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GENE EXPRESSION

The yin and yang of enhancer–promoter interactions

Transcription factors can facilitate the physical interaction between enhancers and promoters and looping of the intervening DNA between them. Such loops are formed within larger, insulated chromosomal loops (also known as topologically associating domains (TADs)), which are formed by dimerization of the zinc finger protein CTCF bound to chromatin. Weintraub *et al.* now show that, analogously to CTCF, the protein yin and yang 1 (YY1) is a structural mediator of enhancer–promoter looping interactions.

CTCF does not generally bind enhancers and promoters, so the authors searched for proteins that could bind to these elements and facilitate their interaction. They identified another zinc finger protein, YY1, which, like CTCF, is essential for cell viability and is ubiquitously expressed. Importantly, co-immunoprecipitation of differentially tagged YY1 proteins confirmed that YY1 can form homodimers.

> “deletion of YY1 binding motifs… reduced contact frequency between the promoters and their cognate enhancers”

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In various mouse and human cell types, YY1 occupied enhancers and promoters genome-wide. As expected from the cell-type specificity of enhancer function, YY1 enhancer occupancy tended to be cell-type specific. Using methods such as HiChIP, which combine chromatin immunoprecipitation with chromosome conformation capture, the authors showed that YY1 mainly associated with enhancer–promoter interactions, including more complex contacts between super-enhancer elements and their target promoters. By contrast, the majority of CTCF-associated interactions connected insulator elements, in agreement with their role in forming TADs.

To examine whether YY1 could facilitate enhancer–promoter looping interactions, YY1 was tested in an *in vitro* DNA circularization assay. The addition of purified YY1, which had DNA binding capacity, increased the rate of circularization, and this depended on the presence of YY1 binding motifs in the DNA. In living cells, deletion of YY1 binding motifs in the promoters of two genes resulted in reduced YY1 binding, reduced contact frequency between the promoters and their cognate enhancers and, in one of the genes, reduced expression. The lack of reduced expression of one of the genes was probably due to YY1 binding at other, less optimal motifs; indeed, YY1 depletion resulted in decreased expression of both genes.

Next, using an inducible protein degradation system, the genome-wide effects of YY1 depletion were measured. The expression of thousands of genes was changed (increased or decreased), and in general the genes with the greatest changes following YY1 depletion were those with promoters originally occupied by YY1. HiChIP analysis showed that interactions between YY1-occupied enhancers and promoters decreased significantly after YY1 depletion. This was accompanied by changes in the expression of the majority (60%) of genes that were connected by YY1 enhancer–promoter loops.

In summary, YY1 globally mediates enhancer–promoter interactions by binding to DNA and facilitating the formation of chromatin loops, probably through its dimerzation. This general function could account for the variable reported functions of YY1, which include both gene activation and gene repression.

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ORIGINAL ARTICLE Weintraub, A.S. *et al.* YY1 is a structural regulator of enhancer–promoter loops. *Cell* https://doi.org/10.1016/j.cell.2017.11.008 (2017)

FURTHER READING Soutourina, J. Transcription regulation by the Mediator complex. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm.2017.115 (2017)