Scientist uncovers switch controlling protein production

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A scientist from the Florida campus of The Scripps Research Institute has discovered a molecular switch that controls the synthesis of ribosomes. Ribosomes are the large machineries inside all living cells that produce proteins, the basic working units of any cell. These new findings offer a novel target for potential treatments for a range of diseases, including cancer.

The study is published in the December 24, 2010 edition of the Journal of Molecular Biology.

The study identified the molecular switch, essentially formed by a small sequence of RNA, that controls a critical part of ribosome synthesis to allow for strict, albeit temporary, regulation of the process.

"These kinds of switches in RNA are thought to be slow acting," said Katrin Karbstein, an assistant professor in the Department of Cancer Biology at Scripps Florida who helped lead the study. "That suggests a point where we might intervene to modify the process – then you could potentially shut down the pathway, because if you don't produce ribosomes, you cannot make proteins. Thus, cells can't grow. That would be a desirable outcome in cancer, for example."

This slowness may be there precisely so these regulatory points can be introduced for cells to downregulate growth when nutrition is scarce.

"Perhaps, nature has found a way to exploit RNA's Achilles' heel – its

propensity to form alternative structures that can lead to protein misfolding, which, in turn, can cause diseases ranging from Alzheimer's to diabetes," Karbstein said. "Nature might be using this to stall important biological processes and allow for quality control and regulation."

The synthesis of proteins involves ribosomes, large macromolecular machines required for cell growth in all organisms. Ribosomes read the genetic code carried by messenger RNA and then catalyze or translate that RNA code into proteins within cells, assembling them from amino acids.

To produce mature ribosomal RNAs (rRNAs), the catalysts that control protein synthesis in all cells, the body first needs perfectly formed intermediate or pre rRNAs, which can be further processed into fully functioning ones. The intermediate form is produced as an RNA transcript that is cleaved or cut in multiple steps to produce mature rRNA.

"While we believe that this switch is essential for ribosome assembly, it seems unlikely that this is the only event that regulates cleavage," Karbstein said. "However, tight regulation of ribosome synthesis is essential to ensure the structural integrity of mature ribosomes."

Cutting Extra Material

The ribosomal RNA that is transcribed has extra material in it, Karbstein said, so it is necessary to cut it down – that's why these cuts or cleavages are so essential to the process of producing the final rRNA product.

The study also suggests RNA itself exploits its own natural ability to form these stable structural switches to order and regulate various RNA-dependent biological processes.

"What is interesting," Karbstein said, "is that as the organism becomes more complex, the number of cleavages needed increases. This may make the process more accurate and that may be an evolutionary advantage, but even in bacteria this cutting is not done in a simple way. We still don't know exactly why that is."

Perhaps these strictly ordered cleavage steps are introduced to produce singularly perfect intermediates, she added. This is important because cleavage is an irreversible energy-releasing process with the potential to shift the landscape of assembly towards the final product. As a result, cleavage steps should be carefully controlled and should only occur if the assembly intermediate is correct.

"Ribosomes make mistakes rarely, on the order of one in 10,000 amino acid changes," Karbstein said. "A lot of this accuracy depends on conversations between different parts of the ribosomes, so if the structure of the RNA isn't correct, these conversations can't happen. And that means more mistakes, and that's not good because it can lead to any number of disease states."

For now, Karbstein said she's interested in looking at small molecules that perturb the switch, and finding out if this affects the quality of the ribosomes produced.

"Certain kinds of antibiotics work by making the ribosomes produce more mistakes – it's not a huge increase but it's enough to make these cells die," she said. "Maybe we can find molecules that similarly lead to the production of 'worse' ribosomes."

More information: In addition to Karbstein, Allison C. Lamanna is an author of the study, "An RNA Conformational Switch Regulates Pre-18S rRNA Cleavage" doi:10.1016/j.jmb.2010.09.064

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