

Mitochondrial L-2-hydroxyglutarate: Rethinking metabolite repair as physiological signaling

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L-2-hydroxyglutarate (L-2-HG) has long been regarded primarily as a pathological and toxic metabolite whose abnormal accumulation is associated with L-2-hydroxyglutaric aciduria, mitochondrial dysfunction, hypoxic stress and cancer-associated metabolic states. The prevailing oncometabolite framework was established for D-2-HG in isocitrate dehydrogenase (*IDH*)-mutant cancers. Shaped by this framework, L-2-HG has often been interpreted as a metabolite-repair substrate whose accumulation reflects defective clearance by L-2-HG dehydrogenase (L2HGDH). However, a recent study by Chakrabarty *et al.* published in *Nature* (2026) represents a paradigm-shifting contribution to the fields of mitochondrial metabolism and epigenetic regulation, as it systematically challenges this traditional view and demonstrates that mitochondrially localized L-2-HG is not merely a metabolic waste product but a *bona fide* physiological signaling metabolite that meets three stringent criteria: (i) regulated steady-state levels, (ii) defined molecular targets, and (iii) measurable physiological function.¹ The work extends the concept of mitochondria as signaling organelles and invites reconsideration of low-abundance metabolites previously dismissed as metabolic noise.²

The first major achievement of this study is the meticulous elucidation of the enzymatic regulation of L-2-HG levels. The authors demonstrate that an increase in the mitochondrial NADH/NAD⁺ ratio drives malate dehydrogenase 2 (MDH2) — a TCA cycle enzyme — to catalyze the NADH-dependent reduction of 2-oxoglutarate (2-OG) to L-2-HG. This illustrates how enzyme promiscuity can become functionally relevant under reductive stress. Equally important is the demonstration that L2HGDH oxidizes L-2-HG back to 2-OG in the mitochondrial matrix independently of a functional electron transport chain (ETC). This finding uncouples L-2-HG clearance from oxidative phosphorylation and suggests that the L-2-HG/L2HGDH axis can remain active during respiratory impairment, although the relevant electron acceptor remains unresolved. CoQ, cytochrome c, fumarate and molecular oxygen were individually tested and were not required, suggesting either redundant acceptors or an alternative unidentified acceptor.¹ Together, MDH2-dependent production and L2HGDH-mediated clearance form a redox-sensitive production–clearance module that tunes mitochondrial L-2-HG abundance (Figure 1). This regulatory architecture complements previous observations in LPS-activated macrophages, where transcriptional repression of *L2HGDH* promotes L-2-HG accumulation, suggesting that both acute redox-dependent and slower transcriptional mechanisms can tune L-2-HG levels.³

The second major advance is the use of proteome integral solubility alteration (PISA) profiling in mESC nuclear extracts to identify L-2-HG-responsive proteins through treatment-associated changes in protein stability and solubility. This methodology identified the KDM4 family of histone demethylases, which catalyze removal of the repressive H3K9me3 mark in an α -ketoglutarate-dependent manner, as candidate L-2-HG-responsive nuclear proteins. The data therefore imply communication between mitochondrial L-2-HG metabolism and the nuclear metabolite pool; however, the specific route by which L-2-HG reaches the nuclear compartment was not defined and remains an open mechanistic question.¹ This finding is mechanistically elegant: L-2-HG, structurally analogous to 2-OG, acts as a competitive inhibitor of KDM4 demethylases, thereby favoring the retention or accumulation of H3K9me3 at specific genomic loci. In mouse embryonic stem cells (mESCs), elevated L-2-HG repressed the nascent transcription of specific genes and increased H3K9me3 at corresponding loci, supporting a mechanistic link between metabolite abundance, chromatin regulation and tran-

scriptional output. However, PISA does not establish direct binding and used 100 μ M and 1 mM L-2-HG. Reported *IC*₅₀ values for KDM4A and KDM4C are 26 $\pm$ 3 μ M and 97 $\pm$ 24 μ M, respectively, indicating that the lower PISA concentration overlaps the inhibitory range; nevertheless, direct quantitative matching between *in vivo* nuclear L-2-HG levels and KDM4 engagement remains incomplete.¹

The third and most compelling line of evidence comes from the *in vivo* experiments, which provide the physiological function demanded by the third criterion. The authors engineered mice with early embryonic *L2HGDH* overexpression, which systemically reduces L-2-HG levels. These animals exhibited impaired postnatal growth, elevated mortality and selective renal vulnerability. Other tissues, including heart, liver, lung, brain and testis, were examined histologically without comparable overt pathology; liver RNA-seq showed minimal ISR activation, whereas detailed H3K9me3/*L1MdTf* profiling outside the kidney was not reported.¹ In postnatal kidneys of *L2HGDH*-overexpressing mice, reduced L-2-HG was associated with loss of H3K9me3 at *L1MdTf* retrotransposons and increased *L1MdTf* transcription. This retrotransposon derepression coincided with activation of the integrated stress response (ISR) and inflammatory pathways, supporting a possible link between L-2-HG depletion, transposable-element dysregulation and tissue pathology. These findings suggest that physiological L-2-HG contributes to H3K9me3-mediated retrotransposon silencing in the kidney, whereas its depletion is associated with innate immune activation and cellular stress.

The broader innovation of this study lies not merely in identifying L-2-HG-responsive proteins, but in redefining the physiological significance of low-abundance metabolites. The study suggests that metabolite function cannot be categorized as simply harmful or beneficial, but depends on concentration, tissue context, subcellular localization and developmental stage. Although D-2-HG and L-2-HG are stereoisomers that can both influence 2-OG-dependent dioxygenases, their dominant biological contexts differ. D-2-HG is classically framed as an oncometabolite in *IDH*-mutant cancers, whereas the present study shows that L-2-HG can be produced by MDH2 under mitochondrial reductive stress and maintained at low basal levels with homeostatic signaling functions. In immunology, L-2-HG has been shown to regulate macrophage activation and promote epigenetic reprogramming of exhausted T cells.^{3,4} In parallel, our previous work showed that D2HGDH-mediated D-2-HG catabolism enhanced CAR-T-cell activity in an immunosuppressive microenvironment,⁵ highlighting the context- and enantiomer-specific effects of 2-HG metabolism. This study suggests that these immunological effects may represent specific adaptations of fundamental signaling mechanisms rather than pathological abnormalities. Importantly, lowering basal L-2-HG did not markedly alter pluripotency-associated gene expression or multilineage differentiation in mESCs, arguing against a universal requirement for L-2-HG in stem-cell fate.^{1,2} If intervention strategies targeting L-2-HG or *L2HGDH* are developed in the future, tissue specificity, developmental stage, and mitochondrial stress context must be taken into account. Similar issues may also exist with metabolic signaling molecules such as D-2-HG, succinate, fumarate, and lactate.

Despite the breadth of the study, several causal questions remain unresolved. First, the tissue specificity of the *L2HGDH*-overexpression phenotype — with the kidney being disproportionately affected — suggests that L-2-HG's physiological functions may be highly context-dependent, raising questions about the relative importance of L-2-HG signaling in other organs and developmental stages. Second, the relative contribution of KDM4 inhibition

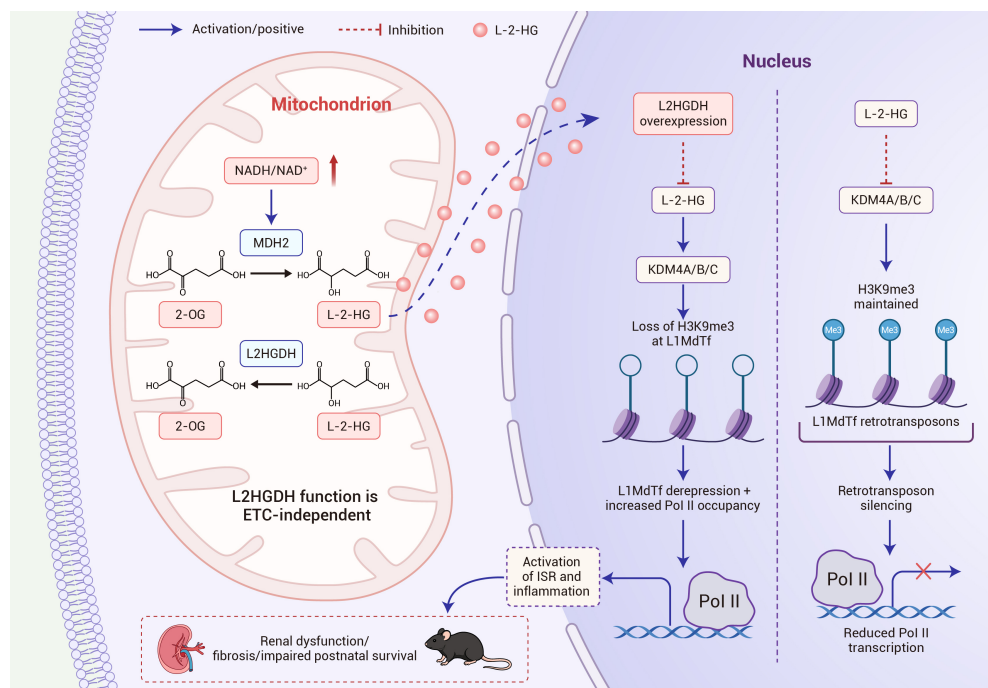


Figure 1. Schematic model of mitochondrial L-2-HG as a physiological signaling metabolite An increased mitochondrial NADH/NAD⁺ ratio promotes MDH2-dependent conversion of 2-OG to L-2-HG, whereas L2HGDH oxidizes L-2-HG back to 2-OG independently of an intact electron transport chain. Physiological L-2-HG restrains KDM4A/B/C activity, thereby maintaining H3K9me3-mediated silencing of *L1MdTf* retrotransposons. *L2HGDH* overexpression depletes L-2-HG, leading to KDM4 disinhibition, H3K9me3 loss, *L1MdTf* derepression, increased RNA polymerase II occupancy, and activation of stress and inflammatory pathways associated with renal dysfunction, fibrosis, and impaired postnatal survival.

homeostatic regulatory process from simple detoxification.

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versus other potential L-2-HG targets (such as the HIF prolyl hydroxylases implicated in macrophage activation) remains to be systematically dissected across different biological settings. Third, the relationship between physiological L-2-HG signaling and pathological L-2-HG accumulation in L-2-hydroxyglutaric aciduria requires further exploration: at what concentration threshold does a physiological signal become a pathological insult, and can this threshold be modulated therapeutically? Clinical L-2-hydroxyglutaric aciduria represents marked pathological L-2-HG accumulation, whereas the *L2HGDH*-overexpression model interrogates the opposite perturbation—depletion below basal levels—so the present data do not define the concentration threshold separating physiological signaling from toxicity.¹ Finally, the role of L-2-HG in retrotransposon silencing in the kidney raises the broader question of whether other tissues employ similar metabolite-epigenome-transposable element axes for maintaining genomic stability, and whether dysregulation of this axis contributes to age-related inflammatory pathologies.

In summary, Chakrabarty *et al.* provide a new framework for understanding L-2-HG biology. Their study establishes mitochondrial L-2-HG as a regulated signaling metabolite that links mitochondrial redox state to chromatin regulation, retrotransposon silencing and postnatal renal homeostasis. By constraining KDM4 family demethylases, physiological L-2-HG may help maintain H3K9me3-mediated repression, particularly at *L1MdTf* retrotransposons in the kidney. Conversely, excessive L-2-HG depletion leads to H3K9me3 loss, retrotransposon derepression, activation of the integrated stress response and inflammatory pathways, and ultimately renal dysfunction and fibrosis. The broader lesson from this study is that metabolite repair should be viewed not simply as detoxification, but as quantitative control of signaling metabolites within a context-dependent physiological window. Defining when, where, and at what levels L-2-HG functions as a physiological signal will therefore be essential for distinguishing metabolite repair as a

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AUTHOR CONTRIBUTIONS

Dingyuan Bai: Data curation, Methodology, Investigation, Writing – original draft, Formal analysis, Validation. Yuxuan Zhou: Data curation, Formal analysis, Software, Validation, Investigation. Quanjun Yang: Methodology, Supervision, Project administration, Conceptualization, Writing – original draft, Funding acquisition. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Not applicable.