How chemical modifications on DNA keep genes silent

December 6 2022

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Several diseases, including certain types of cancer and some neurodevelopmental conditions, have aberrant patterns of DNA methylation, a chemical modification that regulates gene expression in ways that keep genes in the "off" position.

Friedrich Miescher Institute researchers found that DNA methylation keeps genes silent mostly by inhibiting the binding of DNA by transcription factors—proteins that control how genes are expressed. The findings advance our understanding of how chemical modifications on DNA regulate gene expression.

DNA methylation is a process through which a chemical tag known as a methyl group is added onto a nucleotide, one of the building blocks of DNA. When DNA methylation occurs at "CpG islands," DNA regions that tend to be located near sites where gene expression is initiated, the expression of genes is turned off.

However, it's unclear on which process DNA methylation mostly relies to keep genes off: does it keep transcription factors away from the DNA molecule? Or does it silence genes indirectly by recruiting proteins called Methyl-CpG Binding Domain (MBD) proteins?

To address this question, researchers in the Schübeler lab engineered cells to lack all MBD proteins. They found that this didn't reactivate genes repressed by DNA methylation. However, removing DNA methylation altogether did result in the activation of those genes. In neurons, the researchers identified several transcription factors that do not bind to their preferred DNA binding sites when methylation is present.

The findings suggest that DNA methylation keeps genes silent mostly by preventing transcription factors from binding the DNA, the researchers say.

The study is published in the journal *Nature Genetics*.

More information: Sebastian Kaluscha et al, Evidence that direct inhibition of transcription factor binding is the prevailing mode of gene

and repeat repression by DNA methylation, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01241-6