Nutrient availability can cause whole-genome recoding

December 9 2014

The availability of a trace nutrient can cause genome-wide changes to how organisms encode proteins, report scientists from the University of Chicago in *PLoS Biology* on Dec. 9. The use of the nutrient - which is produced by bacteria and absorbed in the gut - appears to boost the speed and accuracy of protein production in specific ways.

"This is in some sense a 'you are what you eat' hypothesis,"' said senior study author D. Allan Drummond, PhD, assistant professor of biochemistry and molecular biology at the University of Chicago. "This nutrient that is absorbed through the gut looks like it can cause the recoding of an entire genome over evolutionary time."

All known organisms store the blueprint of life in their DNA, and use the information to produce proteins - the structural components and molecular engines for almost every function in a cell. To accomplish this, copies of relevant DNA regions must first be made. These copies are strings of chemical letters that serve as instructions, and are read three letters at a time by molecules known as transfer RNA (tRNA). Each tRNA has a preference for a specific three letter combination, or codon, and is attached to a single amino acid. As the instructions are read, tRNAs sequentially bind to their corresponding codon and deposit their amino acid, creating a protein.

tRNAs possess a special property known as "wobble" - a flexibility in one of the binding positions - that allows them to pair with multiple codons. This means that different spellings of genetic code can be used

to create the exact same protein, similar to how sentences can be written using different synonyms. However, this flexibility comes with a cost. Some codons are less reliably read and can introduce more mistakes. As such, certain codons are thought to be favored by natural selection.

To investigate the mechanisms that underlie this process and the evolutionary consequences, Drummond, together with Tao Pan, PhD, professor of biochemistry and molecular biology, and colleagues from Cornell University, analyzed and compared thousands of genes in a dozen different species of fruit fly. They looked for the frequency at which certain codons were used to encode proteins, and how this affected the accuracy and speed of protein production.

To their surprise, they found that the availability of queuine - a trace nutrient produced by bacteria that is only available when absorbed through the gut - played a major role in determining which codons were optimal. Flies which had abundant queuine possessed a higher proportion of tRNAs with a specific modification: a portion of their wobble-binding sites was replaced with a queuine-derived molecule known as queuosine (Q).

The team found that these Q-tRNAs were able to read and process certain codons much faster and more accurately than unmodified tRNAs, and caused changes throughout the flies' genomes. Species with access to plentiful queuine favored codon spellings that were optimized for Q-tRNAs. Species with access to less queuine favored other codon spellings.

"When queuine is abundant, organisms naturally recode its codons to favor the use of ones that are more efficiently translated by Q-modification," Drummond said. "In this way, a single nutrient causes a snowballing effect that leads to wide-spread changes in how proteins are encoded."

The team also studied how this affected the flies as they developed, and found that expression of Q-tRNA varied as flies grew. Q-tRNA levels and the expression of Q-tRNA optimized codons were high in embryos, low in larva and pupae, and high again in adults. The scientists hypothesize that the rapid cell division necessary for growth early in life consumes queuine faster than the organisms are able to acquire it. This means that Q-tRNA optimized codons are most valuable at critical periods in life, and that other codons become more useful when queuine is depleted.

"Cells need help making the right kinds and right amount of proteins at the right time," said Pan. "Q modification chemically enhances the making of certain proteins with specific sequences. Incorporating Q modification at different levels in different cells and at different developmental stages provides the organism a distinct layer of control."

Although Q-modification can be found in almost all organisms and appears to fundamentally alter the coding of genomes, how this ultimately affects protein function and the organism as a whole is still unclear.

"This paper is a major step in understanding why organisms use this modification," Drummond said. "But it's linked to translational fidelity, which is tricky to study. We're still developing tools to understand exactly what's going on, not just in fruit flies, but in human cells as well."

More information: "A Nutrient-Driven tRNA Modification Alters Translational Fidelity and Genome-wide Protein Coding across an Animal Genus," *PLoS Biology*, 2014.

Provided by University of Chicago Medical Center