DEVELOPMENTAL BIOLOGY

Keeping an eye on the tempo

Developmental signalling pathways defy simple job descriptions; partly because nature has effectively recycled them in many capacities, but largely because we are ignorant of just how varied their jobs are. This is illustrated in a recent paper by Joseph Bateman and Helen McNeill. By analysing mutations in the fly eye, they show that the insulin receptor (InR) and Tor pathways — which have a well-conserved function in controlling cell and organ size — have an unexpected role in determining when cells differentiate.

This conclusion was derived from work on a gene, *tsc1* (*tuberous sclerosis complex 1*), which the authors recovered in a genetic screen for fly mutants with defective planar polarity in the eye. As expected from the mutant phenotype of the vertebrate homologue of *tsc1*, which encodes a tumour suppressor, homozygous mutant photoreceptor cells are larger than normal, but otherwise differentiate normally. What was peculiar, however, was that several types of mutant photoreceptor cells — which are studied precisely because their differentiation is so stereotypical — differentiated more precociously than their genetically wild-type neighbours. This speeded-up development did not lead to an abnormal eye unit or to ectopic cell fates, but simply to an acceleration of the normal differentiation program.

How does wild-type *tsc1* control the rate of differentiation? Mutations that activate the InR pathway cause precocious differentiation in the eye, as with mutations in *tsc1*. The converse experiment, in which the InR and Tor pathways were inactivated, led to delays in neuronal differentiation. This work further supports the involvement of *tsc1* in InR and Tor pathways and, importantly, implicates these pathways in the control of developmental timing. The cells that make up each eye unit in the fly are recruited to their fate by reiterative signalling through the Ras/MAPK pathway; however, lack of *tsc1* does not seem to affect this signalling, indicating that *tsc1* acts downstream of known components of this pathway or in parallel to them.

Uncoupling the execution of cell-fate decisions from the time at which the decisions are made might allow

SYSTEMS BIOLOGY

Rewiring the network

Although systems biology helps to make sense of the complex interactions between genes, proteins and other biologically relevant molecules, most studies have provided only snapshots of how these networks operate in specific conditions. A recent paper in *Nature* describes the first genome-scale study of how biological networks are rewired according to the needs of the cell, revealing some important insights into network dynamics.

Luscombe and colleagues first defined a network of known interactions between 142 transcription factors and 3,420 genes in the yeast *Saccharomyces cerevisieae*. They then incorporated data from previous studies that had examined patterns of gene expression during the cell cycle, sporulation, diauxic shift (the switch from anaerobic to aerobic respiration), DNA damage and the stress response, and used an algorithm to identify sub-networks of interactions that are active in these different conditions.

To characterize these sub-networks, the authors devised a statistical method — SANDY (statistical analysis of network dynamics) — for the analysis of interactions both within and between conditions. Overall comparisons grouped the five sub-networks into two categories. The 'exogenous' diauxic shift, DNA-damage and stress-response sub-networks were characterized by the regulation of several genes by each transcription factor, and by shorter pathways leading from transcription factors to their target genes. This fits in with their ability to produce large and rapid responses to changes in the environment. By contrast, the 'endogenous' cell-cycle and sporulation sub-networks allow more precise, multi-stage control, with longer pathways to activation and more inter-regulation between transcription factors.

Although these results might not seem surprising, given the biological functions of the sub-networks, more unexpected patterns emerged when other characteristics were investigated. Static gene-regulatory networks are characterized by the existence of 'hubs' — individual transcription factors that regulate a disproportionately large number of genes. The importance of these hubs suggests that they are likely to function across a range of conditions, as they regulate key pathways, and this is supported by theoretical simulations. However, the authors found the reverse to be true: most hubs (78%) were important in only a single set of conditions and were therefore dubbed transient hubs. Another surprising result was seen when the interactions made by those hubs that do function across several conditions, known as permanent hubs, were examined. Rather than using a similar set of interactions in each condition, these hubs redefined their interactions just as frequently as transient hubs — further evidence that networks are more dynamic than was previously thought.

As Luscombe and colleagues point out, their study was limited to results that were available from previous experiments, although the robustness of the features they describe in response to random noise suggests that similar patterns are likely to emerge from direct studies of *S. cereviseae* network dynamics. The increasing availability of genome-wide data on regulatory interactions in cell types should allow future studies to determine whether these features apply on a wider scale.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER Luscombe, N. M. *et al.* Genomic analysis of regulatory network dynamics reveals large topological changes. *Nature* **431**, 308–312 (2004)
FURTHER READING Barabási, A. L. & Oltvai, Z. N. Network biology: understanding the cell's functional organization. *Nature Rev. Genet.* **5**, 101–113 (2004)
WEB SITE
Web supplement to original research paper:
http://SANDY.TopNet.GersteinLab.org

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.

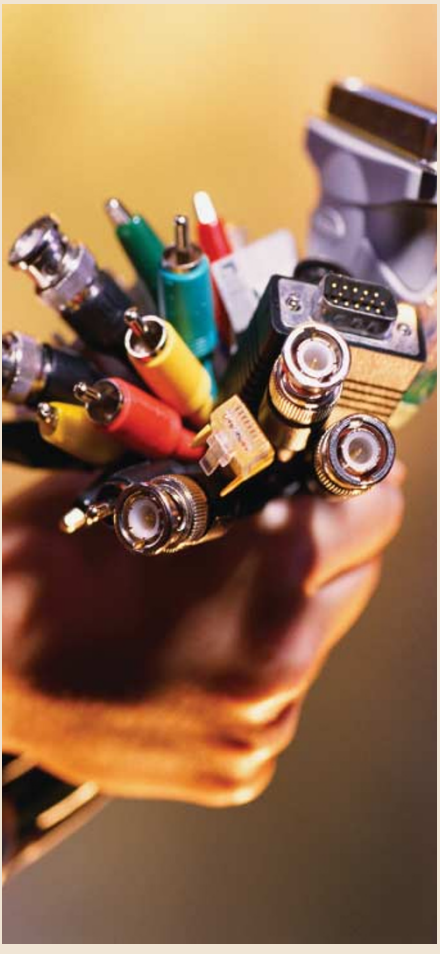
Tanita Casci

References and links

ORIGINAL RESEARCH PAPER Bateman, J. M. & McNeill, H. Temporal control of differentiation by the Insulin receptor/Tor pathway in *Drosophila*. *Cell* **119**, 87–96 (2004)

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.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Mendell, J. T. *et al.* Nonsense surveillance regulates expression of diverse classes of mammalian transcripts and mutes genomic noise. *Nature Genet.* **36**, 1073–1078 (2004)

FURTHER READING He, F. *et al.* Genome-wide analysis of mRNAs regulated by the nonsense-mediated and 5′ to 3′ mRNA decay pathways in yeast. *Mol. Cell* **12**, 1439–1452 (2003)