Stem cell metabolism

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Methylation, acetylation and cell fate

Dan Huang & Ziwei Dai

Metabolism regulates cell fates through the epigenome. Wang, Shi et al. demonstrate that the cell fates of pluripotency, differentiation and ageing emerge from how a nuclear protein channels metabolic fluxes into distinct epigenetic marks by regulating expression of metabolic genes.

The nuclear lamina, a protein network located inside the nuclear envelope, has traditionally been viewed as a structural scaffold that safeguards nuclear shape and anchors heterochromatin. In a new study published in *Nature Metabolism*, Wang, Shi et al.[1] revealed in mouse embryonic stem (ES) cells that, beyond chromatin tethering, the nuclear lamina functions as a metabolic gatekeeper that controls the partition of cysteine flux into distinct epigenetic modifications, acetylation of histone H3 at lysine 9 and lysine 27 (H3K9ac and H3K27ac) and trimethylation of histone H3 at lysine 9 (H3K9me3), thereby driving the cell towards divergent fates. This mechanism extends to biological contexts from mouse embryos to ageing hearts.

Precise control of cell fates during differentiation requires dynamic orchestration of transcription factors, epigenetic modulators and metabolic enzymes[2,3]. Perturbation in any of these layers can disrupt this balance and cause diseases. Among these abnormalities, mutations in *LMNA*, the gene encoding lamin A/C, cause disorders that impair heart and muscle function and lead to premature ageing[4]. These effects have traditionally been attributed to detachment of chromatin from lamina-associated domains (LADs), triggering heterochromatin loss and gene derepression[5,6]. However, the paradox of why *LMNA* mutations cause premature lineage entry in some contexts but renewal failure or accelerated ageing in others remains[7–10].

Wang, Shi et al. began by characterizing the metabolic outcomes of *Lmna* deletion in mouse ES cells. Through multi-omics profiling of gene expression, chromatin accessibility and metabolite abundance, they uncovered greatly remodelled cysteine metabolism. Two metabolic enzymes are at the centre of this rewiring: cystathionine γ-lyase (CTH) and cystathionine β-synthase (CBS), encoded by *Cth* and *Cbs*, respectively.

Multiple lines of evidence in this study support the importance of the two metabolic genes in nuclear lamina-dependent cell fate control. First, lamin A/C directly binds to promoters of *Cth* and *Cbs*, suggesting direct regulatory input from the nuclear lamina. Second, both genes exhibit increased chromatin accessibility, transcript levels and protein abundance on loss of lamin A/C, indicating consistent changes across molecular layers. Third, their promoters are co-regulated by SP1 binding and PRC2-dependent H3K27me3, pointing to shared transcriptional and epigenetic control. Finally, a variety of lamina-dependent cell fate transitions and pathological states can be overridden by manipulating CBS or CTH, confirming their role as a central metabolic hub in lamina-dependent cell fate regulation.

The answer to why CTH and CBS are uniquely positioned to mediate lamina-dependent fate decisions lies in their location within the metabolic network. Cysteine metabolism is tightly coupled to the methionine cycle and the TCA cycle, with reactions catalysed by CBS and CTH bridging these pathways (Fig. 1a): CBS sits at the branch point, diverging flux from the methionine cycle, while CTH channels downstream flux towards pyruvate and the TCA cycle.

The methionine cycle and the TCA cycle are two major metabolic regulators of the epigenome[3]. *S*-adenosylmethionine (SAM) from the methionine cycle provides methyl groups for chromatin methylation, whereas acetyl-CoA produced from cysteine catabolism and entering the TCA cycle fuels chromatin acetylation. Therefore, CTH and CBS jointly channel metabolic flux between the generation of SAM and acetyl-CoA. Suppression of CTH and CBS shifts the epigenome towards SAM-dependent chromatin methylation, whereas their activation favours acetyl-CoA-dependent chromatin acetylation. Lamin A/C thus operates as an upstream organizer of cysteine flux, balancing these two epigenetic outputs, beyond its canonical role in maintaining nuclear structure.

To identify chromatin marks specifically altered by this metabolic rewiring, the authors characterized epigenomic changes upon manipulating lamin A/C or its downstream metabolic targets CBS and CTH. *Lmna* deletion reduced repressive H3K9me3, whereas the gain-of-function $Lmna^{G609G}$ mutation enhanced it in mouse ES cells. By contrast, H3K9ac and H3K27ac showed the opposite trend: enhanced cysteine flux upon loss of lamin A/C directly goes to H3K9ac and H3K27ac as demonstrated by ^{13}C tracing experiments.

The structural–metabolic–epigenetic mechanism uncovered here has wide developmental implications. During naive-to-primed transition, a key process in mammalian embryogenesis, downregulation of lamin A/C releases its inhibitory control of CTH and CBS, leading to increases in H3K9ac and H3K27ac and activation of lineage-specific genes. Loss of lamin A/C in mouse ES cells disrupts the timing of this epigenomic trajectory, leading to abnormal differentiation. Conversely, the $Lmna^{G609G}$ gain-of-function mutation shifts the metabolic–epigenomic balance towards H3K9me3, locking cardiomyocytes into a repressive chromatin state marked by H3K9me3 and impaired DNA repair, ultimately contributing to cell senescence.

A series of bidirectional rescue experiments further strengthen causality by showing that modulating CTH or CBS can redirect cell fate choices and phenotypic outcomes. Notably, the seemingly unrelated cell fates of differentiation and ageing converge at a shared metabolic checkpoint of cysteine metabolism, which toggles the epigenome between methylation-dominated and acetylation-dominated states. This highlights how diverse physiological and pathological outcomes can arise from a metabolic decision as simple as a binary switch.

Although CTH and CBS share regulatory logic and respond similarly to perturbation of lamin A/C, subtle differences in their behaviour reveal how local flux control[11,12] produces divergent downstream effects. Located at the entry of cysteine metabolism, CBS exerts stronger control over SAM availability and H3K9me3, making it a key metabolic checkpoint for H3K9me3-related ageing phenotypes.

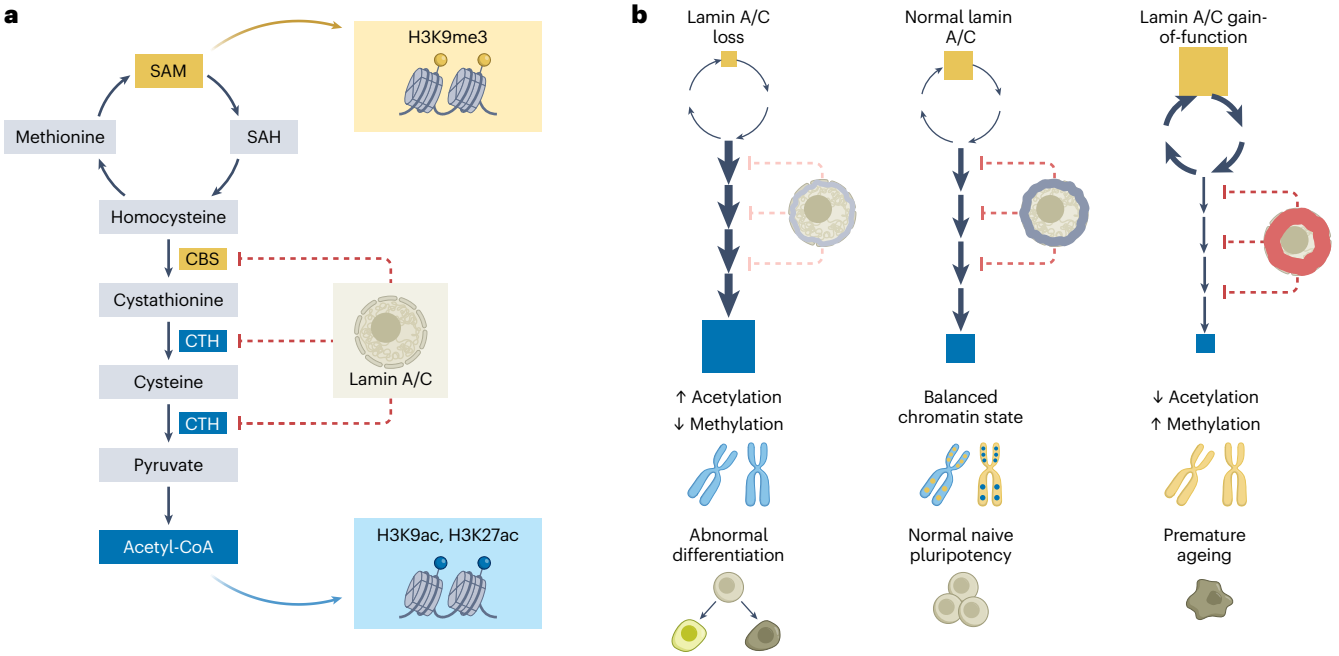

Fig. 1 | Cysteine metabolic flux controlled by lamin A/C establishes a binary decision of chromatin state that shapes cell fate. a, In mouse ES cells, lamin A/C suppresses the activity of CTH and CBS, the metabolic enzymes that position cysteine flux between SAM-dependent histone methylation and acetyl-CoA-dependent histone acetylation. SAH, *S*-adenosylhomocysteine. **b**, Effects of lamin A/C on cysteine metabolism, chromatin state and cell fate. Loss of lamin A/C in mouse ES cells diverts flux towards histone acetylation and causes abnormal differentiation; normal lamin A/C maintains a balanced chromatin state and naive pluripotency; and gain-of-function lamin A/C mutation increases histone methylation and promotes premature ageing in differentiated cells such as cardiomyocytes.

CTH, although less explored in this study, exerts stronger control over acetylation flux and differentiation, consistent with its downstream position in the pathway.

Together, these findings point to a hierarchical topology in the lamina–metabolic–epigenomic regulatory network: the nuclear lamina acts as a master regulator, and CTH and CBS serve as intermediate nodes translating structural inputs into metabolic decisions that rewrite chromatin codes through histone acetylation and methylation.

This work opens several intriguing questions regarding general principles underlying metabolic–epigenomic regulation of cell fate decisions. First, although CTH and CBS share similar functions, only *Cth* resides within the LAD and moves to the nuclear interior upon lamin A/C deficiency; *Cbs* does not. It remains unclear whether genomic location and nuclear positioning of metabolic genes, network topology and kinetics and thermodynamics of metabolic reactions are optimized for efficient information flow and precise control during cell fate decisions.

Second, the directionality of the information flow from nuclear architecture to metabolism, epigenome and cell fate raises the possibility of feedback control. Such feedback loops, long appreciated in systems biology, can give rise to diverse emergent behaviours such as multistability[13], but whether and how they operate in this context remains unexplored.

Finally, CTH and CBS represent only a small subset of metabolic enzymes capable of modifying the epigenome and influencing cell fate decisions. A major open question is how diverse metabolic inputs are integrated to achieve robust and precise control of cell fates, beyond case-by-case findings focusing on specific reactions, enzymes and metabolites. In this sense, while the present work operates within a reductionist experimental framework, its strikingly simple organizing principle that cysteine metabolism functions as a binary switch controlling cell fate points towards the possibility that complex metabolism–epigenome–fate regulation may emerge from a limited set of simple rules.

In summary, this study reveals a unifying mechanism in which three-dimensional genome organization, metabolism and chromatin state converge on a simple metabolic bottleneck. The work underscores the central role of metabolism in epigenetic regulation: not only does it integrate environmental inputs such as diet and microbiome, but it also captures intrinsic structural signals that govern differentiation, development and ageing.

Dan Huang & Ziwei Dai ✉
Department of Systems Biology, School of Life Sciences, Southern University of Science and Technology, Shenzhen, China.
✉e-mail: daizw@sustech.edu.cn

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References

1. Wang, Y. et al. *Nat. Metab.* https://doi.org/10.1038/s42255-025-01443-2 (2026).
2. Balsalobre, A. & Drouin, J. *Nat. Rev. Mol. Cell Biol.* **23**, 449–464 (2022).
3. Dai, Z., Ramesh, V. & Locasale, J. W. *Nat. Rev. Genet.* **21**, 737–753 (2020).
4. Worman, H. J. & Bonne, G. *Exp. Cell Res.* **313**, 2121–2133 (2007).
5. Kind, J. et al. *Cell* **153**, 178–192 (2013).
6. van Steensel, B. & Belmont, A. S. *Cell* **169**, 780–791 (2017).

7. Wang, Y. et al. *Nat. Commun.* **13**, 6663 (2022).
8. Swift, J. et al. *Science* **341**, 1240104 (2013).
9. Sun, L. et al. *Biomater. Res.* **29**, 0256 (2025).
10. Nath, S. et al. *Nucleic Acids Res.* **53**, gkaf615 (2025).
11. Dai, Z. & Locasale, J. W. *J. Biol. Chem.* **293**, 19725–19739 (2018).
12. Rapoport, T. A. *Interface Focus* **14**, 20230024 (2024).
13. Tyson, J. J., Chen, K. C. & Novak, B. *Curr. Opin. Cell Biol.* **15**, 221–231 (2003).

Competing interests

The authors declare no competing interests.