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TRANSCRIPTION

Intragenic enhancers dampen gene expression

> transcription from intragenic enhancers can attenuate transcription of the host gene

Enhancers, which can be extragenic or intragenic, activate RNA polymerase II (Pol II)-mediated transcription and can themselves undergo transcription to produce enhancer-derived RNAs (eRNAs). Cinghu *et al.* now show that transcription from intragenic enhancers can attenuate transcription of the host gene.

By analysing published Pol II chromatin immunoprecipitation followed by sequencing (ChIP–seq) data from mouse embryonic stem cells (ESCs), the authors identified 1,928 intragenic RNA Pol II sites (IRSs) — that is, intragenic sites enriched for Pol II binding. IRSs had chromatin signatures typical of enhancers, bound to transcription factors that commonly bind to enhancers and enhanced gene expression in reporter assays. Thus, IRSs seem to be transcriptionally active intragenic enhancers.

The authors found that the expression of genes containing intragenic enhancers is lower than that of genes associated with extragenic enhancers. Furthermore, in mouse ESCs, intragenic enhancers promoted the expression of a reporter gene to a lesser extent when they were cloned within the intron compared to when they were cloned downstream of the reporter gene. As the ability of extragenic enhancers to promote reporter gene expression was also reduced when they were cloned within the intron of the reporter gene, the position of the enhancer (rather than its intrinsic properties) seems to influence reporter activity, and intragenic enhancers might attenuate expression of their host genes.

The authors found that the Pol II-mediated transcription of intragenic enhancers interferes with the transcription of the host gene, perhaps by causing premature termination of Pol II. Importantly, mouse ESCs that express elevated levels of eRNAs did not show an increase in the attenuation of gene transcription as compared to control cells. These data suggest that the transcription of an intragenic enhancer itself, rather than the eRNAs that are produced by it, attenuate host gene expression.

Finally, the authors used CRISPR–Cas9 to remove intragenic enhancers from genes in mouse ESCs. Removing these enhancers from highly expressed genes decreased host gene expression, suggesting that intragenic enhancers predominantly activate the expression of these genes. However, removing intragenic enhancers from *Meis1* — a moderately expressed gene — increased *Meis1* expression and led to ESC differentiation, which could be partially reversed by silencing *Meis1*. This finding suggests that intragenic enhancers attenuate the expression of *Meis1* and highlights the biological relevance of intragenic enhancer-mediated decreases in gene transcription.

In short, the authors suggest that transcription at intragenic enhancers interferes with and attenuates host gene expression, but that whether this, overall, results in the attenuation, fine-tuning or activation of gene expression depends on the balance between enhancer-mediated gene activation and enhancer-mediated interference at each host gene.

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FURTHER READING Heinz, S., Romanoski, C.E., Benner, C. & Glass, C.K. The selection and function of cell type-specific enhancers. *Nat. Rev. Mol. Cell Biol.* **16**, 144–154 (2015)