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Stress-induced changes in genetic information: New details discovered about the function of a mysterious protein

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Summary: Scientists have researched the function of an enigmatic protein. The biological necessity of this protein, which can chemically alter certain building blocks of the genetic information, has been debated for quite a while. The new study now links the enzymatic action of this protein on small RNA molecules which are important for protein synthesis, to potentially far-reaching consequences for the integrity of genetic information, particularly under stress conditions.

FULL STORY

In a recent study, a research group at MedUni Vienna has published further details about the function of an enigmatic protein. The biological necessity of this protein, which can chemically alter certain building blocks of the genetic information, has been debated for quite a while. The new study now links the enzymatic action of this protein on small RNA molecules which are important for protein synthesis, to potentially far-reaching consequences for the integrity of genetic information, particularly under stress conditions.

Methyltransferases are enzymes that transfer methyl groups to certain building blocks of macromolecules such as DNA (deoxyribonucleic acid, carrier of genetic information), RNA (ribonucleic acid, transmitter of genetic information) and also proteins (products of the genetic information), and hence modulate the function of these macromolecules. The methyltransferase Dnmt2 was originally described as an enzyme that, by chemically altering the base cytosine in DNA (DNA methylation), can directly influence the packaging of genetic information thereby performing epigenetic functions.

However, it was later discovered that Dnmt2 does not mark cytosine in DNA with methyl groups, but rather cytosine in transfer RNAs (tRNAs; molecules that are essential for protein synthesis) and that this cytosine methylation impacts the stability of tRNAs and probably protein synthesis as well.

Dnmt2-like proteins occur in nearly every organism, which led to the early conclusion that these enzymes perform an important function. However, living organisms in which Dnmt2 has been deactivated, for instance by mutations, manage to survive without this methyltransferase. These observations have puzzled biologists for a long time raising the question as to why Dnmt2-like enzymes have been retained over the course of evolution in the repertoire of the genetic information from bacteria to humans.

An international study led by the Division of Cell and Developmental Biology at MedUni Vienna's Center for Anatomy and Cell Biology has now shown that the stabilising function of Dnmt2 on tRNAs is required to guarantee the integrity of genetic information, especially during stress conditions. The researchers used Drosophila melanogaster (fruit fly) as a model organism for their study and describe in the specialist journal "Cell Reports" that

without functional Dnmt2, certain regions of the genetic information are lost or can change as a result of recombination. The key indication that these problems can primarily be explained by the loss of tRNA and not DNA functions came from experiments with another evolutionarily highly conserved RNA methyltransferase (NSun2).

"Deciphering the molecular function of these RNA-modifying enzymes is an important step towards a better understanding of the role of the 'epitranscriptome' in establishing certain gene expression patterns," explains lead investigator Matthias Schäfer from the Division of Cell and Developmental Biology at MedUni Vienna's Center for Anatomy and Cell Biology. "Modulating the expression of certain genes by epigenetic manipulation or by influencing their RNA metabolism through 'epitranscriptomic' changes has huge medical potential."

For example, it might be possible to specifically deactivate damaged genetic information without changing the DNA sequence containing the genetic information by means of 'epigenetic drugs'. On the other hand, "RNA-based therapeutics are already being tested in clinical trials and we will soon know whether 'epitranscriptomic' changes make these medications, for example, more stable or simply allow more efficient transport into target cells or tissues, thereby making them more effective," adds Schäfer. While epigenetics is already a future-oriented field in medicine, which promises many different possibilities for personalised therapies, the potential of 'epitranscriptomics' must still be further defined through continuous basic research before extending personalized therapeutic approaches with 'epitranscriptomic' tools.

The international study led by the Division of Cell and Developmental Biology at MedUni Vienna's Center for Anatomy and Cell Biology was conducted in collaboration with researchers from the German Cancer Research Center and the Institut de Biologie Paris Seine (IBPS). The study was financed by the Austrian Science Fund (FWF) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation).

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Materials provided by **Medical University of Vienna**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Bianca Genenncher, Zeljko Durdevic, Katharina Hanna, Daniela Zinkl, Mehrpouya Balaghy Mobin, Nevcin Senturk, Bruno Da Silva, Carine Legrand, Clément Carré, Frank Lyko, Matthias Schaefer. **Mutations in Cytosine-5 tRNA Methyltransferases Impact Mobile Element Expression and Genome Stability at Specific DNA Repeats**. *Cell Reports*, 2018; 22 (7): 1861 DOI: 10.1016/j.celrep.2018.01.061

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