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When tRNA mischarging becomes a metabolic brake on translation

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LACTATE ENTERS THE tRNA-CHARGING PATHWAY

The role of lactate in tumor metabolism has changed considerably over the years. It was long regarded mainly as an end product of glycolysis, but is now known to re-enter oxidative metabolism as a carbon source and to participate in metabolic coupling between tumor cells. The discovery of histone lactylation further showed that lactate can influence chromatin state and gene expression. Alanyl-tRNA synthetase 1 (AARS1) was subsequently identified as a lactate-sensing enzyme that generates lactyl-adenylate (lactyl-AMP), which can serve as a lactyl donor for protein lactylation.[1] Previous regulatory roles of lactate have centered largely on metabolism, signaling, or protein modification. Wang et al. extend this view to protein translation itself.[2] When intracellular lactate accumulates to excessive levels, AARS1 can use lactate to generate lactyl-AMP and subsequently form lactyl-tRNAs, which interfere with translation elongation. The key point is not simply the identification of another type of lactylated molecule. Rather, lactate can enter the tRNA-charging system for translation directly, without first being relayed through classical signaling pathways. This suggests that the connection between metabolism and the central dogma may be more direct.

The authors establish this mechanism through a relatively compact but convincing set of experiments. Increasing intracellular lactate rapidly suppresses protein synthesis, whereas reducing lactate production or promoting its clearance restores translation. At this early stage, the authors did not observe corresponding changes in AMPK, p38, eukaryotic initiation factor 2α (eIF2α), or mTOR-related translation-initiation signaling. Lactate also suppresses protein synthesis in a cell-free translation system. At the biochemical level, lactyl-adenosine was detected after RNase digestion of charged tRNAs, and recombinant AARS1 was shown to catalyze lactate-dependent tRNA charging. Disrupting the lactate-binding capacity of AARS1 markedly reduced this activity. Compared with normal alanine charging, transfer of lactyl-AMP to tRNA is slower. This kinetic difference allows lactyl-AMP to persist longer and, once formed, to acylate non-cognate tRNAs more broadly (Figure 1A). The resulting lactyl-tRNAs can still interact with eukaryotic elongation factor 1A (eEF1A), but lactate lacks the α-amino group required for peptide-bond formation and therefore cannot support normal elongation. In vitro-generated lactyl-tRNAs also directly suppress protein synthesis. The consequence is a tRNA species that is chemically charged and still recognized by the elongation machinery, yet cannot support productive peptide-bond formation. This "charged but nonproductive" state is central to the broader significance of the study.

WHEN MISCHARGING BECOMES REGULATION

We view lactyl-tRNA as more than an unusual modification product: it represents a metabolically induced, nonproductive tRNA state. Unlike canonical nutrient-sensing pathways, which relay metabolic information through signaling cascades, lactate-dependent charging changes the translation substrate itself. This places metabolic control directly at the level of tRNA chemistry. This mechanism can therefore be viewed as a form of "substrate-level metabolic regulation."

This study also complicates the conventional view of aminoacyl-tRNA synthetase (aaRS) fidelity. aaRSs are generally considered central to maintaining the accuracy of tRNA charging, and cells have evolved proofreading mechanisms to limit mischarging. However, lactyl-tRNA that would normally be classified as an error is not completely eliminated and instead produces a functional consequence when lactate accumulates. Because lactyl transfer is slower than alanyl transfer, non-cognate tRNAs become more accessible substrates. In other words, tRNA mischarging is not simply biochemical noise; it becomes a metabolically conditional form of regulation.

The clearest conceptual result of this study is that there may be a divergence between the charging state and translation competence of tRNA. Uncharged tRNAs cannot support elongation, whereas correctly aminoacylated tRNAs are both delivery- and reaction-competent. Lactyl-tRNA occupies a third state: it is chemically charged and can engage the elongation machinery, but it cannot complete productive peptide-bond formation (Figure 1B). This leads to an important distinction: being charged does not necessarily equal translation competence.

This distinction becomes especially relevant during amino-acid deprivation. In mammalian cells, amino-acid deprivation does not necessarily produce global tRNA uncharging; selective deacylation of particular tRNA species, including $tRNA^{Gln}$, can occur. Moreover, general control nonderepressible 2 (GCN2) activation can also involve ribosome-associated mechanisms, including stalled ribosomes and the ribosomal P-stalk. In the setting examined by Wang et al., blocking lactate efflux attenuated the starvation-induced decrease in the measured charged-tRNA fraction and weakened GCN2–eIF2α signaling. Because the relevant tRNA species were not resolved, these observations are best interpreted as evidence that lactyl-tRNA perturbs the upstream translational-stress signal available to GCN2, rather than simply preventing global accumulation of uncharged tRNAs. Importantly, the attenuated GCN2 response was accompanied by poorer recovery of protein synthesis and cell proliferation after nutrient restoration, consistent with impaired stress adaptation rather than accelerated recovery. Lactyl-tRNA may thus not only interfere with elongation, but also distort how cells sense their own translational stress. At present, this effect on stress sensing has been demonstrated mainly in the context of amino-acid deprivation and should not be generalized to all forms of cellular stress.

WHEN LACTATE PRODUCTION OUTPACES CLEARANCE

Placing this mechanism back into the context of tumor metabolism raises an apparent contradiction that deserves further consideration. Lactate-induced translation repression seems to conflict with the growth advantage associated with the Warburg effect, but the issue becomes clearer once high glycolytic flux is distinguished from excessive intracellular lactate accumulation. Tumor cells can benefit from rapid glycolysis while limiting intracellular lactate accumulation through lactate export, intercellular exchange, or oxidative utilization. Wang et al. found that translation was already markedly suppressed at an early stage after monocarboxylate transporter (MCT) inhibition, whereas glucose uptake and glycolytic flux were not reduced to a similar extent. This argues against the idea that translation repression is merely a secondary consequence of impaired glycolysis. To reconcile this apparent paradox, we propose a production-clearance balance framework: as long as lactate production can be matched by export or oxidative utilization, high glycolytic activity may continue to support tumor growth. Once production exceeds clearance, intracellular lactate may reach a level sufficient to promote AARS1-dependent noncanonical tRNA charging and thereby restrict translation (Figure 1C). In this framework, the AARS1–lactyl-tRNA axis can be viewed as a feedback restraint imposed by excessive glycolytic output on downstream biosynthetic capacity, rather than as a direct inhibitor of the Warburg effect itself. Within our production-clearance balance framework, MCT1/4 may therefore do more than maintain lactate homeostasis: by

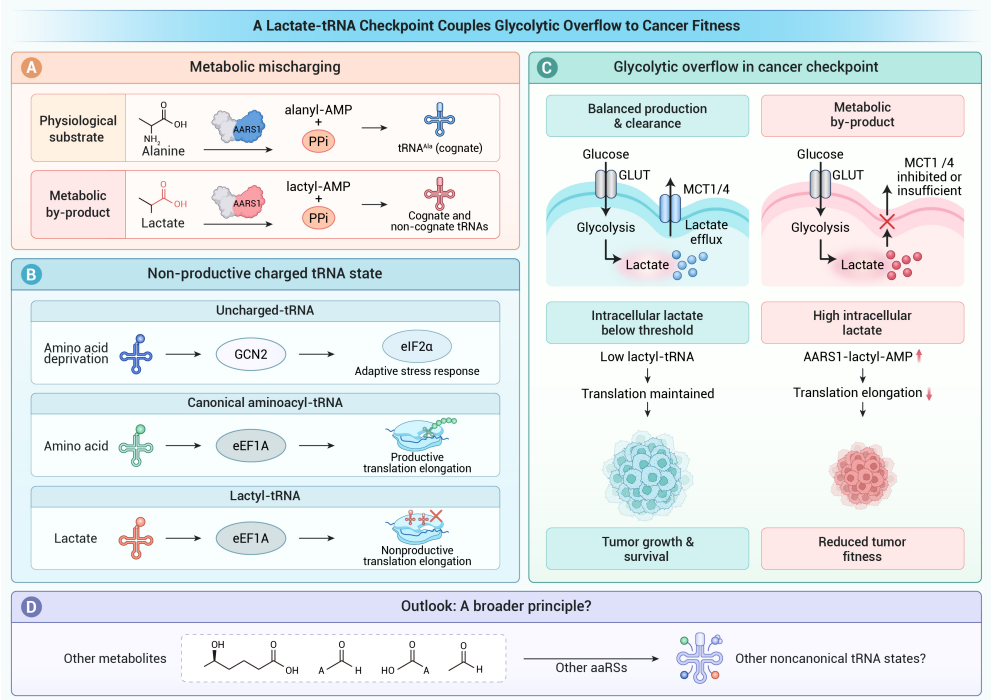


Figure 1. Lactate-dependent tRNA mischarging links glycolytic overflow to translational control (A) AARS1 canonically charges $tRNA^{Ala}$ with alanine, whereas excess intracellular lactate can be converted to lactyl-AMP and transferred to cognate and non-cognate tRNAs, generating lactyl-tRNAs with reduced charging fidelity. (B) Lactyl-tRNA represents a charged but translationally nonproductive tRNA state, uncoupling tRNA charging status from translational competence. During amino-acid deprivation, lactyl-tRNA accumulation may alter the tRNA-derived stress signal available to GCN2 and thereby attenuate GCN2–eIF2α signaling. (C) We propose a production–clearance framework in which efficient lactate clearance preserves translation, whereas glycolytic overflow or impaired MCT1/4-mediated export promotes lactate accumulation, lactyl-tRNA formation, and translational repression. (D) Outlook: Lactyl-tRNA represents a distinct aaRS-based form of metabolite-sensitive tRNA regulation, raising the possibility that other endogenous metabolites may similarly generate noncanonical tRNA states.

preventing excessive intracellular lactate accumulation, they may help preserve translational capacity and allow tumor cells to evade this brake.

Several questions will determine how broadly this model applies. The abundance and tRNA selectivity of lactyl-tRNA in intact tumors remain to be quantified. It is also unclear whether this pathway is mainly a consequence of pathological lactate overload or whether it contributes to translation control during physiological states such as transient hypoxia, exercise, inflammation, or nutrient fluctuation. Another important question is how AARS1-generated lactyl-AMP is partitioned between protein lactylation and tRNA charging. AARS1-mediated lactylation of p53 and YAP–TEAD has been linked to tumor-promoting programs,[1,3] whereas lactyl-tRNA formation under lactate excess represses translation.[2] This divergence suggests that the lactate–AARS1 axis may depend not only on lactate abundance but also on AARS1 localization, substrate accessibility, competing acceptors, and lactyl-AMP transfer kinetics. Defining this partitioning may reveal therapeutic opportunities beyond MCT blockade. How lactyl-tRNAs are proofread and handled by the ribosome will also require more direct biochemical and structural resolution.

TRAPPING LACTATE, AND LOOKING BEYOND IT

The production–clearance balance framework also reinforces the therapeutic explanation for MCT inhibition. In the EO771 breast cancer model, the combined inhibition of MCT1/4 increases intracellular lactate, reduces protein synthesis and ribosomal-protein levels, and markedly restricts tumor progression. However, the entire antitumor effect cannot yet be attributed to lactyl-tRNA, as MCT inhibition also affects redox balance, lactate exchange, and the tumor microenvironment. A direct quantitative relationship between MCT inhibition, accumulation of specific lactyl-tRNA species, translation suppression, and tumor inhibition therefore remains to be established in tumor tissue. Even so, the study provides a plausible therapeutic interpretation: blocking lactate export may force highly glycolytic tumors to bear the cost of their own metabolic output, converting lactate that would otherwise be cleared into a burden on translation.

The broader question is whether lactate is exceptional. Metabolic state is already known to reshape tRNA function and translational fidelity through other routes: tryptophan depletion can drive tryptophanyl-tRNA synthetase 1 (WARS1)-dependent tryptophan-to-phenylalanine substitution,[4] whereas the microbiome metabolites preQ1 and queuine can compete for host tRNA modification and alter translation quality control.[5] Lactyl-tRNA is mechanistically distinct from these precedents because an endogenous central-carbon metabolite directly enters aaRS-mediated tRNA charging and places a noncanonical lactyl group on the tRNA 3′ end in a defined tumor-metabolic context. This raises the broader possibility that other metabolites may similarly exploit aaRS chemistry to generate noncanonical, translationally nonproductive tRNA states (Figure 1D). The lasting implication would then be that tRNA charging is not metabolically insulated: metabolite availability can alter the chemistry, and therefore the functional competence, of the substrates used for translation.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used Generative AI tools to assist with language editing and improving readability. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

REFERENCES

1. Zong Z., Xie F., Wang S., et al. (2024). Alanyl-tRNA synthetase, AARS1, is a lactate sensor and lactyltransferase that lactylates p53 and contributes to tumorigenesis. *Cell* **187**:2375–2392.e33. DOI:10.1016/j.cell.2024.04.002
2. Wang X., Lin C., Zhang Y., et al. (2026). Excess intracellular lactate represses mRNA translation and tumor progression through lactate-tRNA charging. *Mol. Cell* **86**:3529–3544.e9. DOI:10.1016/j.molcel.2026.07.026
3. Ju J., Zhang H., Lin M., et al. (2024). The alanyl-tRNA synthetase AARS1 moonlights as a lactyltransferase to promote YAP signaling in gastric cancer. *J. Clin. Invest.* **134**:e174587. DOI:10.1172/jci174587
4. Pataskar A., Champagne J., Nagel R., et al. (2022). Tryptophan depletion results in tryptophan-to-phenylalanine substitutants. *Nature* **603**:721–727. DOI:10.1038/s41586-022-04499-2
5. Zhang W., Lahry K., Cipurko D., et al. (2025). Two microbiome metabolites compete for tRNA modification to impact mammalian cell proliferation and translation quality control. *Nat. Cell Biol.* **27**:1812–1826. DOI:10.1038/s41556-025-01750-6

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AUTHOR CONTRIBUTIONS

X.X.Z. conceived the central idea of the Editorial and provided overall conceptual guidance. C.Z., X.X.Z., and X.Y. jointly developed the conceptual framework. C.Z. drafted the manuscript. S.S. prepared the figure. H.D., X.Y. and D.C. reviewed and edited the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.