# Risk-free gene reactivation

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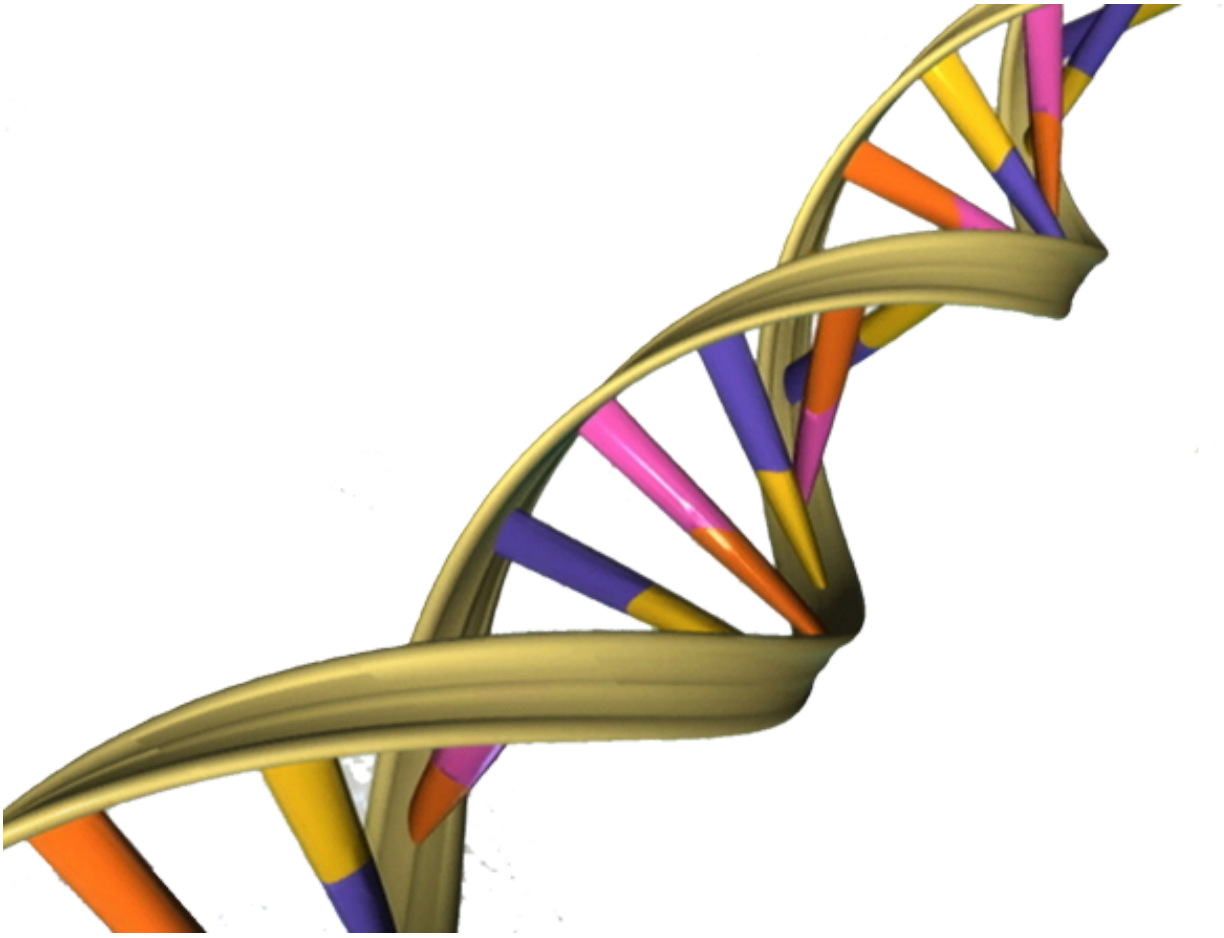

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Chemical modification of DNA subunits contribute to the regulation of gene expression. Researchers from Ludwig-Maximilians-Universitaet

(LMU) in Munich have now deciphered a new pathway can reactivate genes that have been silenced in this way, while avoiding the risk of damaging the DNA.

In multicellular organisms, every cell contains the complete complement of genetic information characteristic of the particular species. However, in any given cell, only a subset of this comprehensive gene library is actually expressed - and it this selectivity that gives rise to diverse cell types with specific functions. At the level of the DNA itself, simple chemical modifications of its subunits can determine which genes are active and which are turned off. But gene regulation must also be flexible, which requires that the activation and inactivation of genes should be reversible. This therefore implies that it must also be possible to remove such DNA modifications. LMU researchers led by Professor Thomas Carell have now described a new mechanism for the reactivation of silenced genes which, unlike other known pathways, does not lead to the generation of potentially deleterious intermediates. The new findings appear in the journal *Nature Chemical Biology*.

Methylation of one of the four basic building blocks found in the DNA - the nucleotide base known as cytidine - plays an important role in the regulation of gene activity. The attachment of a methyl group (CH3) to unmethylated cytidine converts it into 5-methylcytidine, which is known to block gene activity. "This raises the question of how the cell can reverse this inactivating modification to restore the gene to its previous state," says Carell. In order to reactivate the methylated gene, the methyl group must be removed. Up to now, it has been assumed that the methylated cytidine must be excised from the DNA and replaced by the unmethylated form of the base. This however, is a risky process, because it requires cutting one or even both of the DNA strands - and unless promptly repaired, DNA breaks can have grave consequences for the cell.

"We have now shown in mouse embryonic stem cells that there is another mode of demethylation that avoids any break in the continuity of the DNA strand," Carell says. In this pathway, the attached methyl group is enzymatically oxidized to give rise to 5-formylcytidine, which Carell's team first detected in mouse stem cells in 2011. They have now used stable isotopes to label 5-formylcytidine in stem cells and shown that it is rapidly converted unmethylated cytidine. "This mechanism thus allows cells to regulate gene activity at the DNA level without running the risk that the DNA may be damaged in the process," Carell explains. The authors of the new study believe that this pathway could also be of medical interest, as it may provide a way to reprogram stem cells in a targeted fashion. Such a method would in turn open up new perspectives in regenerative medicine.

**More information:** Katharina Iwan et al, 5-Formylcytosine to cytosine conversion by C–C bond cleavage in vivo, *Nature Chemical Biology* (2017). DOI: 10.1038/nchembio.2531

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