rhythms. Correction of circadian rhythmicity with NAD^+ could also be tested for the management of circadian disorders linked to PER2 deregulation, such as those caused by PER2 mutations or shift work.

Paulina Strzyz

ORIGINAL ARTICLE Levine, D. C. et al. NAD^+ controls circadian reprogramming through PER2 nuclear translocation to counter aging. *Mol. Cell* https://doi.org/10.1016/j.molcel.2020.04.010 (2020)
RELATED ARTICLES Patke, A., Young, M. W. & Axelrod, S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat. Rev. Mol. Cell Biol.* **21**, 67–84 (2020) | Reinke, H. & Asher, G. Crosstalk between metabolism and circadian clocks. *Nat. Rev. Mol. Cell Biol.* **20**, 227–241 (2019)

> … the topological influence of PRC1 extends beyond PRC1-bound loci

were driven apart by loss of RING1B. Tissue-specific activation of one of the three genes, *Shh* in E10.5 mouse embryos, correlated with loss of its clustering with the other two genes. Thus, *Shh* can form multivalent interactions with other repressed genes, and these interactions are lost following its developmental activation and loss of polycomb binding. However, loss of PRC1-mediated interactions did not lead to global gene activation.

Thus, although it occupies <1% of the mESC genome, RING1B globally affects nuclear organization. A non-catalytic function of RING1B is required for local and long-range chromatin interactions, which do not necessarily regulate genes, but can facilitate developmental gene activation. Further work is required to elucidate the role of these interactions in development.

Eytan Zlotorynski

ORIGINAL ARTICLE Boyle, S. et al. A central role for canonical PRC1 in shaping the 3D nuclear landscape. *Genes Dev.* http://www.genesdev.org/cgi/doi/10.1101/gad.336487.120 (2020)
RELATED ARTICLE Zheng, H. & Xie, W. The role of 3D genome organization in development and cell differentiation. *Nat. Rev. Mol. Cell Biol.* **20**, 535–550 (2019)

Journal Club

THE MITOCHONDRIAL tRNA CONUNDRUM

In 1981, Ojala, Montoya and Attardi published an article that led to a universally accepted model for mitochondrial DNA (mtDNA) transcription. Memorable papers often provide long-awaited answers but, in this case, it is also the questions that this work has raised that make it unforgettable.

The human mitochondrial genome encodes only 13 proteins, 2 ribosomal RNAs (rRNAs) and 22 mitochondrial transfer RNAs (tRNAs). All these genes are encoded almost contiguously, in a peculiar arrangement where most protein-coding genes are separated by a single tRNA gene. In their paper, Attardi and colleagues showed that each of the two mtDNA strands is transcribed as a single polycistronic transcript, which is later processed by RNases that excise out the tRNA sequences. Each transcription cycle should therefore generate one copy of each encoded mRNA, rRNA and tRNA. This is the elegant 'tRNA punctuation model', which can be found in all textbooks and review articles covering mitochondrial biology (for example, see D'Souza & Minczuk, 2018).

> how do mitochondria manage to translate their protein-coding genes if only one set of tRNAs is produced in each transcription cycle?

But in the elegance of the model lies a hidden mystery: how do mitochondria manage to translate their protein-coding genes if only one set of tRNAs is produced in each transcription cycle? Moreover, if all mitochondrial tRNAs are synthesized at exactly the same rate, how do mitochondrial ribosomes adapt to the bias in amino acid composition of mitochondrial proteins?

In the cytosol of eukaryotic cells, tRNAs are extremely abundant and their relative concentrations are optimized to fit the codon composition of highly translated mRNAs. This is partly because protein-coding genes and tRNA genes are transcribed and processed differently, thereby ensuring a high tRNA to mRNA ratio. There is evidence that the relative abundance of mitochondrial rRNA may depend on slower turnover rates compared with mitochondrial mRNAs, but how mitochondria accumulate enough tRNAs for translation remains unknown.

Is the turnover rate of mitochondrial tRNAs much slower than that of mitochondrial mRNAs? Do mitochondrial genomes undergo 'futile' transcription cycles that generate only tRNAs? Is there an unknown mechanism for the selective transcription of mitochondrial tRNA genes? These questions remain open, awaiting someone to follow in the footsteps of Ojala, Montoya and Attardi.

Lluís Ribas de Pouplana
Institute for Research in Biomedicine (IRB), The Barcelona Institute of Science and Technology & Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Catalonia, Spain
e-mail: lluis.ribas@irbbarcelona.org

The author declares no competing interests.

ORIGINAL ARTICLES Ojala, D. et al. tRNA punctuation model of RNA processing in human mitochondria. *Nature* **290**, 470–474 (1981) | D'Souza, A. R. & Minczuk, M. Mitochondrial transcription and translation: overview. *Essays Biochem.* **62**, 309–320 (2018) | Novoa, E. M. et al. A role for tRNA modifications in genome structure and codon usage. *Cell* **149**, 202–213 (2012) | Litonin, D. et al. Human mitochondrial transcription revisited: only TFAM and TFB2M are required for transcription of the mitochondrial genes in vitro. *J. Biol. Chem.* **285**, 18129–18133 (2010)