ALTERNATIVE SPLICING

Deciding between the alternatives

> …altered splicing patterns might be more important than expression changes in determining complex human traits.

Two recent studies have highlighted the importance of sequences that regulate alternative splicing by contributing to our understanding of how splicing control elements function and showing that sequences that regulate alternative splicing might be important in determining complex traits.

Previously, the formation of stable protein–RNA complexes was thought to be important for splicing control element function. However, a new study by Yu *et al*. challenges this model. The authors used a randomization–selection approach to identify silencers within a pre-mRNA that contained two alternative 5′ splice sites: a weak upstream splice site and a strong proximal splice site. By looking for sequences that favoured the use of the weak splice site, they identified two exonic and four intronic motifs that functioned as strong splicing silencers both *in vitro* and *in vivo*. The authors only observed silencing when a competing upstream 5′ splice site was present. They concluded that the silencers did not work by sequestering or inactivating the strong splice site, but by altering competition between the two splice sites.

The data from Yu *et al*. suggest that the silencers cannot affect a rate-limiting step in the splicing reaction because the authors did not observe a reduction in the function of the strong splice site that was proportional to the activation of the competing weak splice site in the presence of a silencing element. Instead, the silencers must affect a fast kinetic step, such as the joining of the 5′ and 3′ splice sites in a complex committed to a particular splice site choice. The complex interactions necessary for correct splicing could be easily perturbed by relatively small differences in conditions, such as tissue-specific changes in the levels of splicing factors.

In another recent study, Heinzen and colleagues carried out the first genome-wide screen for SNPs that associate with alternative splicing and gene expression in human primary cells. The authors profiled peripheral blood mononucleated cells and cortical brain tissue and found many SNPs associated with total expression or alternative splicing of specific mRNAs. However, fewer than half of the implicated SNPs had effects in both peripheral blood mononucleated cells and cortex, indicating tissue-specific regulation. The authors also found overlap between the polymorphisms that they studied and those that have previously been implicated in human disease, but most of the associated polymorphisms were related to splicing. This indicated that altered splicing patterns might be more important than expression changes in determining complex human traits. The authors suggest that future studies should focus on cataloguing the relationship between genetic polymorphisms and patterns of gene expression and splicing in different types of human primary tissues.

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FURTHER READING Wang, G.-S. & Cooper, T. A. Splicing in disease: disruption of the splicing code and the decoding machinery. *Nature Rev. Genet.* **8**, 749–761 (2007).