better control over the execution of the developmental program. For example, in the case of *tsc1* the temporal control is linked to nutrient conditions through its connection with the insulin pathway — when nutrients are scarce the organism could then coordinate a slow down in its development, in line with its reduced growth. The authors also showed that the temporal control function of InR/Tor pathways holds true for neuronal cell types outside the fly eye, but just how broadly it applies in flies and beyond, and precisely how the control is effected, is not yet known.

Tanita Casci

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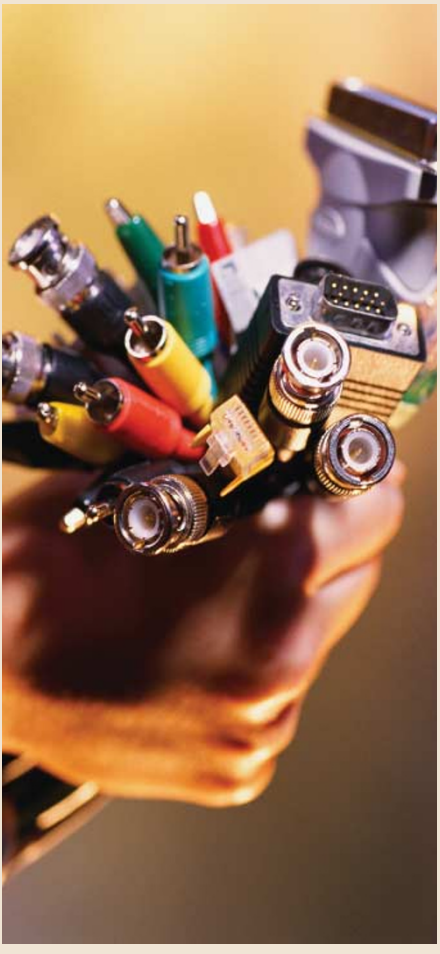
WEB SITE

Helen McNeill's laboratory:
http://science.cancerresearchuk.org/research/loc/london/lifch/mcneillh/



GENE EXPRESSION

The true purpose

Mendell and co-workers have uncovered the physiological function of the nonsense mediated decay (NMD) pathway in higher eukaryotes — it is a crucial mechanism for post-transcriptional regulation, which is interlinked with essential homeostatic mechanisms.

'Whose line is it anyway' — a successful comedy-cum-game show — has entertained audiences on both sides of the Atlantic. The contestants — actors, actresses and other celebrities — are asked to perform a series of tasks. In one, they are presented with an object and asked to indicate through acting as many uses for it as possible. The intended use of the object is not always clear, but in the game, this is beside the point. The real purpose or function of biological phenomena can be frustratingly elusive; this is often because the experimental conditions that are used are artificial. But unlike in the example above, uncovering the natural function is essential in biology.

As its name suggests, NMD is a mechanism that removes mRNAs that carry nonsense mutations. But as Dietz and colleagues point out, this role alone could not account for the evolutionary conservation of the pathway — it must, therefore, have another function.

To uncover it, the authors knocked down the pathway in HeLa cells and, using microarray analysis, they compared transcription profiles of these cells with those in which the pathway was intact. The results revealed that almost 5% of genes were upregulated — the transcripts of these genes are normally eliminated by the NMD pathway. Among them are transcripts that harbour upstream open reading frames that lie in 5′ UTRs, transcripts in which nonsense codons or frameshift mutations have been introduced by alternative splicing, those that contain introns in their 3′ UTRs and transcripts that are derived from ancient transposons and endogenous retroviruses. A common feature of most of these transcripts is the presence of a spliced intron located at least 50 nucleotides downstream of the termination codon — a feature that is sufficient to activate the NMD response.

The authors noted that many of the NMD-pathway substrates are involved in amino-acid metabolism and the cellular response to amino-acid starvation. This observation revealed an interesting homeostatic feedback mechanism. Amino-acid starvation inhibits translation, so as the authors say: "Since NMD requires ongoing translation, it is likely that regulation of these transcripts by nonsense surveillance couples their expression level to translational efficiency. Thus, under conditions of amino-acid starvation, inhibition of translation and NMD would increase expression of transcripts that promote restoration of amino-acid homeostasis". This mechanism of preserving amino-acid homeostasis is evolutionarily conserved — as revealed by the authors' analysis of previously published data on NMD-regulated gene expression in yeast.

The work of Mendell *et al.* has put the role of the NMD pathway in an interesting perspective. Its predominant physiological function seems to involve the regulation of many transcripts, whereas its role in human disease caused by nonsense mutation, although medically important, seems evolutionarily insignificant.

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