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Transvection Goes Live—Visualizing Enhancer-Promoter Communication between Chromosomes

Albert Tsai,[1] Robert H. Singer,[2,3] and Justin Crocker[1,*]
[1]Developmental Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany
[2]Department of Anatomy and Structural Biology, Albert Einstein College of Medicine, Bronx, New York, USA
[3]Janelia Research Campus of the HHMI, Ashburn, Virginia, USA
*Correspondence: justin.crocker@embl.de
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Lim et al. (2018) use live imaging in *Drosophila* embryos to show that enhancers can drive transcription from promoters on another chromosome when they are in close proximity. In addition, they show that multiple promoters can access the same enhancer without competition, potentially sharing a pool of factors in a transcriptional "hub."

Transcriptional enhancers are short DNA fragments that remotely control gene expression, able to drive transcription from promoters located thousands of base pairs away. Several decades have passed since their initial discovery, and we are just beginning to unravel how enhancers and promoters interact *in vivo*. A long-standing question in the field remains: how does the physical interaction between enhancers and promoters impact gene expression?

"Transvection," whereby an enhancer from one chromosome can activate a promoter *in trans* on another chromosome, is a fascinating example of long-distance transcriptional regulation. E.B. Lewis first demonstrated transvection in the fruit fly when he found that a complementary enhancer on the homologous chromosome *in trans* can rescue gene expression when the *cis* enhancer is deleted (Figure 1; Lewis, 1954). Further studies have demonstrated that transvection can occur across different chromosomes as long as the regulatory regions of both alleles contain homologous sequences to enable pairing (Peifer and Bender, 1986). Similar phenomena have been found in organisms ranging from plants, insects, and mice to humans (Rassoulzadegan et al., 2002). Transvection involves long-range interactions to bring enhancers *in trans* to their promoters. However, the mechanism of transvection has remained an enduring question in genetics. What kind of interchromosomal interactions drive transvection? How frequent or stable must be these interactions be? Does transvection compete with promoters *in cis*? How close must the enhancer be the promoter to drive transvection?

As presented in this issue of *Molecular Cell*, Lim et al. (2018) imaged the dynamics of transvection within live *Drosophila* embryos. The authors started by inserting binding sites for fluorescent viral coat proteins (from MS2 or PP7) (Bertrand et al., 1998; Garcia et al., 2013) on reporter mRNAs transcribed from homologous alleles on complementary chromosomes, allowing them to observe the transcriptional output from each allele simultaneously. When only one of the alleles has an enhancer, the signal from the reporter gene *in trans* provides a direct readout for transcription driven through transvection in real time.

Previously, it had been proposed that chromosomal insulators could increase the frequency of chromosomal pairing, facilitating transvection (Kravchenko et al., 2005). To test this, the authors inserted different insulator sequences and observed the levels of resultant transcriptional activation. Without insulators, the authors did not observe transvection in early embryos. However, paired insulators placed on homologous chromosomes near the reporter genes increased transvection to detectable levels. Paired insulators did not increase pairing frequency; however, the fraction of nuclei with stably paired transcription sites nearly doubled. Interestingly, some insulators were more efficient when placed in particular orientations, and the kinetics of transcription differed between classes

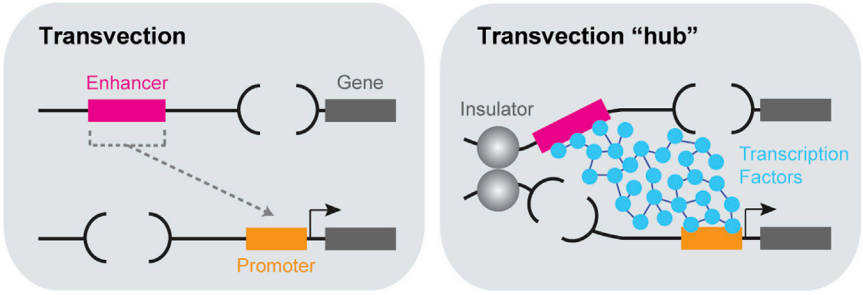

Figure 1. Models of Transvection
The left panel illustrates the classic genetics model of transvection, whereby the enhancer interacts directly with the promoter *in trans* to drive transcription. The right panel shows transcriptional hubs formed through cooperative interactions between insulators, enhancers, promoters, and transcription factors. Such hubs contain a common pool of transcription factors that can be shared between enhancers and promoters without direct competition.

of insulators. These observations suggest that insulators induce different topological domains across chromosomes. In addition, older *Drosophila* embryos also exhibited pairing of transcription sites from related enhancers/promoters without the need for insulators (Tsai et al., 2017). Exploring the mechanisms behind these pairings would further clarify how the chromosomal conformation is interconnected to transcriptional regulation.

The authors then tested if promoters compete for a single enhancer. Surprisingly, they found that the transcriptional outputs of the two promoters were positively correlated. Completely removing the promoter *in cis* led to a reduction in the initial lag before transvection begins, but did not significantly improve the transcriptional output via transvection. These observations suggest that, once the chromosomes have paired, the promoters do not compete for direct contact with the enhancer but instead share a common pool of transcription factors.

Lim et al. demonstrated the power of using *in vivo* imaging to observe transvection directly. Their discovery that promoters can simultaneously share a common enhancer across chromosomes echoes several recent works showing localized transcriptional hubs (Chen et al., 2017; Hnisz et al., 2017). These nuclear microenvironments likely require a network of interactions between multiple regulatory elements, transcription factors, and polymerases working cooperatively (Figure 1; Cisse et al., 2013; Mir et al., 2017; Tsai et al., 2017). This view stands in contrast with the classical model positing direct contacts between individual enhancers and promoters using a well-defined sequence of events. Thus, direct imaging experiments in live embryos, as showcased in this work, will unravel the molecular mechanisms and composition of such transcription hubs. Continued *in vivo* work promises to yield many new insights into the mechanisms behind robust and accurate transcriptional regulation during development.

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