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Scientists Find New Mechanism in the Development of Severe Inherited Disease

Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have shown that the genetic defect that causes Cockayne Syndrome affects a key function of the cell – the transcription of genes coding for ribosomal RNA.

Cockayne Syndrome is a recessively inherited disorder that belongs to a group of diseases in which defects in one of the numerous DNA repair systems lead to non-functioning proteins and, thus, to severe health impairments. These disorders also include, for example, Xeroderma pigmentosum and a type of hereditary bowel cancer.

However, symptoms of Cockayne Syndrome, which is a very rare disease, are particularly severe, including dwarfism, mental retardation, hearing and vision impairments; affected individuals have a characteristically formed small head, they age prematurely and die younger. The scale of these defects suggested that a dysfunctional DNA repair mechanism alone cannot be responsible for this whole range of impairments.

Cockayne Syndrome is characterized by a defect in the CSB protein, which is the main component of a particular DNA repair system. Research results of several working groups had already suggested that CSB is additionally involved in transcription, i.e. the conversion of DNA to RNA. However, the exact mechanism had remained unknown.

In each cell, various RNA types are responsible for specific tasks. Thus, the so-called rRNA is a key component of the ribosomes, the protein factories of the cell. A research group headed by **Professor Dr. Ingrid Grummt** of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) has now shown that CSB is pivotal in the production of rRNA molecules.

A basic prerequisite for the conversion of DNA to RNA is the accessibility of genes, which are normally tightly packed in the chromosome. Only if the genes are accessible can the enzyme RNA polymerase go about its work and synthesize new RNA molecules according to the DNA code. This is where CBS comes into play: It functions as an adapter between polymerase and the G9a protein, which acts like an icebreaker - making specific regions of the genetic material accessible for polymerase by chemically modifying the protein scaffold of the chromosome.

Without functioning CBS, the binding of polymerase I and G9a fails and the genes coding for rRNAs remain inaccessible for polymerase. The lack of rRNAs eventually leads to a standstill of protein synthesis in the cell – the most dramatic of imaginable consequences for an organism. This newly discovered function of CBS explains why a defect of this enzyme has such severe effects on the organism.

Xuejun Yuan, Weiijun Feng, Axel Imhof, Ingrid Grummt and Yonggang Zhou: Activation of RNA polymerase I transcription by Cockayne Syndrome group B (CSB) protein and histone methyltransferase G9a. Molecular Cell, August 19, 2007

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