When it comes to genetic code, researchers prove optimum isn't always best

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Imagine two steel springs identical in look and composition but that perform differently because each was tempered at a different rate.

A team of researchers including a Texas A&M University molecular biologist has shown that concept—that the speed of creation affects performance—applies to how a protein they studied impacts an organism's circadian clock function. This discovery provides new insights into the significance of the genetic code for controlling the rates at which critically important proteins are synthesized, and could lead to better understanding of cancers and other diseases.

"Living organisms' inner clocks are like Swiss watches with precisely manufactured spring mechanisms," said Matthew Sachs, a professor in the Texas A&M Department of Biology. "For example, if you fast-temper a critical spring, the watch may be unable to keep time, as opposed to slow-tempering it. It's not just about the composition of the components, such as which alloy is used. It's about the manner in which the components are made. Our research says the genetic code is important for determining both composition and fabrication rate for a central component of the circadian clock, and that the fabrication rate also is critical. And that's essentially a discovery."

The research was selected for Advanced Online Publication (AOP) in the prestigious journal "*Nature*."

The team, which is led by Yi Liu, a researcher in the Department of

Physiology at the University of Texas Southwestern Medical Center, was perplexed when it found a paradoxical result years ago: that optimizing the use of codons (a sequence of three nucleotides that form a unit of genetic code in a DNA or RNA molecule) specifying an essential biological clock component actually abolished the organism's circadian rhythms.

The group's research indicates that the protein in the fungal genus Neurospora they studied, frequency, performs better when the genetic code specifying it has non-optimal codon usage, as is normally found. However, when the genetic code is deliberately altered so that codon usage is optimized, clock function is lost. The reason for this is that non-optimal codon usage slows translation of the genetic code into protein, allotting the frequency protein the necessary time to achieve its optimal protein structure. The team's results also demonstrate that genetic codons do more than simply determine the amino acid sequence of a protein as previously thought: They also affect how much protein can be made as well as the functional quality of that protein.

"We found that less is more, in many cases," Liu said.

Because many genetic diseases are the result of improperly functioning proteins, Sachs says knowledge about how proteins are made and why they have impaired functions is critical to understanding almost all diseases.

"Understanding gene expression is crucial for understanding cancer and other diseases, because ultimately many of these processes involve either mutations of genes or altered expression of genes," said Sachs, who was asked by Liu to help on the research because of his translational expertise in Neurospora.

More information: www.nature.com/nature/journal/ …

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