GENE REGULATION

Transcription and translation get together

Eukaryotes have evolved sophisticated mechanisms to fine tune gene and protein expression, but this complexity can come with a cost: the more regulatory steps involved the less rapid will be the response to any environmental cue. Robert Tjian and colleagues now show that, in *Drosophila melanogaster*, transcription and translation can be coupled, by using internal ribosome entry sites (IRESs), to guarantee a rapid response to a lack of nutrients.

The authors studied the highly conserved INR–IGF (insulin-like receptor–insulin-like growth factor) pathway that has a central role in regulating metabolic homeostasis and organ size. In the presence of nutrients, INR activity drives cells towards growth and proliferation, triggering a signalling cascade that leads to the stimulation of protein translation by inactivating the translation initiation inhibitor 4E-BP (also known as THOR). Conversely, in the absence of nutrients, 4E-BP is active and binds the 7-methyl-guanosine (m7G) cap-binding protein Eukaryotic initiation factor 4E (eIF-4E), preventing the cap-dependent translation of most cellular mRNAs.

The authors had previously shown that under low-nutrient conditions *InR* is upregulated through a transcriptional feedback loop, mediated by the transcription factor forkhead box, subgroup O (FOXO). In the new study, they took a closer look at the *InR* gene structure and found that three promoters regulate *InR* expression, producing three transcripts that are expressed according to nutrient availability during each developmental stage. Interestingly, each transcript is characterized by a unique and unusually long 5′ UTR.

The finding that *InR* is not only transcriptionally upregulated but also actively translated, as shown by increased protein synthesis in the presence of radiolabelled amino acids, under conditions in which 4E-BP maintains a global downregulation of translation, prompted the authors to investigate whether the long 5′ UTRs could engage the translational machinery in an unconventional, cap-independent manner. Indeed, they found IRESs in the long *InR* 5′ UTRs that allow, both *in vitro* and *in vivo*, eIF-4E-independent INR protein synthesis. Therefore they propose that coupling INR transcription and translation, which is further facilitated by the availability of the translation machinery because of 4E-BP global inhibition of translation, is a mechanism to amplify the INR signalling pathway as soon as nutrients become available.

Beyond adding new insights into the regulation of the INR–IGF pathway, this work provides new evidence for the role of cellular IRESs in a physiological response.

Francesca Pentimalli

ORIGINAL RESEARCH PAPER Marr, M. T., D'Alessio, J. A., Puig, O. & Tjian, R. IRES-mediated functional coupling of transcription and translation amplifies insulin receptor feedback. *Genes Dev.* **21**, 175–183 (2007)

EVOLUTION

The genetic code sees off rivals

There are many possible three-letter genetic codes that could adequately encode protein sequences, but what about the need to encode higher-order information on binding and splicing sites? New research shows that the actual genetic code is better than potential alternatives at encoding such information at the same time as encoding protein.

The main function of coding regions is to specify the amino-acid sequence. However, these regions also need to include other elements — sequences for splicing out introns and for mRNA secondary structures, sequences that allow the regular binding of histones, and even some regulatory-protein binding sequences lie within coding regions. These higher-order requirements can often conflict with the main task of protein coding, so Itzkovitz and Alon looked at whether this conflict was minimized in the actual genetic code in comparison with the alternatives.

It is already known that there are some constraints on the code. The effect of translational misreads is minimized by having similar codons encoding similar amino acids, and smaller amino acids have more codons as they are required more often in protein assembly. The authors therefore compared only the possible three-letter codes that conformed to these constraints. They then considered higher-level sequence

EVOLUTION

Translation makes a difference

The changes in gene expression that fuel evolution are not all down to alterations in transcription. A new study provides evidence that differences in translational efficiency have also catalysed phenotypic divergence.

The translational efficiency of a particular mRNA can be predicted from how closely its codon composition matches the available tRNAs. Man and Pilpel characterized the tRNA pools in nine phylogenetically diverse yeast species, and investigated the predicted translational efficiency of around 2,800 sets of orthologous genes. These predictions seem to be biologically relevant; for example, as expected, proteins that are known to physically interact had similar predicted translational efficiencies.

Comparing translational efficiencies between orthologues highlighted some striking correlations with phenotypic differences between species. In one example, the translational efficiency of genes involved in respiration was much higher in aerobic yeasts than in anaerobes, whereas the reverse was true for fermentation genes. Importantly, these correlations cannot be explained simply by closer evolutionary relationships between species with similar translational efficiencies for particular genes. So, selection for changes in codon use, and therefore translational efficiency, seems to have been important during adaptation to different environments.

Applying the same approach to other groups of organisms should reveal whether selection on

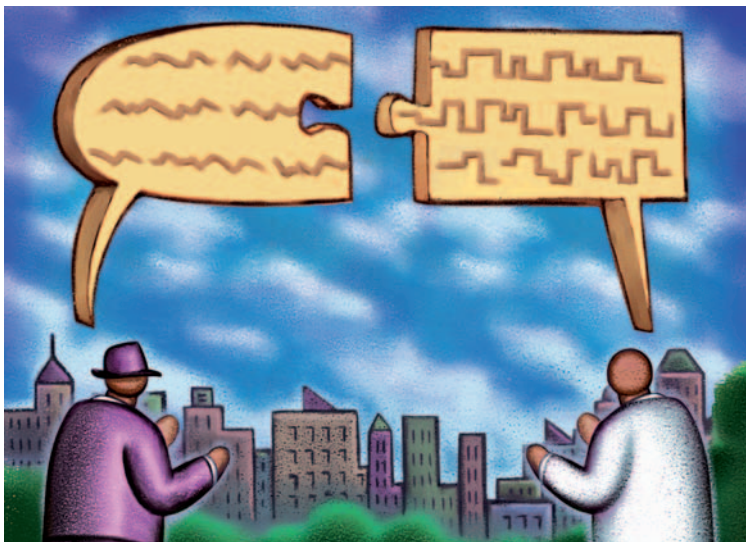
requirements for motifs of different lengths. For example, if a binding protein requires a particular five-base sequence, how likely is it that that sequence can be included in an average gene without compromising the structure of the protein that it encodes? The motif can appear in any of the three reading frames, but a reading frame will be excluded if the motif creates a stop codon in it. Less extremely, the probability that a particular motif can be included in a particular reading frame will depend on the usage frequencies of the codons that it contains.

The authors added together the probabilities of all motifs between 4 and 25 bases in length appearing in each of their potential genetic codes. They found that the real genetic code could accommodate more arbitrary motifs in coding sequence than almost any of the other possibilities — it has a higher information content. One reason for the real genetic code's superiority is the fact that its stop codons, when frame-shifted, tend to form common codons, whereas in other codes frame-shifted stop codons form rarer codons or even other stop codons.

The reverse of this — that common codons can be frame-shifted into stop codons — might explain the initial adoption of the real genetic code. When a ribosome skips a reading frame energy is expended in creating a useless or even harmful protein. In the real genetic code the probability of encountering a stop codon after such a mistake, and therefore saving energy, is maximized. The authors suggest that selection on this, rather than for the ability to encode higher-level information, might be the explanation for the actual code, as the code was probably fixed before such higher-level complexity arose. The mammoth task now is to uncover all the higher-order codes that are contained in the genome.

Patrick Goymer

ORIGINAL RESEARCH PAPER Itzkovitz, S. & Alon, U. The genetic code is nearly optimal for allowing additional information within protein-coding sequences. *Genome Res.* 9 February 2007 (doi:10.1101/gr.5987307)
FURTHER READING Condon, A. Designed DNA molecules: principles and applications of molecular nanotechnology. *Nature Rev. Genet.* **7**, 565–575 (2006)



translational efficiency is a phenomenon with general significance. A key challenge will be to dissect the relative contributions of transcriptional and translational alterations in gene expression, both of which might bring about evolutionary change at the same gene.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Man, O. & Pilpel, Y. Differential translation efficiency of orthologous genes is involved in phenotypic divergence of yeast species. *Nature Genet.* 4 Feb 2007 (doi:10.1038/ng1967)
FURTHER READING Chamary, J. V., Parmley, J. L. & Hurst, D. L. Hearing silence: non-neutral evolution at synonymous sites in mammals. *Nature Rev. Genet.* **7**, 98–108 (2006)
WEB SITE
Pilpel laboratory: http://longitude.weizmann.ac.il

IN BRIEF

CHROMOSOME BIOLOGY

Centromere identity maintained by nucleosomes assembled with histone H3 containing the CENP-A targeting domain.

Black, B. E. *et al. Mol. Cell* **25**, 309–322 (2007)

Chromosome segregation requires specific epigenetic marking of the centromere to allow proper assembly of the kinetochore. It was already known that the centromere-targeting domain (CATD) from the centromere-specific histone H3 variant (CENP-A) can be added to normal H3 to target it to centromeres. Using transgenesis in yeast and RNAi against a wild-type CENP-A in human cell lines the authors now show that CATD-containing H3 is sufficient for proper centromere function in both species.

MOUSE MODELS

Reversal of neurological defects in a mouse model of Rett syndrome.

Guy, J. *et al. Science* 8 February 2007 (doi:10.1126/science.1138389)

Rett syndrome is a severe autism spectrum disorder that is caused by mutations in an X-linked gene, *MECP2*. At the cellular level, it is characterized by neuronal abnormalities but not neuronal death. The authors show that inducing expression of *Mecp2* in mice in which the endogenous locus has been silenced reverses Rett-like neurological defects in both immature and mature adult animals. Although these data do not suggest an immediate therapeutic approach, they establish that Rett-associated neurological damage is not irreversible.

DEVELOPMENT

Dickkopf-1 is a master regulator of joint remodeling.

Diarra, D. & Stolina, M. *et al. Nature Med.* **13**, 156–163 (2007)

Degenerative and inflammatory joint diseases bring about remodelling of joint architecture, leading to disability. These authors show that inhibiting Dickkopf-1, an inhibitor of Wnt signalling, reverses bone resorption in a mouse model of rheumatoid arthritis and promotes osteoarthritis-associated bone formation. Although this leads to the formation of bony nodules, no bone is lost. They show that in the mouse model and human disease DKK1 is induced by tumour-necrosis factor-α. Taken together, the data implicate the Wnt pathway as a key regulator of joint remodelling.

CHROMATIN

Nuclear reorganisation and chromatin decondensation are conserved, but distinct, mechanisms linked to Hox gene activation.

Morey, C. *et al. Development* 24 January 2007 (doi:10.1242/dev.02779)

The authors showed that Hoxd activation in the limb bud is accompanied by chromatin decondensation but no movement of the region out of the chromosome territory. After its activation during embryonic stem cell differentiation and embryonic tailbud development Hoxd decondenses and loops out from the chromosome territory, as is commonly seen for active loci. So, although overall remodelling mechanisms are conserved and pre-date the duplication of mammalian Hox loci, different modes of regulation can modify Hoxd chromatin depending on developmental contexts.