Enzyme controls transport of genomic building blocks

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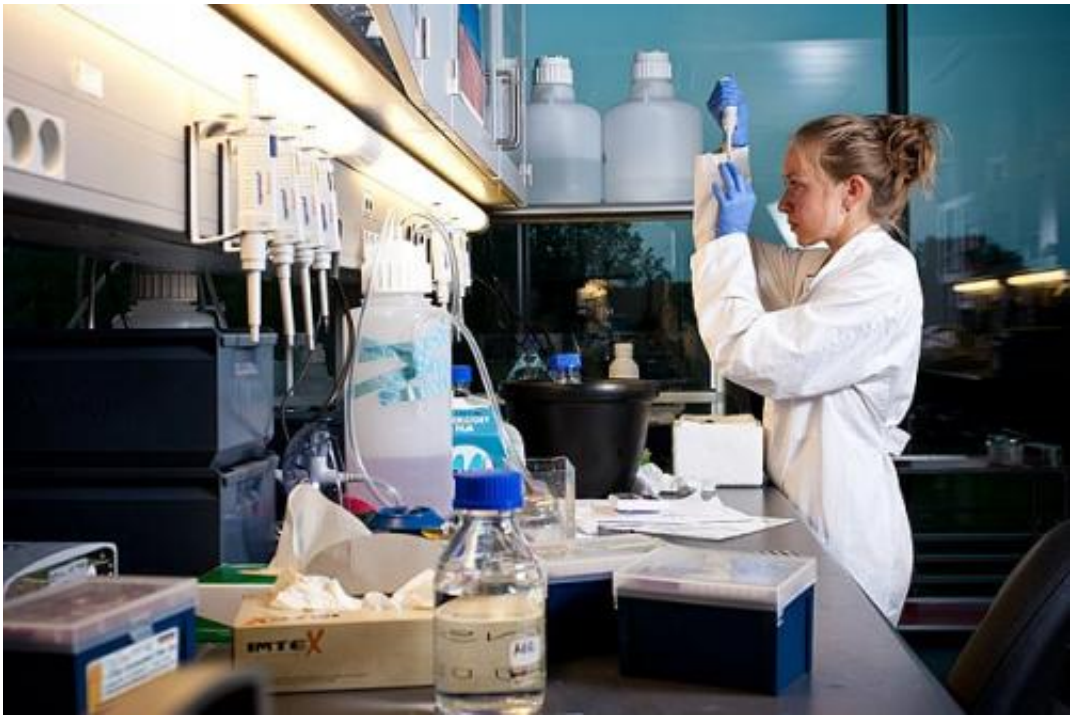

This is Ilnaz Klimovskaia in the lab. Credit: Anja Groth, BRIC

Our DNA and its architecture are duplicated every time our cells divide. Histone proteins are key building blocks of this architecture and contain crucial information that regulates our genes. Danish researchers show how an enzyme controls reliable and high-speed delivery of histones to DNA copying hubs in our cells. This shuttling mechanism is crucial to maintain normal function of our genes and prevent disease.

The results are published in the journal *Nature Communications*.

Interdisciplinary research team finds cellular high-speed shuttle

An interdisciplinary team of researchers from BRIC, University of Copenhagen and University of Southern Denmark have identified a cellular transport mechanism so fast and finely tuned that it compares to an Asian fast-speed train.

"Using advanced laboratory techniques, we have revealed how an enzyme called TLK1 regulates the transport of histones to DNA copying hubs in our cells. Such a devoted supply of histones, is crucial to maintain the genomic architecture when our cells divide", says Ilnaz Klimovskaia who has been spearheading the experimental work as part of her PhD-studies at BRIC.

The new results show that TLK1 controls the activity of a molecule called Asf1. Asf1 act as a freight train that transports histones to the nuclei of our cells where the DNA is copied during cell divisions. The enzymatic activity of TLK1 turn Asf1 into a fast-speed train, capable of precise, fast and timely transport of histones to newly formed DNA.

TLK1 contribute to cellular identity

Histones play an important role for the activity of our genes, as they contain information that can turn on or off genes. The information is communicated only when DNA is wrapped around the histones, to form the ordered genomic architecture called chromatin. As all our cells contain exactly the same genes, the histone information is crucial to activate only the sub-set of genes necessary to maintain a certain cellular identity. For example, heart genes needs only to be turned on in heart

cells, but turned off in other cell types.

"We show that TLK can boost the supply of histones at critical time points. By controlling the transport of histones to our DNA, TLK and Asf1 ensure that the chromatin architecture and its information are copied correctly during cell division, so that cell identity is maintained", explains Ilnaz Klimovskaia.

Loss of chromatin integrity in cancer development

A tight coordination between DNA duplication and supply of major chromatin building blocks like histones, are crucial to maintain normal function of our cells. If the chromatin architecture is wrong, it can affect both gene expression as well as the stability of our DNA. Together, this is a dangerous cocktail that might fuel cellular changes and lead to cancer development.

"Our research adds a new layer to the understanding of how chromatin is maintained when cells in our body divides. This information is crucial to understand how cells maintain their identity and protect their genome, which is essential to avoid cancer development", says associate professor Anja Groth, who has been heading the research team.

The next step for the research team is to dig deeper into the understanding of how chromatin duplication is controlled. The team is also exploring whether targeting of the TLK enzyme could be useful in cancer therapy, as they speculate that reducing the supply of histones in highly dividing cancer cells, might make tumor cells more vulnerable to already existing cancer drugs.

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