Researchers identify enzyme that removes molecular modifications from transfer RNA

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New research by scientists from the University of Chicago demonstrates that the enzyme ALKBH1 can remove molecular modifications from transfer RNA, causing a measurable effect on protein translation in the cell. The study, published Oct. 13 in *Cell*, sheds new light on how cells control gene expression, and suggests the possibility that transfer RNA (tRNA) influences cellular processes beyond protein translation.

"The ability to reverse something, to remove something, confers the possibility of dynamics," said Tao Pan, PhD, professor of biochemistry and molecular biology at the University of Chicago, and a senior author of the study. "I would say that the ribosome is the hardware of the computer, the messenger RNA is somebody who enters the information to instruct on how to do something, and the tRNA is the software on how to translate that into something. So now we know that the software itself can be tweaked, or modified, or dynamically changed."

Trillions of cells make up the human body, all performing essential and diverse functions that facilitate the complex endeavor of daily life. But how do cells "know" what role they have in the body; for example, how is a liver cell so different from a white blood cell? How is it that cells can change their behavior based on signals from their neighbors, or even cells in entirely different parts of the body? How is a complete human body formed from a single cell in early development?

These fundamental questions have fascinated scientists for decades, and a large part of the answers to them has to do with the processes that

determine which regions of a cell's DNA are used to make particular proteins at a particular time. Proteins perform virtually every task within cells, and the composition of the ensemble of proteins present at a given time generally determines cellular behavior.

When a cell needs a certain protein, a copy of the DNA that codes for that protein called messenger RNA is generated, and is used as a template by a ribosome, the cell's protein synthesis machinery. Proteins are in essence strings of a set of a family of molecules known as amino acids, the patterns of which determine the function of the protein. The messenger RNA provides a code that dictates the order and type of amino acids to use to make a particular protein in a process known as translation - the conversion of the "language" of RNA to that of proteins. Another key player in translation is a group of molecules called transfer RNAs, or tRNAs. Each of the twenty-one amino acids used by the human body has a tRNA binding partner that carries it to the ribosome where it can be incorporated at the appropriate point into a growing protein.

Scientists have discovered many points of regulation in the process of using a specific DNA template to make a protein, known as gene expression, that allow the cell to control how much of a certain protein is made at a certain time. By the 1980s, it was established that the addition or removal of several small molecules to or from DNA could affect gene expression.

More recently, groundbreaking work done by Chuan He, PhD, professor of chemistry at UChicago and the other senior author of the new study, has demonstrated that a similar method of regulation exists for messenger RNA. The latest research demonstrates that the enzyme ALKBH1 can remove a small molecule added to tRNA, and that the presence or absence of this modification has a measureable effect on protein translation.

While it has been understood for some time now that tRNAs are heavily decorated with small molecules such as methyl groups (carbon atoms bound to three hydrogens), the unprecedented discovery that one of these modifications can be removed suggests that tRNA has a regulatory role in the process of protein translation. ALKBH1 can take off a specific methyl group present on many tRNAs, without which tRNAs are degraded by the cell.

An especially important tRNA that ALKBH1 acts on is tRNAiMet, a tRNA molecule carrying the amino acid methionine, which initiates translation for all proteins. Thus, high ALKBH1 activity can globally decrease the amount of proteins made in a cell, as the researchers observed in a human cell line with abnormally high levels of ALKBH1. Not only did these cells have a lower rate of protein synthesis, they also divided less frequently than those with normal or low levels of ALKBH1, suggesting that this enzyme has a powerful effect on cellular health. They also observed that in normal cells, the amount and activity of ALKBH1 varied with environment; cells deprived of energy sources increased ALKBH1 action to conserve resources.

It has been noted by other groups that genetically modified mice lacking ALKBH1 have severe neuronal defects along with other developmental deficiencies, information that takes on new significance now that the function of ALKBH1 has been defined. Prof. He sees two, most likely overlapping, interpretations. One is straightforward - during development, cells are assuming their identities and need precise control over protein production, so cells lacking a gene expression regulation mechanism are bound to have defects, particularly in the case of specialized cells like neurons. The second possibility, namely that tRNA influences processes beyond translation, is perhaps more interesting to both Pan and He.

"Scientists are starting to realize that there are non-translational roles for

tRNA. This methylation is key for the stability of the tRNA," said He. "The other side of the coin is that demethylation by ALKBH1 could be a way to promote non-translational roles. This is something we wish to explore in the future."

In any case, Pan and He are confident that their work on ALKBH1 will open up a new area of investigation in the study of RNA modifications, and that more enzymes that de-modify tRNA will be discovered in the near future. More broadly, this landmark discovery has illuminated an unexplored avenue in scientists' understanding of how cells control gene expression, and could incite a fresh wave of innovation in this ever growing field.

More information: "ALKBH1-Mediated tRNA Demethylation Regulates Translation," *Cell*, 2016.

Provided by University of Chicago Medical Center

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