New insights into cooperativity in gene regulation

December 16 2015

In a study published in *Nature*, Dirk Schübeler and his group at the Friedrich Miescher Institute for Biomedical Research (FMI) describe how the interplay between transcription factors and epigenetic modifications of DNA influences gene regulation. The scientists found that transcription factors can cooperate indirectly, via changes in DNA methylation patterns: by removing methyl groups, some transcription factors prepare surrounding regions for the binding of other transcription factors. This research thus elucidates a further aspect of the complex role methyl groups play in gene regulation.

The process whereby genes in a cell are read out is highly complex. Transcription factors bind to specific motifs on the DNA – binding sites with clearly defined sequences of bases. They thus determine which genes in the cell are active and which are not. Interestingly, though large numbers of these motifs occur in our genome, only a fraction are recognized and bound. Whether a motif is bound by a transcription factor therefore depends not only on the particular sequence, but also on its accessibility.

In a publication in Nature, Dirk Schübeler and his group at the FMI have now demonstrated that certain transcription factors can only bind to unmethylated binding sites. In their study, Silvia Domcke and Anaïs Bardet (the two first authors) removed all the methyl groups from the DNA in stem cells and then determined once again where transcription factor binding occurs. Domcke says: "We showed that in the absence of DNA methylation certain sensitive transcription factors, such as NRF1,

occupy many additional binding sites, leading to increased transcription. Because of the epigenetic marks, these binding sites were not previously accessible." If these sites are subsequently remethylated, the transcription factors are displaced and these genes are no longer read out.

However, the scientists also showed that some transcription factors are insensitive to methylation: these factors can bind to methylated DNA and even trigger its demethylation, thus paving the way for sensitive factors. In the study, this is illustrated by the example of NRF1, a sensitive factor which relies on other factors to remove methylation from its binding sites. Bardet explains: "We postulate that, around the NRF1 motifs, other proteins are active which are not methylation-dependent and which trigger the removal of methyl groups. These prepare the ground for NRF1 and thus restrict and define its activity."

Commenting on the broader context, Schübeler says: "With our experiments in living cells, we've shown that there's a hierarchy between different transcription factors, mediated by methylation patterns. There are some transcription factors which cannot bind to methylated DNA. This means they are dependent on other transcription factors which determine whether their motif is methylated or not."

More information: Competition between DNA methylation and transcription factors determines binding of NRF1. *Nature*, 2015. DOI: 10.1038/nature16462

Provided by Friedrich Miescher Institute for Biomedical Research

Citation: New insights into cooperativity in gene regulation (2015, December 16) retrieved 28 April 2024 from https://phys.org/news/2015-12-insights-cooperativity-gene.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.