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Scientists override errant form of genetic signaling for first time

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In a new study published today in the journal *Nature*, scientists discovered an entirely new way to change the genetic code. The findings, though early, are significant because they may ultimately help researchers alter the course of devastating genetic disorders, such as cystic fibrosis, muscular dystrophy and many forms of cancer.

The genetic code is the set of instructions in a gene that tell a cell how to make a specific protein. Central to the body's protein production process is messenger RNA, or mRNA, which takes these instructions from DNA and directs the steps necessary to build a protein. For the first time, researchers artificially modified messenger RNA, and in doing so changed the original instructions for creating the protein. The end result: A different protein than originally called for.

"The ability to manipulate the production of a protein from a particular gene is the new miracle of modern medicine," said Robert Bambara, Ph.D., chair of the Department of Biochemistry and Biophysics at the University of Rochester Medical Center. "This is a really powerful concept that can be used to try to suppress the tendency of individuals to get certain debilitating, and sometimes fatal genetic diseases that will forever change their lives."

Protein production is not a perfect process – far from it. Frequent mutations or mistakes in DNA and messenger RNA can lead to flawed proteins that have the potential to cause serious harm. In the study, researchers focused on a common type of mutation that occurs when an

mRNA molecule contains a pre-mature "stop" signal, known as a pre-mature stop codon. A premature stop codon orders a cell to stop reading the genetic instructions partway through the process, resulting in the creation of an incomplete, shortened protein.

Researchers were able to alter mRNA in a way that turned a stop signal into a "go" signal. As a result, the cell could read the genetic instructions all the way through and create a normal, full-length protein. The team produced these results both in vitro and in live yeast cells.

"This is a very exciting finding," said Yi-Tao Yu, Ph.D., lead study author and associate professor of Biochemistry and Biophysics at the Medical Center. "No one ever imagined that you could alter a stop codon the way we have and allow translation to continue uninterrupted like it was never there in the first place."

The findings are important because current estimates suggest that approximately one third of genetic diseases are caused by the presence of pre-mature stop codons that result in shortened proteins. The results could aid the development of treatment strategies designed to help the body override stop codons and produce adequate amounts of full-length proteins, whose absence causes diseases like cystic fibrosis and contributes to different types of cancer.

Yu, along with first author John Karijolich, Ph.D., used another type of RNA – guide RNA – to modify messenger RNA. Guide RNAs are short RNAs that bind to specific sequences in RNA and allow just one particular site to be modified. "Guide RNAs give us tremendous power to zero in on one spot in the genome and make very targeted changes," noted Bambara.

The team developed an artificial guide RNA and programmed it to target and change a specific stop codon in an mRNA.

"The fact that this strategy worked – that the guide RNA we created found its way to its target, the stop codon, and directed the desired structure change – is pretty remarkable. Guide RNAs weren't thought to have access to messenger RNA, so no one believed they could target messenger RNA for modification," said Karijolich, who conducted the research as a graduate student at Rochester, but is now a postdoctoral fellow in the Department of Biochemistry at the Robert Wood Johnson Medical School. "Our results bring up the question of whether a similar process may be happening naturally."

"Previous research has presented other ways to modify the genetic code, but what is really unique about our method is that it is at the RNA level and it is site specific. We can express the artificial guide RNA in a cell and direct it to make a modification at a single site and only that site," said Yu.

Altering messenger RNA in this way may be another mechanism human cells use to create many different types of proteins. Given our complexity, humans have surprisingly few genes. While it is well established that the majority of human genes code for more than one protein, mRNA modification may be an unrealized way that humans are able to do this.

Yu plans to pursue this research further, studying whether and how targeted mRNA modification is happening naturally.

Provided by University of Rochester