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Journal club

TURNING THE TIDE ON 3D NUCLEAR ORGANIZATION

In the mid-1980s, I was a graduate student in Philadelphia, working on coordinated gene control, and became fascinated by transcriptional enhancers. Enhancers were defined functionally as DNA sequences that could increase transcription of a linked promoter, regardless of the orientation of the enhancer or whether it was located upstream or downstream of the gene. In those days, the genome was a vast ocean of darkness and most researchers working on eukaryotic systems had only hard-fought, short segments of DNA sequence in the immediate vicinity of their gene to work with.

The discovery that enhancers could be tens of kilobases away from their target genes fired the imagination of many, who were intrigued by the possible mechanisms of how this long-distance action could be achieved. Many researchers favoured a looping mechanism in which the enhancer contacted the promoter directly by looping out the intervening DNA. Evidence from prokaryotes supported this model, but those were effects over tens or hundreds of base pairs and were perhaps considered by many to be more accurately described as DNA bending. Another favoured model postulated that distal enhancers could act as entry sites for transcription factors or polymerases, which could then slide along the DNA to find the promoter in a more efficient, 2D scanning mechanism. Others suggested that factors that bind to enhancers induce a torsional stress that could be transmitted through the DNA to open the promoter.

What turned the tide for me was a paper published in 1989 by Müller, Sogo and Schaffner, who described simple, elegant experiments showing that an enhancer fragment linked via a non-covalent, biotin–streptavidin bridge to a β-globin gene could increase transcription *in vitro*. This unlinked the two elements and provided a potential mechanism that could explain the influence of enhancers over tens or hundreds of kilobases, as well as enhancer transvection.

It took another dozen years to obtain direct evidence of long-range enhancer looping in cell nuclei. The development of the highly versatile chromosome conformation capture and related methodologies and the elucidation of entire genomic sequences have since opened the floodgates in our understanding of 3D genome organization and how we experimentally approach it. We are now far away from that elegant experiment, which seems trivial by today's standards, but back then represented a considerable conceptual leap forward.

“It took another dozen years to obtain direct evidence of long-range enhancer looping”

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ORIGINAL ARTICLES Müller, H-P., Sogo, J. M. & Schaffner, W. An enhancer stimulates transcription in *trans* when attached to the promoter via a protein bridge. *Cell* **58**, 767–777 (1989) | Carter, D., *et al.* Long-range chromatin regulatory interactions *in vivo*. *Nat. Genet.* **32**, 623–626 (2002) | Dekker, J., *et al.* Capturing chromosome conformation. *Science* **295**, 1306–1311 (2002) | Schmitt, A. D., Hu, M. & Ren, B. Genome-wide mapping and analysis of chromosome architecture. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm.2016.104 (2016)