

Lactate-pyruvate routing separates mitochondrial fuel signaling from exercise-performance claims

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Abstract

Background: Lactate and pyruvate are often described as exercise metabolites, mitochondrial fuels, and signaling molecules. Recent skeletal-muscle studies make that description more precise but also narrower: transporter context, substrate abundance, and training state determine whether the observed endpoint is TCA-cycle routing, mitochondrial biogenesis, epigenomic remodeling, or whole-performance change.

Objective: This working paper defines an evidence-bounded lactate-pyruvate routing model for skeletal-muscle mitochondrial adaptation and separates fuel-signaling claims from exercise-performance or treatment claims.

Methods: PubMed and PubMed Central were searched on 2026-10-05 for primary studies linking lactate, pyruvate, monocarboxylate transporters, high-intensity interval training, PGC-1 α , mitochondrial biogenesis, TCA flux, respiration, substrate use, or skeletal-muscle performance. Ten primary records were coded by organism, perturbation, endpoint class, timing, support lane, and claim boundary. Endpoint classes included skeletal muscle molecular, morphology, function, and clinical performance. No pooled estimate was calculated because the evidence mixed human biopsy time courses, mouse transporter or obesity models, and C2C12 exposure systems.

Results: Seven coded records supported a mitochondrial routing claim, one was mixed, and two were constraint records. Lactate/MCT evidence supported transporter-sensitive effects on mitochondrial proteins, TCA flux, respiration, fatty-acid oxidation, and multi-omics adaptation [1-3]. Human interval-training studies supported mitochondrial-biogenesis signaling and performance adaptation after acute or repeated exercise but did not isolate lactate as sufficient [4-6,10]. Pyruvate cell studies supported substrate-linked mitochondrial remodeling while warning that respiratory-chain content can dissociate from substrate use and PGC-1 α directionality [8,9]. The clearest discriminating test is therefore not whether lactate rises after exercise, but whether matched transporter state and carbon-entry measurements separate molecular adaptation from performance sufficiency.

Conclusions: The public claim supported by the evidence is that lactate-pyruvate routing can participate in skeletal-muscle mitochondrial fuel signaling and adaptation. The evidence does not support lactate supplementation, pyruvate exposure, or a single transporter marker as a stand-alone performance intervention, disease treatment, or clinical prescription rule.

Keywords: skeletal muscle; lactate; pyruvate; mitochondrial biogenesis; TCA flux; high-intensity interval training

1 Introduction

Skeletal muscle adapts to exercise through repeated changes in energy demand, redox state, calcium signaling, substrate flux, transcriptional control, and mitochondrial turnover. Lactate and pyruvate sit at the center of this network because they report glycolytic flux, feed or modulate mitochondrial carbon entry, and influence cytosolic redox balance. A translation problem follows: a molecule that participates in adaptation is not automatically sufficient to reproduce exercise.

The research question emphasized fuel inputs, oxidative phosphorylation, TCA-cycle routing, mitochondrial biogenesis, and exercise adaptation. It was narrowed into a public evidence question: which parts of lactate-pyruvate skeletal-muscle evidence support a mitochondrial routing model, and which claims exceed the primary data?

The competing interpretation constrained here is a simple metabolite-addition model, in which adding lactate or pyruvate is assumed to reproduce exercise-induced mitochondrial adaptation or improve performance. The alternative model evaluated in this paper is context dependent. Lactate-pyruvate routing may be necessary or supportive for some molecular adaptations while remaining insufficient for performance or clinical benefit unless training dose, transporter state, tissue state, and endpoint are directly measured.

2 Methods

The search date was 2026-10-05. PubMed and PubMed Central searches used combinations of lactate, pyruvate, monocarboxylate transporter, MCT1, MCT2, skeletal muscle, TCA flux, mitochondrial biogenesis, respiration, high-intensity interval training, PGC-1alpha, SIRT1, AMPK, and substrate utilization. Eligible records were primary studies in human skeletal muscle, mammalian skeletal muscle, or skeletal-muscle cell systems that measured lactate, pyruvate, transporter, exercise, TCA-cycle, mitochondrial-biogenesis, respiration, substrate-use, or performance endpoints. Reviews, non-muscle papers, commentaries, and papers without mitochondrial or substrate-routing endpoints were excluded from coding. PMID, DOI where available, organism, design, endpoint class, and abstract-level findings were checked against PubMed or PubMed Central metadata before inclusion.

Each source was coded into the accompanying evidence table by citation key, design, perturbation, endpoint class, timing, observed evidence, interpretive limitation, and support lane. Endpoint level followed the exercise and muscle guidance where applicable: blood proxy, skeletal muscle molecular, morphology, function, and clinical performance. Timing was coded as baseline, acute response, training adaptation, disease model, or cell exposure. A record was supportive when it directly supported lactate-pyruvate routing or exercise-linked mitochondrial adaptation, mixed when it supported molecular routing while limiting performance sufficiency, and constraint when it narrowed a stronger interpretation.

Two accounts were compared under the same claim boundary. The metabolite-addition account predicts that adding lactate or pyruvate should reproduce the relevant exercise adaptation, including performance, when substrate is available. The routing account predicts a narrower pattern: transporter state, carbon entry, and training context should modify molecular mitochondrial endpoints, while performance remains dependent on the broader exercise program. Evidence was treated as discriminating only when it separated those predictions through transporter perturbation, substrate-routing endpoints, timing, or a mismatch between mitochondrial markers and functional substrate use. A contrary result would weaken the routing model if lactate or pyruvate alone reproduced exercise performance with matched transporter and training controls, or if transporter perturbation failed to change

TCA flux, respiration, or adaptation despite verified exposure.

Counts were computed from the coded evidence table. Sensitivity checks were labeled by role. The cell-only pyruvate exclusion was a robustness check; the transporter-inhibition exclusion was decision-changing because it altered whether lactate flux could be framed as necessary; the human-only restriction was exploratory because it preserved exercise adaptation while removing mechanistic lactate isolation. Figure source data, evidence coding, public explainer copy, manuscript source, generated figures, geometry measurements, QA records, and build reports accompany the bundle. No identifiable patient data were used.

3 Results

3.1 Evidence synthesis

Transporter and substrate-routing evidence formed the first result step. The first coding step separated transporter-mediated lactate flux from generic metabolite availability. In the MCT1 skeletal-muscle study, lactate transport was tied to PGC-1alpha, NAD⁺/SIRT1 activity, mitochondrial proteins, cell respiration, mitochondrial activity, TCA routing, and running phenotype in mice [1]. In high-fat-diet mice, post-exercise lactate promoted fatty-acid oxidation, TCA-cycle activity, mitochondrial oxygen consumption, and lower skeletal-muscle triglyceride content [2]. These records support lactate as a mitochondrial-routing input in skeletal muscle, especially when transporter state and substrate abundance are measured.

Exercise-biogenesis timing evidence formed the second result step. Human interval-training and exercise-biopsy studies supplied the exercise-adaptation lane. Two weeks of low-volume high-intensity interval training increased time-trial performance, citrate synthase and cytochrome c oxidase activity, mitochondrial proteins, Tfam, nuclear PGC-1alpha, SIRT1, glycogen, and GLUT4 in a small cohort of healthy men [4]. A single all-out interval session increased p38/AMPK signaling, nuclear PGC-1alpha after recovery, mitochondrial-gene mRNA, and later mitochondrial protein or enzyme markers [5]. Foundational human and training-time-course studies showed transient PGC-1alpha transcriptional bursts and repeated mRNA responses before protein-level adaptation [6,10].

The multi-omics HIIT/lactate study added a claim boundary. Exogenous lactate and HIIT produced overlapping methylome and transcriptome remodeling, and MCT1/2 inhibition blunted exercise-linked molecular adaptation [3]. However, chronic lactate alone did not reproduce the running-performance benefit. The evidence therefore supports lactate flux as relevant, and possibly necessary in that model, but not sufficient for the full exercise phenotype.

These data locate mitochondrial adaptation in a repeated exercise context. They do not prove that lactate is the sole mediator. The appropriate endpoint-level wording is therefore training-linked molecular and performance adaptation, with lactate-pyruvate routing treated as a mechanistic participant rather than a complete replacement for exercise.

Pyruvate constraint evidence formed the third result step. The pyruvate studies prevented overstatement in the opposite direction. In C2C12 and primary myoblast models, pyruvate increased mitochondrial protein expression, basal respiration, and maximal oxidative capacity without requiring PGC-1alpha [8]. In myotubes, however, high pyruvate increased respiratory-chain content while suppressing PGC1alpha, glucose uptake, palmitate uptake, and oxidation; dichloroacetate and glutamine shifted parts of the phenotype [9]. Rodent exercise-timing evidence also indicated that early mitochondrial-biogenesis markers can precede increases in PGC-1alpha protein, consistent with activation or timing effects rather than a single expression readout [7].

The synthesis consequence is direct. Pyruvate can be a mitochondrial remodeling input in skeletal-muscle cells, but respiratory-chain content alone is not interchangeable with improved substrate use. PGC-1alpha directionality also cannot be interpreted without timing and context.

3.2 Evidence-coded sensitivity analysis

The synthesis was robust to excluding cell-only pyruvate records [8,9] for the broad lactate/HIT routing claim because transporter, mouse, and human exercise records still supported mitochondrial adaptation [1-6,10]. The synthesis was decision-changing when transporter-inhibition evidence was excluded: without MCT1/MCT2 perturbation evidence, lactate could be described as associated with exercise-like molecular changes but not as a tested flux requirement [1,3]. The human-only restriction was exploratory and more conservative; it supported exercise-induced mitochondrial adaptation but could not isolate lactate-pyruvate routing as causal [4-6,10].

4 Discussion

The evidence supports a routing model rather than a metabolite-addition model. Lactate and pyruvate connect glycolytic flux to mitochondrial carbon handling, redox-linked signaling, and transcriptional adaptation, but their interpretation depends on transporter state, dose, tissue state, and endpoint. Lactate/MCT studies provide mechanistic leverage in mice and multi-omics intervention settings [1-3]. Human exercise studies demonstrate mitochondrial adaptation and performance change in response to interval training, but do not isolate lactate as sufficient [4-6,10].

The concept figure summarizes this boundary. Exercise produces a metabolite pulse, transport and substrate entry shape cellular context, signaling integration links to mitochondrial endpoints, and a claim ceiling prevents a molecular result from becoming a treatment or performance claim. Solid links denote observed evidence classes. Dashed links denote hypotheses about responder stratification by transporter context, baseline mitochondrial state, and exercise dose.

This framing also clarifies why pyruvate evidence is useful. Pyruvate-induced biogenesis in myoblasts supports

substrate-sensitive mitochondrial remodeling [8], whereas pyruvate-induced suppression of substrate utilization in myotubes shows that more mitochondrial protein content does not automatically mean better metabolic function [9]. That contrast is a practical warning for public communication about mitochondrial boosters.

The research decision changed by this synthesis is modest but concrete. Future validation should pair lactate/pyruvate exposure or training with transporter measurement, TCA or substrate-flux readouts, respiratory function, and a performance endpoint in the same biological scope. A null transporter interaction would argue against routing necessity; a molecular-only effect without performance improvement would support the claim ceiling; and a performance effect without transporter or flux dependence would favor the simpler metabolite-addition account.

5 Limitations

This working paper is a claim-bounded evidence synthesis rather than a registered systematic review. Searches were current and source-verified, but screening was not exhaustive across every

exercise-metabolism database. The coded evidence included human, mouse, and cell systems, so no pooled effect estimate was appropriate. Some sources used young male participants or male mice, limiting sex- and age-specific inference. Several mechanistic papers used high-dose or genetic perturbations that are not direct analogues of ordinary exercise or supplementation. No patient-level data were reanalyzed.

6 Conclusions

Current primary evidence supports lactate-pyruvate routing as a skeletal-muscle mitochondrial fuel-signaling axis. The strongest public claim is that lactate and pyruvate participate in context-dependent mitochondrial adaptation through transporter-sensitive flux, TCA routing, respiration, transcriptional/epigenomic signaling, and exercise-biogenesis timing. The evidence does not support stand-alone lactate or pyruvate supplementation claims, clinical treatment claims, or single-marker performance prescription.

Table 1. Primary-study evidence matrix with endpoint class, timing, support lane, and claim boundary.

ID	Model and perturbation	Key finding	Interpretive limitation
[1]	Skeletal-muscle MCT1 deletion and metabolic-flux analysis in mice; MCT1 loss; lactate/TCA flux tracing	MCT1-linked lactate transport modulated PGC-1alpha, NAD+/SIRT1 activity, mitochondrial proteins, respiration, TCA routing, and running phenotype.	Mechanistic mouse evidence; transporter loss is not equivalent to lactate dosing or human training efficacy.
[2]	High-fat-diet obese mice; Post-exercise lactate administration	Lactate promoted skeletal-muscle fatty-acid oxidation, TCA-cycle activity, mitochondrial oxygen consumption, and lower muscle triglyceride content.	Mouse obesity model; does not establish human weight-loss or performance benefit.
[3]	Young male mice with HIIT, lactate administration, and MCT1/2 inhibition; Six-week HIIT, lactate dosing, transporter blockade	Lactate and HIIT remodeled methylome/transcriptome features; MCT1/2 inhibition blunted HIIT molecular adaptation, while lactate alone did not improve running performance.	Integrated omics supports necessity of lactate flux for molecular adaptation, not sufficiency for whole-performance gains.
[4]	Seven healthy men; Two weeks of low-volume high-intensity interval training	Training increased time-trial performance, citrate synthase and COX activity, mitochondrial proteins, Tfam, nuclear PGC-1alpha, SIRT1, glycogen, and GLUT4.	Small young male cohort; lactate was not isolated as the causal input.
[5]	Eight healthy men; Single low-volume all-out interval session	Acute HIT increased p38/AMPK signaling, nuclear PGC-1alpha at 3 h, mitochondrial-gene mRNA, and downstream mitochondrial protein/enzyme markers.	Acute biopsy design; no isolated lactate arm and no long-term clinical endpoint.
[6]	Human knee-extensor training model; Exercise bout in trained and untrained leg	Exercise induced transient PGC-1alpha transcription and mRNA responses during recovery in human skeletal muscle.	Foundational human signaling evidence; does not distinguish lactate from other exercise signals.
[7]	Rodent skeletal muscle; Exercise-induced mitochondrial biogenesis time course	Mitochondrial biogenesis markers rose as rapidly as, or faster than, PGC-1alpha protein expression, supporting activation-first timing.	Rodent timing study; supports pathway timing, not human intervention efficacy.

ID	Model and perturbation	Key finding	Interpretive limitation
[8]	C2C12 and primary mouse myoblasts; 72-h supraphysiologic pyruvate exposure and PGC-1alpha knockdown/null conditions	Pyruvate increased mitochondrial protein expression, basal respiration, and maximal oxidative capacity without requiring PGC-1alpha.	Cell-level pyruvate exposure; concentration and developmental context limit direct exercise translation.
[9]	C2C12 myotubes; 72-h pyruvate, dichloroacetate, and glutamine exposures	High pyruvate increased respiratory-chain content but suppressed PGC1alpha, glucose uptake, palmitate uptake, and oxidation; DCA/glutamine reversed parts of the phenotype.	Constraint evidence: more respiratory-chain content did not equal improved substrate use.
[10]	Human high-intensity interval-training time course; Seven-session training series	Repeated mRNA bursts preceded changes in transcriptional, mitochondrial, and dynamics-related proteins during training.	Training-time-course evidence; metabolite causality was not isolated.

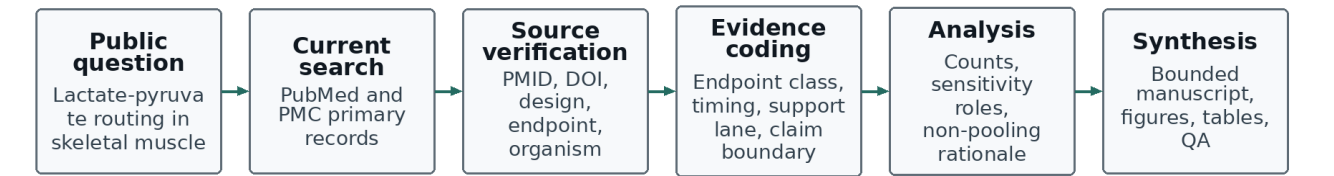


Figure 1. Analysis process for the lactate-pyruvate routing synthesis. Solid connectors show the workflow from question framing through current literature search, source verification, endpoint coding, sensitivity analysis, synthesis, and artifact QA.

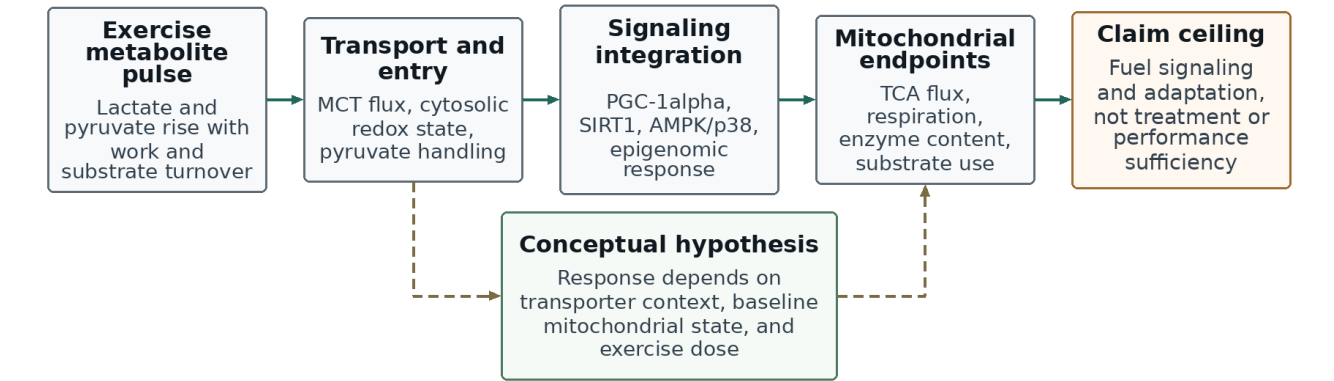


Figure 2. Conceptual summary of lactate-pyruvate routing in skeletal muscle. Solid links identify observed evidence classes connecting exercise metabolite pulses, transport and entry, signaling integration, mitochondrial endpoints, and claim ceilings; dashed links mark hypotheses about responder context that require direct testing.

Declarations

Data and code availability. The repository deposit includes the manuscript source, evidence table, source data, analysis code, figures, measured figure geometry, biological-audit supplements, layout reports, QA record, Gemini review and checksums needed to replay the table, counts, figures and artifacts. Private replay inputs are retained locally and excluded from public manifests.

Source verification. The biological audit is a manuscript-integrity ledger, not proof of biological truth or clinical efficacy. Corpus anchors and archived normalized source files were replayed against recorded hashes; UNKNOWN or NOT_RUN biological interpretation statuses remain visible.

Ethics statement. This literature synthesis used no identifiable patient data and required no new human-participant or animal research.

Funding. No external funding was reported for this working paper.

Competing interests. The author reports no competing interests for this working paper.

Author contributions. Andrew Friedl conceived the project, directed the analysis, reviewed the evidence package, and approved the manuscript for repository review.

AI assistance. AI tools assisted literature synthesis, drafting, data visualization, formatting and QA preparation. Gemini independently reviewed the exact rendered PDF. Andrew Friedl remains solely responsible for the content and is the sole author.

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