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- TerpVision
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College Park, MD -- Working with a gene that interacts with HIV, University of Maryland researchers have discovered that some human genes have an alternate set of operating instructions written into their protein-making machinery. The alternate instructions can quickly alter the proteins' contents, functions and ability to survive.

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This phenomenon, known as programmed ribosomal frameshifting, was discovered in viruses in 1985. But the UMD study, published online July 9, 2014 in the journal Nature, is the first to show that a human gene uses programmed ribosomal frameshifting to change how it assembles proteins, said senior author Jonathan Dinman, UMD professor of cell biology and molecular genetics.

In the immune system-related gene that Dinman and his colleagues studied, programmed ribosomal frameshifting triggers a process the body can use to eliminate some immune system molecules, thereby reining in potentially harmful side effects such as fever, inflammation and organ failure. The discovery could lead to better treatments for AIDS, allergies and rejection of transplanted organs, Dinman said.

“This has useful implications in situations where you want to shut down the immune response in one part of the body but not in another, or shut down one facet of the immune response,” Dinman said. “It could lead to very specific therapies without side effects.”

The ribosome, the protein factory in every living cell, gathers amino acids and assembles them into protein chains to make almost anything the cell needs. A strand of ribonucleic acid, or messenger RNA, is the template. Each amino acid is represented by a group of three molecules called nucleotides; each triad is called a codon. Specialized molecules called transfer RNAs “read” each codon and deliver the matching amino acids to the ribosome for assembly. Some codons act as stop signs, instructing the ribosome to release the finished protein chain.

Imagine the messenger RNA is a text made up of three-letter words (codons), spaces, and punctuation (stop codons), like this:

Can any fat cat fly?

To assemble proteins in the right order, the ribosome has to read all three parts of each codon, the spaces, and the stop codons. But sometimes the messenger RNA contains signals that reprogram the ribosome to jump forward or back by one or two places – that is, to shift the frame that it is reading. This alters the text. The transfer RNA now reads either new commands to fetch completely different proteins, or meaningless, nonsense RNA, like this:

Ana nyf atc atf ly?

Frameshift signals are common in some viruses, which use them to cram multiple sets of commands onto a single RNA strand. Dinman has long suspected that human cells also have frameshift signals, and that they are useful.

“These are really complex RNA structures. It takes a lot of computer memory to search for them in human cells,” said Dinman, who has been studying ribosomal frameshifting since the 1990s. “It wasn’t until the past decade that computers were fast and powerful enough to find these signals.”

Dinman and lead author Ashton Trey Belew, a UMD research associate, looked at CCR5, a gene on the surface of humans’ white blood cells. CCR5 is important to the immune system, but some forms of HIV use it to enter healthy cells.

The researchers found a molecular pattern that acts as a frameshift signal in CCR5. In tests on live human cells and rabbit cell extracts, they found the signal prompted the ribosome to frameshift 10 to 15 percent of the time. Using mass spectroscopy, they confirmed frameshifting was happening within CCR5 at the sequence predicted to be the frameshift signal. Then they searched another laboratory’s published database of human ribosomes and found confirming evidence of frameshifts in that

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AUGUST 21

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spot, at about the same rate.

They also found that a small specialized piece of RNA, called microRNA-1224, attaches itself to CCR5's messenger RNA at the frameshift site. The microRNA braces the messenger RNA, making it less flexible and causing the ribosome to stop there and slip by one or two spaces more often.

"The biggest question in this field has been, what regulates frameshifting? And that's essentially what microRNA-1224 is doing," Dinman said. "Then the question becomes, what are the consequences?"

In the case of CCR5, the frameshift changes the codons behind it into nonsense RNA. Since the ribosome can't read them, other components of the cell step in and destroy the messenger RNA and its associated proteins.

This might seem like a bad thing. But symptoms like fever are caused by our bodies' immune response, not the underlying illness. And the immune response occasionally gets out of control, causing serious, sometimes fatal side effects.

Dinman believes that by killing the messenger RNA and its array of immune system proteins, frameshifting acts like a dimmer switch, lowering the immune response to a safe level.

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"Ribosomal frameshifting in the CCR5 mRNA is regulated by miRNAs and the NMD pathway," Ashton Trey Belew, Arturas Meskauskas, Sharmishtha Musalgaonkar, Vivek M. Advani, Sergey O. Sulima, Wojciech K. Kasprzak, Bruce A. Shapiro and Jonathan D. Dinman, was published online July 9, 2014 in Nature and can be downloaded at http://dx.doi.org/10.1038/nature13429