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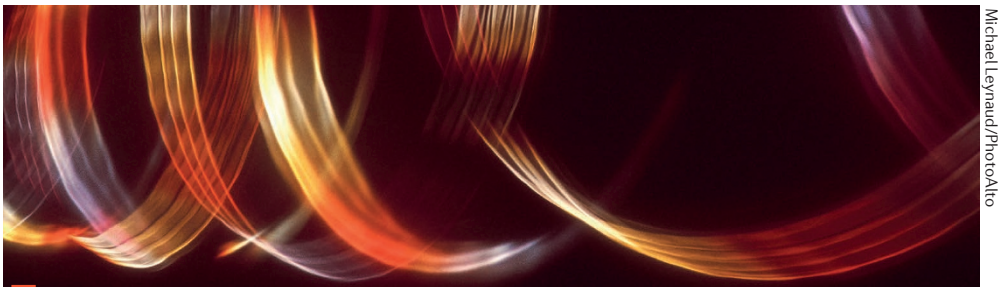

Michael Leynaud/PhotoAlto

GENE EXPRESSION

Dynamic enhancer–promoter interactions for transcriptional bursting

> “single enhancers can drive coordinated bursting of two different reporters”

Transcriptional bursts are believed to be a general property of gene expression. They involve multiple consecutive RNA polymerase complexes being released from promoters to rapidly produce several transcripts, followed by a period of little activity. A new study uses live-imaging techniques to monitor transcriptional bursts in *Drosophila melanogaster* embryos during development and shows that enhancers can dynamically and coordinately regulate burst frequencies at multiple promoters.

Fukaya, Lim and Levine constructed a system of reporter genes that are integrated into the genome and are situated upstream or downstream of known enhancers. Nascent RNAs were detected through live-cell fluorescence microscopy of either MS2 coat protein (MCP)–GFP fusions, which recognize the MS2 loops in the transcripts, or PP7 bacteriophage coat protein (PCP) fused to tdTomato, which recognize PP7 loops in the transcripts. They monitored transcription throughout nuclear cycle 14; this is a key developmental step that establishes cell fate and culminates with the invagination of the mesoderm, and it involves the localized expression of hundreds of patterning genes. The group focused most of their analyses on distal 3′ enhancers ~7.5 kb downstream of the reporter transcription start site, owing to the discrete transcriptional bursts driven by these enhancers and the similarity to the ~10 kb median separation between promoters and enhancers observed in whole-genome assays.

The investigators observed that different enhancers drive different bursting frequencies but have similar burst sizes (that is, a similar number of transcripts per burst). This suggests that burst frequency is a key parameter in controlling gene activity. These changes in frequency lead to spatial and temporal patterning of gene expression: for example, the *snail* (*sna*) shadow enhancer drives frequent bursts and results in similar expression patterns across cells of the mesoderm, whereas the *Krüppel* (*Kr*) CD2 enhancer drives differential bursting frequencies in central regions.

A widespread model of enhancer–promoter interactions is that enhancers randomly select a single promoter for activation through DNA looping to bring the specific enhancer–promoter pair into contact. Contrary to this, Fukaya and colleagues saw that single enhancers can drive coordinated bursting of two different reporters placed upstream and downstream of the enhancer, indicating that the enhancer can activate separate promoters simultaneously. This implies that the topologically associated domains (TADs), which consist of several genes and a few hundred enhancers, are more topologically dynamic than assays of chromosome conformation capture currently suggest.

The possibility of a more dynamic higher-order chromosome organization led the team to investigate the use of the *gypsy* insulator element to block enhancer–promoter interactions. Although the presence of the *gypsy* insulator element between the enhancer and one of the promoters reduced burst frequency of that reporter several fold, it did not completely eliminate its transcription, and when bursts occurred they were generally synchronized with bursts of the other reporter without the intervening *gypsy* element. This unexpected result suggests that TADs can more dynamically switch configurations (here, two alternative topologies activating one versus two target genes) compared to what has previously been observed.

Overall, this study provides valuable insight into how transcriptional bursts across genes and cell populations are controlled by enhancers *in vivo* during a crucially important period in *D. melanogaster* development. It will be interesting to determine how widespread these principles are shared across additional species and systems.

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ORIGINAL ARTICLE Fukaya, T., Lim, B. & Levine, M. Enhancer control of transcriptional bursting. *Cell* http://dx.doi.org/10.1016/j.cell.2016.05.025 (2016)
FURTHER READING Coulon, A. *et al.* Eukaryotic transcriptional dynamics: from single molecules to cell populations. *Nat. Rev. Genet.* **14**, 572–584 (2013)