Study Goes ‘Back to the Future’ to Learn More About DNA Codes

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The genetic information of our chromosomes is encoded into the language of DNA. This language is composed of code words, each representing one of the 20 amino acids found in proteins. How do cells translate the language of genetic information into functioning proteins?

The language of DNA requires a modern-day cell to have some 40 translators, transfer RNA molecules (tRNA) that read the genetic information for the synthesis of proteins. Some of these translating tRNAs are less specific than others: They can read multiple codes but for the same amino acid. Dr. Francis Crick, Nobel Laureate and co-founder of the DNA molecule and its double-helix structure, called this “wobble.”

The tRNAs are either more or less specific at their jobs because they’re modified in different ways by the cell before being called into action as translators.

In a study published in the June 2007 edition of *Nature Structural and Molecular Biology*, North Carolina State University’s Dr. Paul F. Agris, professor of molecular and structural biochemistry, his postdoctoral fellow, Dr. Franck Vendeix, and academic colleagues from England and Poland show for the first time how a specific modification allows the translating tRNA to read not one or two DNA code words, but four.

That’s important because this particular modification to uridine, one of the four nucleosides comprising RNA molecules, permits just six tRNAs to read 24 code words. “Considering there are only 61 codes for amino acids, this is an astonishingly large number of codes to be read by so few tRNAs, and that has significant evolutionary consequences,” Agris says. Thus, the modification may have afforded ancient cells the opportunity to have far fewer tRNAs to translate the genetic language than modern-day cells. Or the modification could have evolved to enhance the efficiency and accuracy of reading the code words.

The scientists used x-ray crystallography and nuclear magnetic resonance to show that the uridine modification structurally and biochemically alters the tRNA before decoding genetic information on the ribosome, the cell’s protein synthesis machinery. At an atomic level of observation – in which researchers can distinguish atom from atom – and working with a tRNA specific for the amino acid valine, Agris and his colleagues show how the modified nucleoside enabled tRNA to read the four codes for valine in genomic information on the ribosome.

“We’ve defined the mechanism by which multiple codes are accurately and efficiently read through this modification,” Agris said.

Crick attempted to square the disparity between the number of codes and the number of amino acids – there are three times as many codes as amino acids – with his Wobble Hypothesis. He based this theory on the first report of a tRNA molecule’s chemical structure discovered by Robert Holley in 1963.

Normally, RNA molecules are composed of four nucleosides: adenosine, guanosine, cytosine and uridine (A,G,C,U). But the tRNA molecule Holley studied included a modified nucleoside called inosine (I), Agris says. Seeing this inosine in an important area of the tRNA molecule – an area that reads the three-letter DNA codes when the cell synthesizes proteins – led Crick to believe that a single tRNA used inosine to read more than one code, and that therefore the 61 codes were decoded by fewer than 61 tRNAs.

As an example, Agris used the amino acid alanine, which has four codes. Crick’s hypothesis would allow that only two tRNA molecules could be capable of decoding all four alanine codes. Using the modified nucleoside I in place of A, G, C or U,

one tRNA may be able to read three codes, effectively “wobbling” the reading.

Twenty-five years after the Wobble Hypothesis, Agris proposed his Modified Wobble Hypothesis. It stated that modified nucleosides other than inosine would in some cases expand tRNAs’ ability to translate codes by wobbling to greater numbers of three-letter codes, whereas other modified nucleosides would restrict wobble to only one or two codes.

The recent paper adds the modification to uridine as another example of how Agris’ alteration to Crick’s hypothesis was correct: Cellular modification of tRNA alters chemistry and structure in a manner critical for tRNA to decode more than one three-letter code.

Our understanding of evolution and the future possibilities of genes rests not only in deciphering the encoded information, but in knowing the mechanism by which cells use the information. “By understanding how modifications restrict or expand recognition of the code words in DNA for the synthesis of protein, we will be able to engineer new proteins or target the protein synthesis machinery in pathogens,” Agris said.

Source: NC State

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