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Zoom Registration

Direct binding of ESRP1 to regulated transcripts is required for position-dependent splicing regulation

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Abstract

Coordinated regulation of alternative splicing is essential to the establishment of cell identity. The Epithelial Splicing Regulatory Proteins (Esrps), ESRP1 and ESRP2, are highly conserved paralogous proteins required for organogenesis of multiple organ systems and compromised function of Esrps contributes to human diseases and pathologies. Esrps are robustly expressed in the epithelial cells of the epidermis, large and small intestines, salivary glands, stomach, and a variety of other tissues, where they are vital in promoting an epithelial splicing network. Although ESRP1 and ESRP2 share partial functional redundancy, ESRP1 appears to play a larger role in regulating gene expression.

Using a combination of enhanced immunoprecipitation coupled with high throughput sequencing (eCLIP) in the epithelial cells of mouse epidermis and RNA sequencing analysis of alterations in splicing and total gene expression that result from epidermal ablation of Esrp1 and Esrp2 we generate a map of Esrp1 binding to RNA. We show that ESRP1 regulates splicing primarily through direct binding in a position-dependent manner to either promote exon inclusion or skipping. In particular, we show that Esrp1 binding upstream of or withing alternatively spliced exons suppresses exon inclusion, whilst binding downstream of the non-constitutive exon promotes exon inclusion. In addition, we identified widespread binding of ESRP1 in 3' and 5' untranslated regions (UTRs) of genes enriched for epithelial cell function suggesting that it directly regulates post-transcriptional gene expression steps in addition to splicing.