Researchers describe mechanism central to maintaining healthy protein levels, avoiding disease states

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A new scientific study conducted by a team of leading geneticists has characterized how cells know when to stop translating DNA into proteins, a critical step in maintaining healthy protein levels and cell function. In the study published in *Cell*, researchers studied short pieces of genetic material called messenger RNA, or mRNA, that serve as a go-between a person's DNA and the proteins it encodes. Researchers were searching for insight into a cellular mechanism that has been a mystery – how do cells sense it is time to stop making mRNA and coordinate cellular machinery to shut down the process?

Jeff Coller, PhD, director of the Center for RNA Molecular Biology at Case Western Reserve University School of Medicine helped lead the study that discovered an enzyme called "DEAD-box protein Dhh1p" assesses mRNA molecules and determines if they are needed, or need to be removed. Cells produce mRNAs representing small subsets of genes when they need a specific protein, but once the cell no longer needs the protein the corresponding mRNAs are destroyed. The process of destroying an unneeded mRNA is complicated. Several cellular enzymes collaborate to recognize portions of mRNA and chop it up so that it can no longer be used to make protein. Coller's study found Dhh1p is responsible for assessing mRNAs and targeting those that are being translated too slowly for destruction.

"We knew there had to be some way to communicate how fast the

genetic code was read to the machinery that ensures the message is removed from the cell," said Coller. "There had to be a way to put on the brakes."

Together with colleagues from Johns Hopkins University School of Medicine, Coller discovered Dhh1p assesses specific molecular sequences in mRNA. Enzymes called ribosomes rapidly translate common mRNA sequences into proteins, and translate less common sequences more slowly. Coller found Dhh1p attaches itself to mRNA molecules with sub-optimal sequences and physically interacts with slow-moving ribosomes. According to the paper, "Dhh1p is a sensor of slow ribosomes and communicates this information to the mRNA decay machinery." The study showed genetic sequences are a key determinant in mRNA stability, and even 10% changes in sequences can affect the fate of an mRNA molecule.

Coller's study describes how Dhh1p assesses mRNA sequences to inform gene expression and ensure cells make the right amount of protein at the right time. The study provides important insight into how protein production is regulated within cells and may inform the development of therapeutics designed to augment the process.

"Our study provides a new way to look at the genetic code," said Coller. "We're so used to looking at how DNA mutations cause a change in protein function. We must also consider how enzymes like Dhh1p sense the speed at which ribosomes interpret the genetic code. Now I can look at the genetic code in terms of speed and rate, and with reasonable accuracy predict how much protein is going to come from a gene. There's huge application for that in human biologics, proteins that are easily taken by injection."

Said Coller, "There are rare genetic diseases attributed to RNA being read too slow or too fast. We can now manipulate this process to dial up

or down protein expression. The speed at which the ribosome reads the genetic code and is sensed by Dhh1p could open up a new set of mutation types that could indicate disease states we are unaware of today."

More information: Aditya Radhakrishnan et al. The DEAD-Box Protein Dhh1p Couples mRNA Decay and Translation by Monitoring Codon Optimality, *Cell* (2016). DOI: 10.1016/j.cell.2016.08.053

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