Direct communication between cell's surveillance and protein synthesizing machinery eliminates genetic errors

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New research out of Case Western Reserve University School of Medicine describes a mechanism by which an essential quality control system in cells identifies and destroys faulty genetic material. The findings were published online December 23 in *Nature Communications*.

Kristian Baker PhD, associate professor in the Center for RNA Molecular Biology at Case Western Reserve University School of Medicine led the study that provided evidence for direct communication between the cell's protein synthesis machinery – the ribosome – and the protein complex that recognizes and destroys defective genetic intermediates called messenger RNAs (mRNAs).

"We aimed to understand how cells are able to recognize mRNA that is defective and distinguish it from normal mRNA. For most cells this process is critical for survival, but we didn't yet understand how it works, especially when the difference between the two is very subtle," said Baker. "Our findings clearly show that surveillance machinery involved in identifying faulty mRNA functionally interacts with the ribosome, the apparatus responsible for synthesizing proteins in the cell. It is now clear that these two elements communicate and work closely together to recognize and eliminate aberrant mRNA from the cell."

Cells convert sections of DNA encoding genes into mRNA that serves as a blueprint for the synthesis of a protein. In some cases, the DNA

template has suffered damage or errors occur when copying the information such that the mRNA contains a "premature stop codon." Premature stop codons cause the ribosome to halt synthesis early, before the entire protein is made, resulting in a truncated protein that often lacks function, or worse, can wreak havoc on other normal processes in the cell. Baker's research focused on how cells identify when an mRNA has a premature stop codon and then target the faulty genetic intermediate for rapid disposal to avoid the harmful effects of truncated proteins.

"Consider a car maker," said Baker. "If a faulty brake pedal sneaks past quality control and gets installed into a new car, the primary result is an improperly functioning car, which, in itself, is bad. However, failure to remove the car from the road could have grave secondary consequences if it leads to the damage of other cars, drivers or roads. Efficient quality control processes are therefore necessary, and ones that identify and remove faulty genetic intermediates from the cell are absolutely critical for avoiding downstream consequences that could negatively impact the function of the entire cell."

In the new study, Baker and her team of researchers uncovered that ribosomes were stalled on mRNA at premature stop codons. This observation led to the discovery that one of proteins in the surveillance complex, UPF1, was important for interacting with the stalled ribosome and assisting with its release from the mRNA. The inability of UPF1 to properly communicate with the ribosome results in the failure of the mRNA to be targeted to rapid elimination and inactivates the whole surveillance system. Moreover, Baker's findings indicated that UPF1 harnesses energy found in adenosine triphosphate – a reserve for energy storage in the cell – to influence the function of the ribosome, and that this step in the cellular checkpoint is necessary for recognizing and destroying mRNA with premature stop codons.

Baker's efforts could potentially be leveraged for the future treatment of genetic diseases. "About one-third of all genetic diseases involve a gene mutation that introduces a premature stop codon into the corresponding mRNA. In some cases, a therapeutic strategy that either instructs the ribosome to bypass this stop or that interferes with the recognition or elimination of the mRNA could restore some level of functional protein and lessen disease symptoms in patients," said Baker. "What is most exciting is that once developed, such a strategy could be applied not just to a single genetic disease, but to any that occur as a consequence of these particular mutations."

More information: Lucas D. Serdar et al, ATP hydrolysis by UPF1 is required for efficient translation termination at premature stop codons, *Nature Communications* (2016). DOI: 10.1038/ncomms14021

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