DEVELOPMENT

Alternative splicing switches on the brain

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URLs
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Expasy: http://expasy.org/
MEF2
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PTB
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Alternative splicing is an important mechanism in development that can account for some of the differences in gene expression between cell types. A new study shows that a switch between two alternative-splicing proteins is a key event in the differentiation of neurons.

The polypyrimidine tract binding protein (PTB) represses the splicing of certain alternative exons by altering the assembly of the spliceosome. One common result of this is to introduce a premature stop codon and hence induce nonsense-mediated decay (NMD) of the transcript. Indeed, PTB regulates its own expression in this way.

PTB is expressed in many cell types, but its expression is low in the mammalian brain, which causes many alternative exons to be included in this tissue. By contrast, a paralogous protein, neural PTB (nPTB), is expressed at relatively high levels in the brain and, despite high sequence similarity between the two proteins, different exons are repressed.

The authors looked at precisely which cells in the brain expressed PTB and nPTB using antibodies. Undifferentiated cells expressed PTB, but those that differentiated into neurons switched to expressing nPTB. Non-neuronal cells continued to express PTB only.

How does this switch come about? The authors used RNA interference of PTB to show that it was responsible for the repression of nPTB: it prevents the inclusion of a specific exon in the nPTB transcript and induces NMD. They showed that the loss of PTB expression during neuronal development was sufficient to turn on nPTB expression.

So what are the consequences of this switch? The authors used splicing-sensitive microarrays to see which genes are differentially regulated by the two proteins. The proteins regulate overlapping but distinct sets of genes, with some exons being repressed by one or other protein, some by both, and some being positively regulated. The genes that are affected by the two proteins included those involved in cytoskeletal rearrangement and vesicular transport. One regulated protein of particular interest is MEF2, a transcription factor that regulates many neuronal function genes and is repressed by PTB but not nPTB.

One key unanswered question relates to how PTB expression is lost on differentiation; an understanding of the kinetics of the switch will be important in finding this out. In addition, the large range of targets of the two proteins identified by the authors should help to define the sequence requirements for splicing repression by the proteins.

Patrick Goymer, Associate Editor
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ORIGINAL RESEARCH PAPER Boutz, P. L. *et al.* A post-transcriptional regulatory switch in polypyrimidine tract binding proteins reprograms alternative splicing in developing neurons. *Genes Dev.* **21**, 1636–1652 (2007)
FURTHER READING Xing, Y. & Lee, C. Alternative splicing and RNA selection pressure — evolutionary consequences for eukaryotic genomes. *Nature Rev. Genet.* **7**, 499–509 (2006)