Case researcher in RNA biology makes waves by challenging current thinking

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In the January 18th issue of *Molecular Cell*, Case Western Reserve University School of Medicine researcher Kristian E. Baker, Ph.D. challenges molecular biology's established body of evidence and widely-accepted model for nonsense-mediated messenger ribonucleic acid (mRNA) decay.

With her collaborator, Ambro van Hoof, Ph.D. of The University of Texas Health Sciences Center, Baker directly tested the "faux 3' UTR" model and proved it could not explain how cells recognize and destroy deviant mRNA. This landmark discovery will redirect mRNA research and expand opportunities for new discoveries in understanding the cells' ability to protect itself from these potential errors.

In all cells, including human, mRNA is a copy of the information carried by a gene on the DNA. Occasionally, mRNA contains errors that can make the information it carries unusable. Cells posses a remarkable mechanism to detect these aberrant mRNAs and eliminate them from the cell – this process represents a very important quality control system for gene expression. "A significant amount of past research in this area of RNA biology has collected data to support the 'faux 3' UTR' model for mRNA quality control, and, as a result, has shaped present research directions in the field," said Baker. "Our recent findings preclude this explanation and will, undoubtedly, result in a rethinking by many as to how to experimentally approach this important cellular process."

For decades researchers have been puzzled by cells' ability to

differentiate between “normal” mRNA and those carrying certain types of mutations. mRNA transports DNA’s genetic coding information to the sites of protein synthesis: ribosomes. Cells are able to identify mRNA carrying a mutation and prevent it from reaching the protein synthesis phase. Once identified, the cell destroys the abnormal, mutated mRNA. This naturally occurring process ensures malfunctioning proteins are not produced. Using a yeast model system, Baker’s research offers a better understanding of this mRNA quality control process which closely mimics the process in human cells.

Baker’s research on nonsense-mediated mRNA decay not only provides an advanced understanding of an important process in the regulation of gene expression, but may help lead to new therapeutic strategies in the treatment of genetic diseases. Many inherited conditions, including cystic fibrosis, are a consequence of mutations resulting in the recognition of non-functional mRNA and the subsequent elimination by nonsense-mediated mRNA decay. Because cells eliminate the abnormal mRNA, no protein is produced.

With genetic diseases, researchers are hypothesizing it might be beneficial for the cell to express the protein, even though it is not completely functional. The rational is it will be better for these patients to have protein of some function rather than no protein at all. Cystic fibrosis clinical trials are currently underway with a goal of producing the partially functional proteins, before the cell’s natural elimination process takes place. Using Baker’s findings, researchers will have a better understanding of how to modulate the recognition of the abnormal mRNAs as to allow the mRNA to remain in the cell and produce the protein.

“This finding is an important step in advancing our understanding of mRNA function,” said Baker. “In addition, it emphasizes the important link between basic and clinical science; the more we understand the

basic biological processes that are underway in the cell, the better equipped we are to directly address clinical therapies."

Source: Case Western Reserve University