Defect in transport system causes DNA chaos in red blood cells

March 12 2012

Within all our cells lies two meters of DNA, highly ordered in a structure of less than 10 micro meters in diameter. Special proteins called histones act as small building bricks, organising our DNA in this structure. Preservation of the structure is necessary to maintain correct function of our genes, making histones detrimental for maintaining a healthy and functional body. The research group of Associate Professor Anja Groth from BRIC, University of Copenhagen, has just elucidated a function of the protein Codanin-1, shedding light on the rare anemic disease CDAI where development of the red blood cells is disturbed. The new results also contribute with important knowledge on how our DNA-structure is maintained and how our genes are regulated.

"We became interested in Codanin-1 as it was well-known that mutations in the gene cause CDAI, whereas the function of the protein was entirely unknown. Our new results show that Codanin-1 is detrimental for the transport of newly synthesized histones and for the ordering of our DNA, when our cells are dividing. As this function is partly defect in CDAI, we could use the disease as a model to gain important knowledge in some of the basic processes that are crucial for normal cell division and development," says Associate Professor and group leader, Anja Groth.

Loss of guard function result in defective blood cells

Our DNA is copied and each identical copy is passed on to each of the

two daughter cells when our cells divide. The ordered DNA structure also needs to be copied, which demands a constant supply of new histones. The histones are transported into the nucleus of our cells, through a molecular transportation system. Here they serve as small bricks that the DNA is wrapped around in an orderly structure, guided by information carried by the histones. The new results show that codanin-1 is crucial for the regulation of the histone transport. Mutations in Codanin-1 make the protein incapable of regulating the transport, giving rise to defects in the development of the red blood cells.

"Codanin-1 appears to function as a guard, which we think can detect internal and external signals to our cells. The protein then regulates the transport of new histones to the nucleus of our cells, based on this information. This transportation mechanism is defect in patients with CDAI, and for some reason that we do not yet fully understand, does this primarily affect the red blood cells," says postdoc Zuzana Jasencakova, who has been responsible for the laboratory experiments together with Ph.D. student Katrine Ask.

Basal biology and disease research goes hand in hand

Anja Groth's research group intensively studies the basal biological mechanisms that control our DNA-structure and thereby the activity of our genes. Accordingly, they normally work with general biological model systems, but for this project, they used the characteristic of the disease CDAI to answer some basal biological questions:

"It is mostly the other way around, that basal biological findings are used to understand the development of disease. But here, we have used the defect protein of CDAI to elucidate some basal biological mechanisms. The fact that Codanin-1 serves a detrimental role in all our cells, but that defects primarily affect the red blood cells is very interesting. Hopefully we can use this detail to gain further knowledge on how our cells

maintain a correct DNA-structure and regulates the genes," says Anja Groth.

More information: The results have just been published in *EMBO Journal*: "Codanin-1, mutated in the anaemic diesease CDAI, regulates Asf1 function in S-phase histone supply" , Ask et al, EMBO March 2012.

Provided by University of Copenhagen