Nature Reviews Genetics | Published online 27 Mar 2017; doi:10.1038/nrg.2017.20

REGULATORY ELEMENTS

A boost to RNA processing

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The term 'super-enhancer' is used to denote clusters of enhancer elements that are bound by a high concentration of cell type-specific master transcription factors and that drive the transcription of genes involved in cell-type identity and disease pathogenesis. A new study published in *Cell* finds that super-enhancer function goes beyond a linear assembly of multiple enhancers that regulate transcription and implicates these genomic regions in the cooperative regulation of microRNA (miRNA) biogenesis.

In mouse embryonic stem cells (mESCs) as well as four differentiated mouse cell types, Suzuki *et al.* determined the gene promoters in closest proximity to super-enhancers and typical enhancers, which included a small fraction of miRNA genes. The team found that miRNAs expressed from genes that were spatially close to super-enhancers, so-called super-enhancer-associated miRNAs (SE-miRNAs) exhibited marked tissue specificity and were highly expressed.

Looking at the role of SE-miRNAs in health and disease as well as their conservation, the authors proceeded to characterize a catalogue of SE-miRNAs across 26 human cell and tissue types, including cancer cells. SE-miRNAs were predominantly cell-type specific, and included multiple tumour-suppressive and oncogenic miRNAs. Gene ontology analysis of experimentally validated target genes linked SE-miRNAs to transcription regulation, as expected.

The team then functionally analysed three miRNA-linked super-enhancers (the miR-290-295 super-enhancer in mESCs, the miR-1 super-enhancer in myotubes and the miR-148a super-enhancer in pro-B cells) using the CRISPR–Cas9 system to generate cells lacking individual components of the super-enhancer region. Deletion of individual elements revealed the cooperative function of various super-enhancer constituents and showed that miRNA-associated super-enhancers drive the expression of the corresponding cell type-specific master miRNAs. For example, deletion of all four constituents of the miR-1 super-enhancer in myotubes markedly suppressed miR-1 and miR-133 expression, as well as that of myogenic differentiation markers, mirroring the phenotype of a previously published miR-1 knockdown.

Interestingly, deletion of several super-enhancer constituents also reduced primary miRNA (pri-miRNA) transcript processing. Accordingly, a chromatin immunoprecipitation–quantitative PCR analysis revealed that the two processing factors DGCR8 and Drosha, which cleave pri-miRNA to precursor miRNA (pre-miRNA), were absent from pri-miRNA loci.

Similarly, treatment with the bromodomain and extraterminal domain (BET) inhibitor JQ1, which leads to preferential loss of super-enhancer constituents and transcription activation relative to typical enhancers, reduced the association of DGCR8 and Drosha with SE-miRNA loci and thus the processing of pri-miRNAs to pre-miRNAs.

Since both perturbations affect the cooperativity of super-enhancer elements, the authors propose that the assembly of the super-enhancer and associated enhancer RNAs may trigger the recruitment of DGCR8 and Drosha to the pri-miRNA loci.

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ORIGINAL ARTICLE Suzuki, H. I. *et al.* Super-enhancer-mediated RNA processing revealed by integrative microRNA network analysis. *Cell* http://dx.doi.org/10.1016/j.cell.2017.02.015 (2017)

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