AGEING

Forever young

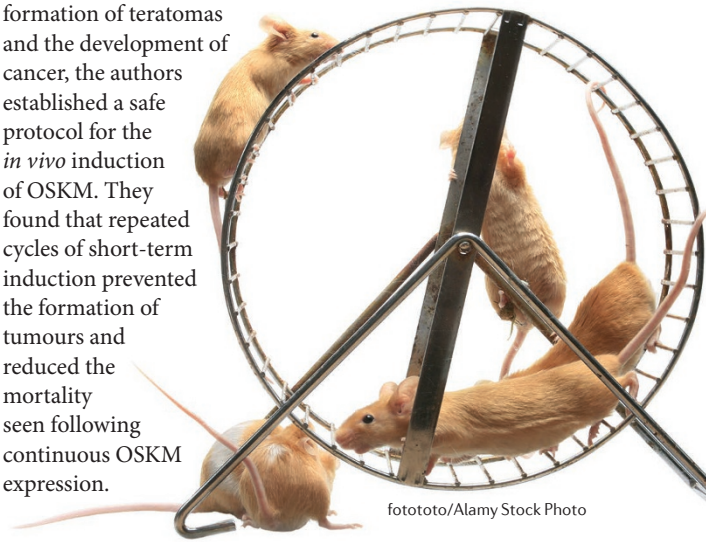
In vitro cellular reprogramming through the expression of the four transcription factors OCT4, SOX2, KLF4 and MYC (OSKM) has been shown to ameliorate age-associated cellular phenotypes, including gene expression profiles, telomere length and oxidative stress. Whether reprogramming can have beneficial effects *in vivo* remains to be explored. Ocampo *et al.* now show that short-term expression of OSKM in mice can reverse some aspects of the ageing process.

A truncated form of lamin A known as progerin causes Hutchinson–Gilford progeria syndrome (HGPS), which is characterized by premature ageing in humans. The authors used a mouse model of HGPS and generated progeria mice carrying inducible OSKM transgenes. Short-term expression of OSKM in fibroblasts isolated from these mice reversed several molecular and cellular changes that are associated with ageing. For example, these cells had fewer histone γ-H2AX foci (a marker of DNA double-strand breaks) and reduced levels of the DNA damage response protein p53 binding protein 1 (TP53BP1), lower expression of age-related stress-response genes and senescence-associated genes, and reduced production of reactive oxygen species (indicative of improved mitochondrial function).

Short-term induction of OSKM also improved nuclear envelope architecture, which is a main driver of premature ageing in HGPS. Moreover, the levels of histone H3 Lys 9 trimethylation (H3K9me3) and H4K20me3, which are usually altered during ageing, were restored to a younger state. Interestingly, the authors found that an increase in H3K9me3 levels preceded the amelioration of DNA damage and nuclear envelope defects and was necessary for them to occur, indicating that epigenetic remodelling may be a main driver of the amelioration of age-associated phenotypes.

So, does a temporary induction of OSKM confer benefits to the organism? As reprogramming *in vivo* has been previously shown to induce the formation of teratomas and the development of cancer, the authors established a safe protocol for the *in vivo* induction of OSKM. They found that repeated cycles of short-term induction prevented the formation of tumours and reduced the mortality seen following continuous OSKM expression.

> “short-term expression of OSKM in mice can reverse some aspects of the ageing process”



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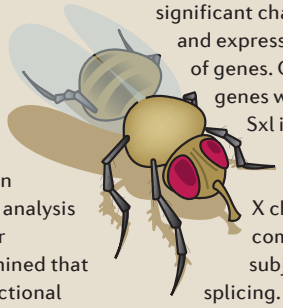
RNA METABOLISM

Modifying sex in flies

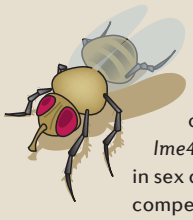
*N*6-methyladenosine (m^6A) is the most common mRNA modification in eukaryotes, but its functions are not well understood. Now, two studies in *Nature* report a role for m^6A in the regulation of sex determination in *Drosophila melanogaster*.

Lence *et al.* set out to explore the function of m^6A in *D. melanogaster*, focusing on the proteins Ime4, Fl(2)d, Virilizer and CG7818, which are orthologues of the components of the methyltransferase complex that catalyses *N*6-adenosine methylation in mammals. Through the analysis of fly embryos and further experiments, they determined that these proteins form a functional complex that is enriched in the nervous system and is required for the promotion of m^6A.



To investigate the role of m^6A in development, they generated flies containing mutations in *Ime4* and *CG7818*. Mutant flies displayed several behavioural abnormalities, all of which could be rescued by neuronal expression of *Ime4*, indicating that m^6A affects behaviour by modulating neuronal function. Transcriptomic analyses of *Ime4* mutants revealed significant changes in the splicing and expression of a large number of genes. One of the affected genes was *Sex lethal* (*Sxl*). Sxl is a master regulator of sex determination and in males of X chromosome dosage compensation and is subject to alternative splicing. Expression of the functional Sxl protein results in female development and the inhibition of dosage compensation.

> “m^6A affects behaviour by modulating neuronal function”



However, the inclusion of an additional exon that incorporates a premature stop codon results in a non-functional protein, which leads to male development. The researchers detected the male-specific *Sxl* splicing isoform in the RNA of female flies that lacked *Ime4*, suggesting a role for m^6A in sex determination and dosage compensation.

In the other study, Haussmann *et al.* set out specifically to investigate a potential role for m^6A in *Sxl* splicing. They, too, generated *Ime4* mutant flies; these lacked m^6A and showed a considerable bias towards the male sex. In addition to the effects on sex determination, they detected significant upregulation of X-linked genes in mutant females relative to wild-type, supporting a role for m^6A in dosage compensation.

Haussman *et al.* also detected the male-specific *Sxl* isoform in females and effects on alternative splicing in a large number of other genes in mutant flies. Notably, the differentially spliced genes were enriched for

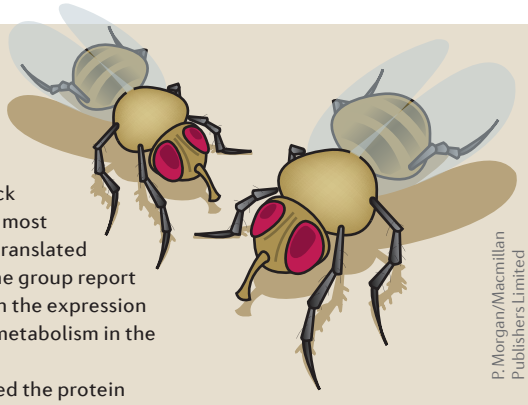
Using this cyclic protocol, the authors treated progeria mice throughout their lives, starting at 8-weeks of age. Strikingly, the appearance of treated mice was improved, and although mice progressively lost body weight, both median and maximal lifespan were substantially increased. Moreover, adult stem cell populations in the muscle and hair follicles were replenished, and cardiovascular alterations and histological changes (in the skin, spleen, kidneys and stomach) that occur during ageing were reversed. Furthermore, the epigenetic changes that were seen *in vitro*, as well as the reduction in the expression of stress- and senescence-associated genes, were also seen in several organs of the treated mice.

Last, the authors investigated whether partial reprogramming could have beneficial effects in wild-type organisms. Ageing is associated with a loss of proliferative capacity of pancreatic β-cells, which can lead to pancreatic dysfunction as well as a loss of skeletal muscle mass (sarcopenia). The authors observed that cyclic expression of OSKM in 12-month-old mice promoted the expansion of the β-cell population, enhanced their recovery from pancreatic injury and ameliorated glucose tolerance following pancreatic injury. Furthermore, treated 12-month-old mice had a greater muscle regeneration capacity following injury.

Together, these observations suggest that partial reprogramming by cyclic short-term induction of OSKM can revert or slow down the decline in regenerative capacity and the loss of tissue homeostasis that occur during ageing. This system could be exploited to study ageing-related diseases and further elucidate the role of epigenetics in ageing.

Kim Baumann

ORIGINAL ARTICLE Ocampo, A. *et al.* *In vivo* amelioration of age-associated hallmarks by partial reprogramming. *Cell* **167**, 1719–1733 (2016)
FURTHER READING Benayoun, B. A., Pollina, E. A. & Brunet, A. Epigenetic regulation of ageing: linking environmental inputs to genomic stability. *Nat. Rev. Mol. Cell Biol.* **16**, 593–610 (2015)



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factors involved in neurotransmission. A detailed analysis of the alternative splicing events that were affected by a lack of *Ime4* revealed that most occurred in the 5′ untranslated region. In addition, the group report widespread effects on the expression of genes involved in metabolism in the absence of m^{6}A.

Both teams identified the protein YT521-B as the reader of m^{6}A in *D. melanogaster*. YT521-B bound to m^{6}A, and the phenotype and behaviour of, as well as the differential splicing of *Sxl* and other genes were similar in *YT521-B* mutants and *Ime4* mutants. Together, these findings indicate that the effects of m^{6}A on splicing are mediated by YT521-B. Finally, Lence *et al.* identified an additional protein called Spenito as a novel component of the m^{6}A methyltransferase complex in *D. melanogaster*.

These studies provide important insights into the biogenesis and function of m^{6}A and raise the possibility that it has widespread regulatory roles in development that may extend across species.

Denise Waldron, Associate Editor, Nature Reviews Genetics

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ORIGINAL ARTICLES Lence, T. *et al.* m6A modulates neuronal functions and sex determination in *Drosophila*. *Nature* http://dx.doi.org/10.1038/nature20568 (2016) | Haussmann, I. U. *et al.* m6A potentiates *Sxl* alternative pre-mRNA splicing for robust *Drosophila* sex determination. *Nature* http://dx.doi.org/10.1038/nature20577 (2016)
FURTHER READING Zhao, B. S., Roundtree, I. A. & He, C. Post-transcriptional gene regulation by mRNA modifications. *Nat. Rev. Mol. Cell Biol.* **18**, 31–42 (2017)

IN BRIEF

NON-CODING RNA

A class of their own

The transcription and processing of long intervening noncoding RNAs (lincRNAs), which are a class of lncRNAs expressed independently of protein-coding genes, are poorly understood. Schlackow *et al.* studied 285 lincRNAs that are highly expressed in HeLa cells using mNET-seq, which enables monitoring of the kinetics of transcription and co-transcriptional processes. The levels of co-transcriptional splicing in lincRNAs were considerably lower than in mRNAs, and transcription termination occurred at multiple positions along the transcripts. lincRNAs were weakly polyadenylated, and transcription termination and transcript stability were almost entirely independent of 3′ cleavage and polyadenylation. Although lincRNAs and mRNAs are often similarly abundant at the chromatin, lincRNAs were less abundant in the nucleoplasm, as they were cleaved at multiple positions and then degraded by the nuclear exosome complex. The exosome was recruited to lincRNAs by DGCR8, independently of the microRNA-processing function of DGCR8.

ORIGINAL ARTICLE Schlackow, M. *et al.* Distinctive patterns of transcription and RNA processing for human lincRNAs. *Mol. Cell* **65**, 25–38 (2017)

DEVELOPMENT

Metabolism regulates lymphangiogenesis

Wong *et al.* report that metabolism — more specifically, fatty acid β-oxidation (FAO) — promotes lymphatic development. They found that FAO is high in lymphatic endothelial cells (LECs; which line lymph vessels) and that inhibition or LEC-specific loss of CPT1A, which is a rate-controlling enzyme of FAO, impaired the differentiation of LECs from their precursors, venous endothelial cells, both *in vitro* and in mice. The transcription factor PROX1 and vascular endothelial growth factor receptor 3 (VEGFR3) are known inducers of LEC differentiation through the upregulation of lymphatic genes. The authors report that PROX1 upregulates FAO by inducing *CPT1A* expression, thereby increasing the levels of FAO-derived acetyl-CoA, which is used by p300 to acetylate histone H3 at Lys9 at key lymphatic genes, including *VEGFR3*. Moreover, they propose that selective activation of lymphatic genes is enhanced through PROX1 binding to p300 and preferentially recruiting it to PROX1-target genes.

ORIGINAL ARTICLE Wong, B. W. *et al.* The role of fatty acid β-oxidation in lymphangiogenesis. *Nature* http://dx.doi.org/10.1038/nature21028 (2016)

TRANSLATION

Ubiquitylation mediates quality control

Terminally stalled ribosomes can initiate degradation of nascent polypeptides and the dissociation of ribosome subunits, a process known as ribosome-associated quality control (RQC). Using a reporter that quantitatively measures ribosome terminal stalling, Juszkiewicz and Hegde found that most ribosomes in human cells stalled when they encountered an array of 21 AAA Lys codons (AAA_{21}) and that degradation of the 'arrested' nascent polypeptides was mediated by RQC. Depletion of the putative ubiquitin E3 ligase ZNF598 abolished terminal stalling at the AAA_{21} region. Moreover, ZNF598-mediated ubiquitylation of several ribosomal proteins, primarily 40S ribosomal protein S10, was necessary for RQC activation. Because translation of only poly(A) sequences that are longer than endogenous sequences can effectively trigger RQC, this mechanism could be tuned to prevent translation of the poly(A) tail.

ORIGINAL ARTICLE Juszkiewicz, S. & Hegde, R. S. Initiation of quality control during poly(A) translation requires site-specific ribosome ubiquitination. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2016.11.039 (2017)