the spinal cord to the fingertip, where they are then activated to make new proteins.

"What would the condition be of the mRNA to keep it silent? The possibility is it doesn't have a cap on it, and if it doesn't, it can't be translated. Maybe cytoplasmic capping in neurons is a function that allows that message to be translated at just the right time," Schoenberg said.

Or, in the case of cancer: "What if one of the things that happens is you are making shortened proteins instead of full-length proteins and the regulatory part of the protein is missing in the shortened protein? If that's true, can you interfere with this process and interfere with malignancy as a result?"

For now, these scientists can only speculate about what this unexpected biological process really means. Schoenberg's lab plans to investigate the phenomenon more thoroughly in a line of breast cancer cells.

PHYS.ORG

Provided by Ohio State University

Citation: To cap or not to cap: Scientists find new RNA phenomenon that challenges dogma (2012, August 27) retrieved 25 April 2024 from https://phys.org/news/2012-08-cap-scientists-rna-phenomenon-dogma.html

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.