Mechanism elucidated for a rare disease

May 4 2010

(PhysOrg.com) -- Scientists at the Friedrich Miescher Institute for Biomedical Research (FMI) have dissected one of the molecular mechanisms underlying Friedreich's ataxia. In doing so, they have shed new light on the pathogenic mechanism of the disease. These findings could lead to the development of new therapeutic approaches for what is, as yet, an incurable condition. The results of the study were recently published in the journal *EMBO Molecular Medicine*.

The defective gene responsible for Friedreich's ataxia was identified over 20 years ago, but so far our ideas of how this gene causes the disease have been merely speculative. It was assumed that, as a result of the mutation, the gene could no longer be transcribed because this stretch of DNA was inaccessible. FMI Group Leader Marc Bühler and

his team have now carried out experiments demonstrating that this is not the case and revealing what actually happens in Friedreich's ataxia.

Friedreich's ataxia is caused by a deficiency of the protein frataxin. Frataxin is essential for iron metabolism in mitochondria - the cellular components responsible for energy production. Accordingly, mitochondria are especially important in cells with substantial energy requirements, such as nerve cells or heart muscle. It is therefore not surprising that these cells are particularly affected in Friedreich's ataxia: patients with this condition experience degeneration of the large sensory neurons and spinocerebellar tracts, but also cardiomyopathy.

In patients with Friedreich's ataxia, a nucleotide sequence in the gene coding for frataxin is repeated up to 1000 times, compared with only about 30 times in healthy individuals. The FMI researchers were able to confirm that, owing to this expanded repeat tract, the gene is not correctly transcribed. Specifically, they showed that transcription of the gene into messenger RNA (mRNA) is blocked at the elongation step. As a result, transcription of the gene is prematurely terminated and the protein is not synthesized. In contrast to the current view that densely packed chromatin causes silencing of the gene, the researchers showed that the repetitive DNA on its own already constitutes on obstacle for the transcription machinery.

Friedreich's ataxia is a rare inherited disease, affecting only about 4 in 100,000 people. Often, however, the pathogenic mechanism can be precisely elucidated in the case of rare conditions - as Marc Bühler has now demonstrated for Friedreich's ataxia. This knowledge may then be valuable for other more common diseases. The development of a treatment for Friedreich's ataxia, addressing the problem of incomplete mRNA transcription, would thus not only help to cure a previously incurable disease, but also be useful for other conditions with a similar pathogenic mechanism.

Provided by Friedrich Miescher Institute for Biomedical Research