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GENE REGULATION

Yin and Yang of Polycomb/Trithorax response elements

> there must be other very specific molecules that interact with the ncRNAs locally at PRE/TREs

Polycomb group (PcG) and Trithorax group (TrxG) proteins are epigenetic repressors and activators, respectively, that are essential for the transcriptional control of cell differentiation and development. Their antagonistic action is mediated through switchable regulatory DNA elements called PcG/TrxG response elements (PRE/TREs). Now, a PRE/TRE element has been shown to alter its function by transcribing two different, mutually exclusive non-coding transcripts.

Leonie Ringrose (Institute of Molecular Biotechnology, Vienna, Austria) and her team set out to investigate the mechanisms by which PRE/TREs switch between active and silent states, particularly in different developmental contexts, using the *Drosophila melanogaster vestigial* (*vg*) locus. This locus harbours the *vg* gene, which is expressed in different cell types and at various developmental stages and is known to be regulated by PcG proteins, as well as a PRE/TRE that lies downstream of the gene.

The researchers found that the *vg* PRE/TRE was transcribed into long non-coding RNAs (ncRNAs) arising from both DNA strands. The transcripts were localized to the same tissues as the *vg* mRNA, but they exhibited highly dynamic developmental regulation: whereas in embryos both strands of the PRE/TRE were transcribed, in larval wing discs and brains, only transcripts from the forward strand were found. Moreover, transcription of the PRE/TRE reverse strand correlated with *vg* gene activation in embryos, whereas transcription of the element's forward strand correlated with *vg* gene repression in larvae. "We were very surprised to see the exquisite developmental and spatial regulation of the opposing ncRNAs, and the fact that this regulation was recapitulated by transgenic reporters," remembers Ringrose. "We envisage PRE/TRE switching as a collection of multiple cooperative mechanisms that stabilise each state, and that oppose each other, and these RNAs are a new part of that very complex puzzle."

To unravel the underlying mechanisms, the team assayed the *in vitro* H3K27 methyltransferase activity of recombinant Polycomb repressive complex 2 (PRC2), which is necessary for silencing, in the presence of the *vg* PRE/TRE forward or reverse strand transcripts or control RNAs. Surprisingly, this analysis showed that the ncRNAs interact equally well with the PRC2 complex *in vitro*, and that both have a strong inhibitory effect on its histone methyltransferase activity. "We were expecting the 'silencing' transcript to bind and recruit PRC2, and the 'activating' transcript not to do so," recounts Ringrose. However, *in vivo* the activating (reverse) transcript bound PRC2 with strong specificity, whereas the silencing (forward) transcript did not bind PRC2.

"We think there must be other very specific molecules that interact with the ncRNAs locally at PRE/TREs, and that prevent the PRC2 interaction with some ncRNAs and thus allow silencing," explains Ringrose. "This hypothesis demands a rethink of current recruitment models and may help shift the field towards the idea of regulated inhibition instead."

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ORIGINAL RESEARCH PAPER Herzog, V. A. *et al.* A strand-specific switch in noncoding transcription switches the function of a Polycomb/Trithorax response element. *Nature Genet.* http://dx.doi.org/10.1038/ng.3058 (2014)
FURTHER READING Fatica, A. & Bozzoni, I. Long non-coding RNAs: new players in cell differentiation and development. *Nature Rev. Genet.* **15**, 7–21 (2014)