Researchers demonstrate that messenger RNA are lost in translation

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Case Western Reserve University School of Medicine assistant professor in the Center for RNA Molecular Biology, Jeff Coller, Ph.D., and his team discovered that messenger RNA (mRNA) predominately degrade on ribosomes, fundamentally altering a common understanding of how gene expression is controlled within the cell. The study, "Co-translational mRNA decay in *Saccharomyces cerevisiae*", is published in the latest issue of *Nature*.

"Many genetic diseases are linked to mutations that can cause mis-regulation of RNA destruction so it's important to know the when, where and how the cell normally controls the process of mRNA decay," said Dr. Coller.

mRNA communicates genetic information from DNA to ribosomes where the information is converted to proteins. Proteins catalyze the reactions of life and how much protein is made is critical to fine tune the function of the cell. This means that the amount of mRNA present within the cell is vital for overall cellular health.

The rates of RNA synthesis and destruction determine the overall levels of mRNA. While the details of mRNA synthesis have been studied intensely over the years, the mechanism(s) controlling mRNA decay remain unclear. Prior to Dr. Coller's study it had been thought that once an mRNA had ended its utility it was removed from ribosomes and possibly transported to specialized structures within the cell, called P-bodies, where they are eventually destroyed.

Contrary to this prediction, Dr. Coller's research demonstrates that decay takes place while mRNAs are associated with actively translating ribosomes.

"The data clearly indicate that sequestration into a ribosome-free state (like a P-body) is not a prerequisite for initiation of mRNA decay," said Dr. Coller. Moreover, Dr. Coller and colleagues believe that this new understanding provides an evolutionary explanation for the nature of the decay pathway and may lead into new insights into how cytoplasmic gene regulation occurs, offering insight into disease states that result when things go awry.

"A lot is known about how mRNAs are made, but much less is understood about the mechanisms that control their destruction," said Michael Bender, Ph.D., who oversees RNA processing grants at the National Institutes of Health's National Institute of General Medical Sciences. "This work breaks new ground by shedding light on one of the cell's major mRNA degradation pathways—a key regulatory point for gene expression—and by challenging accepted models of mRNA decay."

Dr. Coller's findings raise several interesting mechanistic questions, for instance how mRNA's are destroyed at different rates. Some are long lived, some short lived. Scientists currently do not understand how these differences in mRNA decay rate are determined, but clearly this understanding is vital for predicting how mutations will impact cellular function.

"Now that we have found that mRNAs are degraded on ribosomes we can begin to understand how the degradation machinery interacts with ribosomes and how it is triggered to destroy the message," said Dr. Coller. "Eventually, we hope to create a rule book that would allow us to predict which mRNA is going to last only a few minutes and which will be expressed hours or days. This has huge impact on cellular protein

levels and perhaps this understanding would lead to new advances in gene therapy and viral vaccinations."

Source: Case Western Reserve University (news : web)