DEVELOPMENT

Alternative splicing switches on the brain

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, causing 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 RNAi of PTB to show that it was responsible for the repression of nPTB through preventing the inclusion of a specific exon in the nPTB transcript and inducing 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. They 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 involves how PTB expression is lost on differentiation; understanding the kinetics of the switch will be important in finding this out. In addition, the large range of targets of the two proteins that the authors have identified should help to define the sequence requirements for splicing repression by the two proteins.

Patrick Goymer

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)

IN BRIEF

EVOLUTION

Widely distributed noncoding purifying selection in the human genome.

Asthana, S. *et al. Proc. Natl Acad. Sci. USA* 12 July 2007 (doi:10.1073/pnas.0705140104)

Functional sequences in the human genome are expected to be under negative, purifying selection. Therefore, looking for regions that are highly conserved between and within species is a way of identifying functional elements. Outside of coding regions, several regions have been identified as conserved non-coding sequences (CNSs). The authors looked for conservation at the single-base level, by identifying bases that were the same in humans and four other species. Surprisingly, 71.4% of such positions that were under purifying selection were not in CNSs.

GENOME INSTABILITY

Restriction of DNA replication to the reductive phase of the metabolic cycle protects genome integrity.

Chen, Z. *et al. Science* **316**, 1916–1919 (2007)

Saccharomyces cerevisiae cells that are grown in nutrient-limiting medium oscillate between glycolysis and respiration. Superimposed onto this is a compartmentalization of cellular processes — cell division occurs during the respiratory phase whereas DNA replication occurs during the glycolytic phase. Chen *et al.* show that mutants that are unable to restrict their cell division to coincide with respiration have an increased spontaneous-mutation rate. Moreover, mutations in a DNA checkpoint kinase uncouple the metabolic and cell cycles, suggesting that the coupling of circadian, metabolic and cell-division cycles serves to preserve genome integrity.

GENE EXPRESSION

Noise in gene expression determines cell fate in *Bacillus subtilis*.

Maamar, H., Raj, A. & Dubnau, D. *Science* 14 June 2007 (doi:10.1126/science.1140818)

Phenotypic diversity among genetically identical cells is achieved by random variation in gene expression. ComK regulates competence for DNA uptake in *Bacillus subtilus*. The authors show that variation in *comK* expression selects cells for competence, and that reducing this variation decreases the number of competent cells. They also show that the timing of transitions coincides with the reduction in *comK* transcription. They conclude that stochastic transitions are regulated and that noise characteristics are subject to evolutionary pressures.

HUMAN GENETICS

Identification of common genetic variation that modulates alternative splicing.

Hull, J., *et al. PLoS Genet.* **3**, e99 (2007)

The authors looked for associations between the alternative splicing of specific exons and local SNPs in 22 HapMap individuals. They looked at SNPs within 500 kb of the intron–exon boundary and, for 6 out of 70 splice variants, found significant variation between individuals. In 5 of these 6 cases, the SNP that had the greatest effect on splicing was the one situated closest to the intron–exon boundary. The effect of SNPs on alternative splicing might be an important factor in genetic susceptibility to several diseases.