Researchers identify two proteins important for the demethylation of DNA

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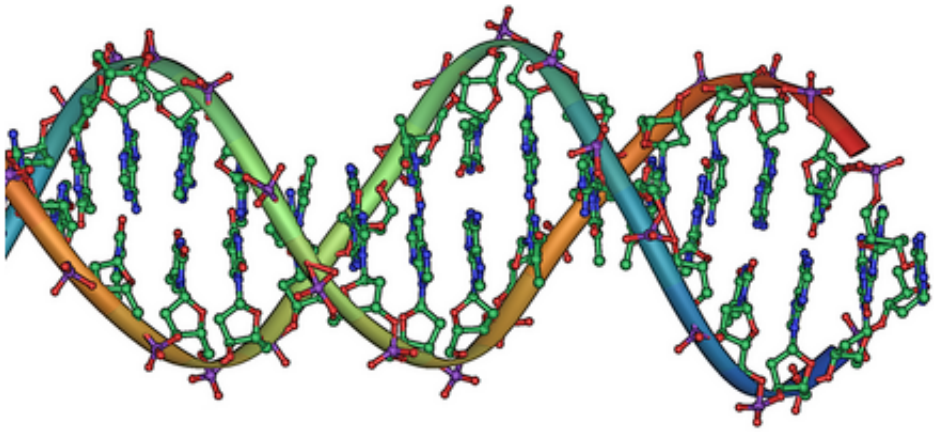

DNA double helix. Credit: public domain

Scientists at the Institute of Molecular Biology (IMB) in Mainz have identified a missing piece of the puzzle in understanding how epigenetic marks are removed from DNA. The research on DNA demethylation sheds new light on a fundamental process that is important in development and diseases such as cancer.Epigenetics is defined by heritable changes in gene expression that do not derive from changes in the DNA sequence itself.

Epigenetic processes play a central role in a broad spectrum of diseases, such as cardiovascular disease, neurodegenerative disorders and cancer. One of the most prominent epigenetic processes is DNA methylation, where one of the four bases of animal DNA is marked by a methyl group . DNA methylation typically reduces the activity of surrounding genes.

A lot is known about how methyl marks are put onto the DNA, but how they are removed – a process called DNA demethylation – and, thus, how genes are reactivated is still not well understood. In their recent study, published in *Nature Structural and Molecular Biology*, IMB scientists have identified two proteins, Neil1 and Neil2 that are important for the demethylation of DNA. "These proteins are a missing link in the chain of events that explain how DNA can be efficiently demethylated," said Lars Schomacher, first author on the paper.

Intriguingly, DNA demethylation has been shown to involve proteins of the DNA repair machinery. Thus epigenetic gene regulation and genome maintenance are linked. Schomacher and his colleagues identified in Neil1 and Neil2 two more repair factors that not only protect the DNA's integrity but are also involved in DNA demethylation. The researchers showed that the role of Neils is to boost the activity of another protein, Tdg, which is known to be of central importance for DNA demethylation.

Both the Neils and Tdg are essential proteins for survival and development. Schomacher et al. carried out experiments where they removed either one of these proteins in very early frog embryos. They found that the embryos had severe problems developing and died before reaching adulthood.

Failure in setting and resetting methyl marks on DNA is involved in developmental abnormalities and cancer, where cells forget what type they are and start to divide uncontrollably. Understanding which proteins

are responsible for DNA demethylation will help us to understand more about such disease processes, and may provide new approaches to develop treatments for them.

More information: Lars Schomacher et al. Neil DNA glycosylases promote substrate turnover by Tdg during DNA demethylation, *Nature Structural & Molecular Biology* (2016). DOI: 10.1038/nsmb.3151

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