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ALTERNATIVE SPLICING

Regulating *Alu* element 'exonization'

> "aberrant incorporation of *Alu* elements is controlled through the competitive binding of two RNA-binding proteins"

Alu elements are the most abundant transposable elements in the human genome. They contain characteristic cryptic splice sites that are used under rare circumstances, such that *Alu* elements are incorporated into a mature transcript. This 'exonization' is a source of evolutionary innovation, but it also poses a threat to transcriptome integrity. In a recent paper, Zarnack *et al.* identified a mechanism whereby such aberrant incorporation of *Alu* elements is controlled through the competitive binding of two RNA-binding proteins.

The authors improved the iCLIP method, which identifies RNA–protein interactions at single-nucleotide resolution, to provide a quantitative picture of the binding sites of two RNA-binding proteins. These were heterogeneous nuclear ribonucleoprotein C (HNRNPC), a regulator of alternative splicing, and U2 auxiliary factor 65 kDa subunit (U2AF65), a key factor in splice-site recognition. Zarnack *et al.* showed that these two proteins compete for RNA-binding sites — particularly in the polypyrimidine tracts of alternative exons that HNRNPC is known to repress. Further evidence for this competitive binding was found in *HNRNPC*-knockdown HeLa cells, where they showed that intronic sites no longer concealed by HNRNPC are occupied by U2AF65. Interestingly, most HNRNPC–U2AF65 competitive binding events were found to occur at intronic locations that are far from known exons.

The authors assessed the effects of this competitive binding on transcript maturation using RNA sequencing in the *HNRNPC*-knockdown cells and showed that over a thousand intronic *Alu* elements are incorporated as exons on the loss of HNRNPC. This is because *Alu* elements become accessible to U2AF65, leading to recognition of cryptic splice sites. Additionally, the authors were able to show that known disease mutations that disrupt HNRNPC binding to *Alu* elements cause such exonization.

The competitive mechanism identified here can be modulated by mutations that create new exons, which may result in evolutionary innovation. However, on the whole exonization is regulated to prevent *Alu* exons from damaging the transcriptome. The potential role of HNRNPC as a competitive guardian of the transcriptome at other types of transposable elements remains to be determined.

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ORIGINAL RESEARCH PAPER Zarnack, K. *et al.* Direct competition between hnRNP C and U2AF65 protects the transcriptome from the uncontrolled exonization of *Alu* elements. *Cell* **152**, 453–466 (2013)