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Uncovering a New Function of Cis-Regulatory Elements in Alternative Splicing

Cis-regulatory elements have recently been shown to play a much broader range of functional roles beyond simple gene expression regulation. In this work, we uncover a novel role for cis-regulatory elements in alternative splicing regulation. By studying the regulatory interplay between chromatin architecture and alternative splicing during the epithelial-to-mesenchymal transition (EMT)—a key process in development and disease progression, such as metastasis—we identify a distal regulatory region located 30 kb from the alternatively spliced exons 2 and 3 of the CTNND1 gene, which functions as a long-range alternative splicing regulator (LASR).

To investigate this role, we used 4C-seq to map three-dimensional chromatin interactions between the LASR and the alternatively spliced exons, CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) to modulate LASR activity, and CRISPR/Cas9-engineered deletions to validate its function and uncover underlying mechanisms. These approaches confirmed a three-dimensional interaction between the LASR and the alternatively spliced exons, particularly in epithelial cells, where it primes the exons for future inclusion. Furthermore, we show that while the LASR does not affect CTNND1 total gene expression levels, it specifically disrupts the alternative splicing patterns of CTNND1 exons, in part through a CTCF-based mechanism.

Our findings underscore the importance of long-range regulatory elements in controlling alternative splicing patterns and provide novel insights into the complex mechanisms governing alternative splicing, specifically at the interface between DNA and RNA, where much remains to be uncovered. More broadly, our work further demonstrates that cis-regulatory elements can exert a wide range of unexpected functions beyond transcriptional regulation. As research continues to uncover new roles for these elements, it is likely that additional, yet-unexplored regulatory mechanisms will be identified. Finally, our study highlights the potential of targeting long-range regulatory elements for therapeutic intervention.

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