News & views

Molecular biology

An added layer of gene repression

Michael Uckelmann & Chen Davidovich

A protein complex called the rixosome helps to degrade RNA transcripts that linger after gene expression ceases. This discovery points to distinct roles for the rixosome in regulating chromatin in different species. See p.167

After gene expression ends, components of the gene-transcription machinery can remain in the vicinity of DNA, along with RNA transcripts. There are known pathways for transcript degradation and for gene repression in human cells – but, so far, these pathways have not been directly linked. On page 167, Zhou *et al.*[1] describe a pathway for the removal of RNA from inactive human genes that is triggered by key players of the gene-repression machinery.

The DNA of multicellular organisms is packed into a structure called chromatin, which is composed of DNA and histone proteins. Whereas DNA holds genetic information, histone proteins carry another type of information, the histone code[2] – various chemical modifications that convey cell-type-specific information about which genes should be active and which ones repressed. When genes are repressed in a given cell type, they are packed into a compact chromatin structure called facultative heterochromatin. A subset of repressive histone modifications is abundant in – and considered a hallmark of – facultative heterochromatin.

Among the enzymes that add these repressive modifications are two polycomb repressive complexes, PRC1 and PRC2. PRCs repress RNA synthesis at facultative heterochromatin through several mechanisms: they mark genes for repression; trigger compaction of chromatin; prevent gene-activation factors from binding to chromatin; and possibly also prevent the addition of some active histone marks[3] (Fig. 1a).

But how RNA that has already been synthesized is cleared away from facultative heterochromatin has been unclear. This is a fundamental question, because chromatin-associated RNA is linked to chromatin structure[4,5], genome stability[6] and genome function[7].

Zhou *et al.* set out to investigate a possible role for a protein complex called the rixosome in gene-repression pathways in human cells. The authors investigated two enzymatic functions of the rixosome: first, as an endonuclease that cleaves RNA; and, second, as a kinase that attaches phosphate groups to the cleaved molecule, flagging it for degradation[8]. These activities of the rixosome were previously shown[9] to have a role in laying down repressive histone marks in yeast cells.

The authors showed that the rixosome co-localizes with PRCs at facultative heterochromatin in human cells, and directly interacts with PRC1. The researchers therefore generated a mutant form of PRC1 that cannot bind to the rixosome. PRC-mediated histone modification occurred as normal in cells carrying the mutant protein, but the rixosome could not localize to facultative heterochromatin.

Zhou and colleagues next analysed cells in which the rixosome was mutated to prevent either its endonuclease or its kinase activity. In each case, a subset of genes normally repressed in facultative heterochromatin were expressed.

Together, the authors' data support the following model. First, PRC1 recruits the rixosome to facultative heterochromatin. Next, the rixosome uses its endonuclease and kinase activities to cut RNA and prepare it for degradation. Finally, another enzyme – the exoribonuclease XRN2 – finishes the job by degrading the phosphorylated RNA. Thus, PRCs trigger a cascade of molecular events that eventually wipe out RNA selectively at facultative heterochromatin in human cells (Fig. 1b).

In yeast, the enzymatic activities of the rixosome are required for correct histone modification in heterochromatin[9]. But these are different from the histone modifications deposited by PRCs – and yeast heterochromatin is very different from human facultative heterochromatin, because the latter evolved to support diverse transcription programs in various cell types. In fact,

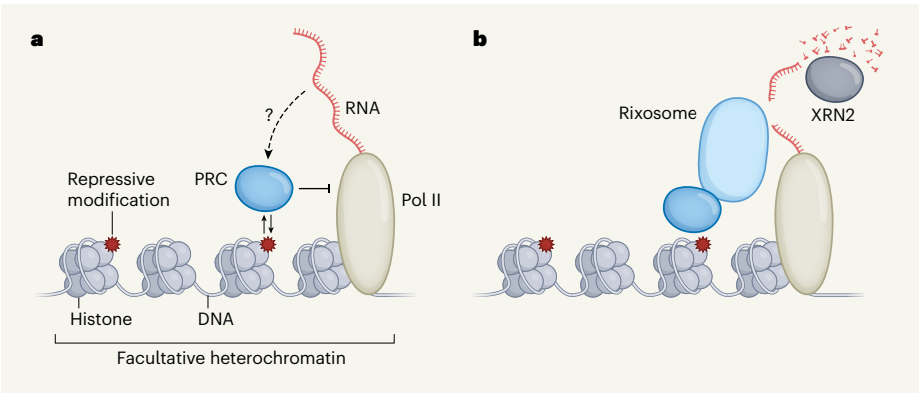

Figure 1 | Complex regulation of gene repression. a, In regions of the genome where gene expression is highly repressed, DNA and histone proteins are tightly packaged together in a structure called facultative heterochromatin. Repression of gene expression in this region involves protein complexes called polycomb repressive complexes (PRCs), which are regulated through intricate feedback loops. For instance, PRCs add repressive chemical modifications to histones to maintain gene repression, and these marks promote the activity of PRCs. PRCs also inhibit transcription of DNA into RNA by the enzyme RNA polymerase II (Pol II) – RNA transcripts left on heterochromatin after gene expression ceases might in turn regulate PRCs. **b**, Zhou *et al.*[1] show that PRCs also trigger the recruitment of an enzymatic complex called the rixosome to facultative heterochromatin. The rixosome cleaves RNA that has been produced by Pol II and prepares it for degradation by another enzyme, XRN2.

commonly studied yeast strains have lost PRCs through evolution[3]. Hence, yeast and human rixosomes have become integrated into two different chromatin-regulating pathways.

The rixosome also has a role in generation of the ribosome — the protein-synthesis machine of the cell[8]. However, Zhou *et al.* demonstrated that the pathway they discovered is independent of ribosome biogenesis. Thus, the rixosome has been repeatedly repurposed through evolution to fill gaps in different pathways across the nucleus. It is tempting to speculate that the rixosome could also participate in other chromatin-related pathways.

Many PRCs interact with thousands of transcripts[10], and the bound RNA seems to regulate the activity of PRCs. Various models have been proposed to explain how this regulation might occur — but the precise molecular mechanisms involved are still a subject of study[11]. Zhou and colleagues' work implies that RNA-mediated regulation of PRCs is a two-way street.

PRCs regulate each other through convoluted feedforward loops that involve their repressive histone marks. This makes it challenging to distinguish between direct and indirect effects when studying the regulation of gene repression by PRCs. Experiments by Zhou *et al.* pinpointed a subunit of PRC1 as a key determinant of the recruitment of the rixosome to facultative heterochromatin. Less was done to investigate how PRC2 regulates the rixosome, although the authors did identify physical interactions between the complexes. There are at least six subtypes of PRC1 complex and two subtypes of PRC2, each of which has different subunit compositions and functions[3]. More work will be needed to identify the subtypes of PRC1 (and perhaps PRC2) that recruit the rixosome to chromatin. Structural studies could reveal how PRCs and the rixosome interact in a way that allows these massive complexes to carry out all their molecular tasks in the context of chromatin.

Mounting evidence points to RNA as a central scaffold that moulds chromatin structure[9] and compartmentalization[5]. The new-found knowledge of the ability of PRCs to trigger RNA degradation, together with their known roles in histone modification and chromatin compaction, cements these complexes as key drivers for shaping the 3D structure and function of facultative heterochromatin.

Michael Uckelmann and **Chen Davidovich** are in the Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria 3800, Australia. **C.D.** is also at EMBL-Australia, Clayton, Victoria.
e-mails: michael.uckelmann@monash.edu; chen.davidovich@monash.edu

1. Zhou, H. *et al. Nature* **604**, 167–174 (2022).
2. Jenuwein, T. & Allis, C. D. *Science* **293**, 1074–1080 (2001).
3. Blackledge, N. P. & Klose, R. J. *Nature Rev. Mol. Cell Biol.* **22**, 815–833 (2021).
4. Creamer, K. M., Kolpa, H. J. & Lawrence, J. B. *Mol. Cell* **81**, 3509–3525.e5 (2021).
5. Quinodoz, S. A. *et al. Cell* **184**, 5775–5790.e30 (2021).
6. Wickramasinghe, V. O. & Venkitaraman, A. R. *Mol. Cell* **61**, 496–505 (2016).
7. Li, X. & Fu, X.-D. *Nature Rev. Genet.* **20**, 503–519 (2019).
8. Fromm, L. *et al. Nature Commun.* **8**, 1787 (2017).
9. Shipkovenska, G., Durango, A., Kalocsay, M., Gygi, S. P. & Moazed, D. *eLife* **9**, e54341 (2020).
10. Davidovich, C., Zheng, L., Goodrich, K. J. & Cech, T. R. *Nature Struct. Mol. Biol.* **20**, 1250–1257 (2013).
11. Almeida, M., Bowness, J. S. & Brockdorff, N. *Curr. Opin. Genet. Dev.* **61**, 53–61 (2020).

The authors declare no competing interests.
This article was published online on 30 March 2022.

Nuclear physics

Cryogenic mastery aids bid to spot matter creation

Jason Detwiler

A cubic metre of tellurium held at cryogenic temperatures over many years has enabled a search for matter created in a rare nuclear process. The feat bodes well for stabilizing other complex systems at low temperatures. **See p.53**

Astrophysical observations reveal that the Universe is made almost entirely of matter, with nearly no antimatter in sight. However, laboratory and particle-collider experiments have so far observed the creation of matter and antimatter in equal parts. Big Bang theories that aim to explain the cosmic matter imbalance predict that matter could be generated without antimatter in a 'little bang', during an ultra-rare nuclear process called neutrinoless

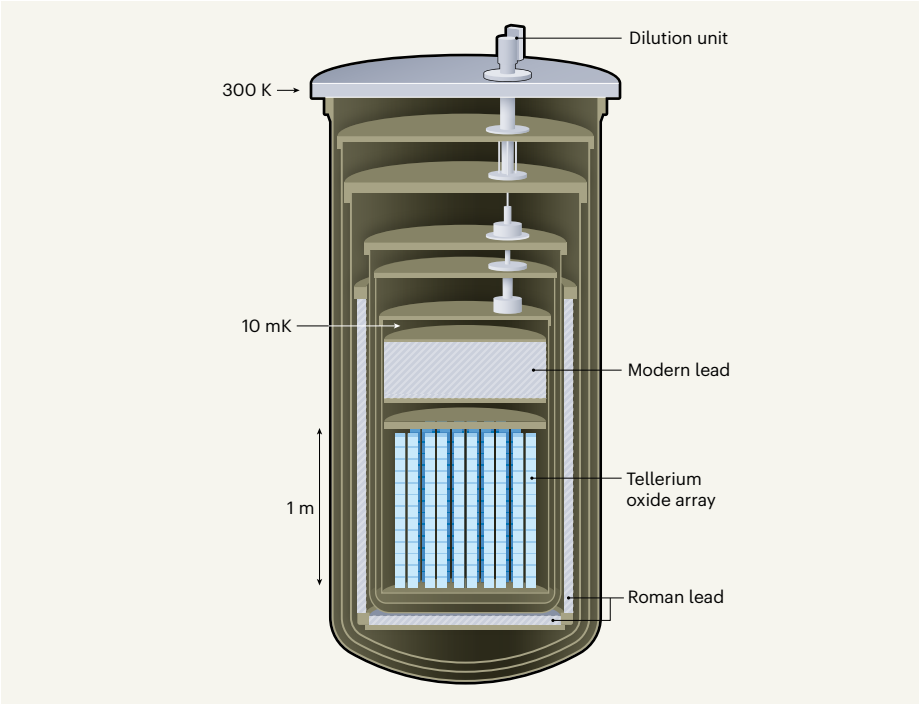

Figure 1 | The coldest cubic metre in the known Universe. The CUORE collaboration[1] searched for an ultra-rare type of nuclear decay using an array of 988 crystals of tellurium oxide, shown here in this simplified schematic. The array is housed inside the world's largest dilution refrigerator, which is a cryogenic device that uses the dilution of helium as a cooling mechanism; a multistage cooling process allowed the team to achieve temperatures of 10 millikelvin in the innermost chamber. Lead shielding was used to block external radiation that could mimic the signature of the decay. As well as modern lead, the team used lead salvaged from a Roman shipwreck in the Sardinian sea, which has lower levels of natural radioactivity. The apparatus is located 1.4 km underground, beneath the Gran Sasso mountain in Italy. (Adapted from Fig. 1 of ref. 1.)