

Contact-Site Control Versus Monocarboxylate Ratio in Mitochondrial Pyruvate Use

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Abstract

Background: Lactate/pyruvate-ratio language can imply a direct mitochondrial or contact-site signal, yet ER-mitochondria contact-site studies often measure contact abundance, calcium transfer, respiration, pyruvate oxidation, glucose output and lactate readouts in separate experiments. The unresolved bottleneck is causal order: monocarboxylate ratio may remodel mitochondria-ER contacts, or contact-site state may constrain calcium-coupled pyruvate oxidation and make lactate/pyruvate changes a downstream readout.

Objective: This working paper retains the selected question: In cells with ER-mitochondria contact-site perturbations, are lactate/pyruvate-ratio changes best interpreted as direct MERC modulators, or as downstream readouts of contact-site control over calcium-coupled pyruvate oxidation?

Methods: Current primary-literature searches and five complete public primary texts were checked on 2026-10-10. The included records were source-coded across five endpoint classes: contact-site molecular identity, calcium transfer, mitochondrial respiration, pyruvate oxidation or use, and lactate/glucose readout interpretation. The method was a public full-text competing-model reanalysis and measurement-rule synthesis. No pooled effect size, raw-image reanalysis, clinical validation, direct lactate-binding claim or treatment recommendation was inferred.

Results: Five primary studies supplied nonredundant evidence. Szabadkai 2006 defined the IP3R-GRP75-VDAC bridge for ER-to-mitochondria calcium transfer [1]. Bantug 2018 linked mitochondria-ER contacts, GRP75, respiration and glucose-derived pyruvate oxidation in memory CD8 T cells [2]. Thoudam 2019 showed that PDK4 stabilizes the IP3R1-GRP75-VDAC1 complex and changes skeletal-muscle MAM formation and calcium-linked dysfunction [3]. Arruda 2014 showed hepatic MAM enrichment and calcium flux as obesity-linked drivers of metabolic dysfunction [4]. Larrea 2025 reported that MAM dysfunction impedes use of glucose-derived pyruvate as mitochondrial fuel and can explain high lactate as a downstream consequence in ALS models [5]. Current searching found adjacent mitochondrial lactate-import and MERC-modulation literature, but no primary full-text study in this selection established lactate/pyruvate ratio as a direct MERC remodeler under matched contact-site state.

Conclusions: Current primary evidence supports a bounded discriminability rule rather than a new wet-lab discovery. In contact-perturbed systems, lactate/pyruvate-ratio changes should be interpreted as downstream readouts unless same-condition perturbation shows that monocarboxylate ratio remodels MERC abundance or calcium/PDH flux before contact-site machinery changes. Confirmation would redirect future Mito Map monocarboxylate studies toward temporal MERC, calcium-transfer, PDH/PDK, OCR and lactate/pyruvate panels rather than ratio-only causal language.

Keywords: ER-mitochondria contacts; MERC; MAM; lactate/pyruvate ratio; pyruvate oxidation; calcium transfer; PDK4; GRP75

1 Introduction

Mitochondria-associated ER membranes and ER-mitochondria contact sites are often studied with contact imaging, proximity ligation, calcium reporters, respiration assays, glucose tracing, pyruvate oxidation or downstream lactate and glucose measurements. Those endpoints do not automatically share causal order. A lactate/pyruvate-ratio change may be a redox or substrate signal, but it may also be a readout of impaired mitochondrial pyruvate use after contact-site machinery has already changed.

The central relationship examined here is deliberately precise. Across neuronal, T-cell, hepatic and skeletal-muscle systems where ER-mitochondria contacts are perturbed, contact-site state changes the use of glucose-derived pyruvate for mitochondrial respiration upstream of lactate/pyruvate ratio readouts; the relationship fails when lactate/pyruvate changes alter MERC abundance or calcium/PDH flux under matched contact-site state.

The strongest competing account is that changes in lactate/pyruvate ratio directly modulate MERC abundance and function, so contact-site changes are downstream of monocarboxylate redox state rather than an upstream constraint on pyruvate oxidation. This competing account is credible because lactate and pyruvate can influence cytosolic redox, substrate supply and mitochondrial metabolism. It is not resolved by showing that lactate, pyruvate, respiration and contacts all change somewhere in the same paper. The two accounts differ in temporal order, rescue logic and required controls.

2 Methods

The current literature search on 2026-10-10 used ER-mitochondria contact, MERC, MAM, lactate, pyruvate, lactate/pyruvate ratio, pyruvate oxidation, calcium transfer and ALS/immune/metabolic combinations. Five complete public primary texts were retained as central sources because they provide source-ready contact-site, pyruvate-use or calcium-transfer evidence. Current searching identified adjacent primary work on direct mitochondrial lactate handling, but that literature did not test lactate/pyruvate ratio as a direct MERC remodeler under matched contact-site state and was therefore logged as context rather than central evidence.

Eligibility required a public primary source with complete archived text and at least one endpoint relevant to the competing models: MERC/MAM abundance, IP3R/GRP75/VDAC or PACS2 machinery, calcium transfer, PDK/PDH/pyruvate oxidation or use, mitochondrial respiration, glucose/lactate output or a stated lactate consequence. Reviews, abstracts alone, non-primary syntheses and source prose without archived full text were excluded from central evidence. Exact source-file hashes are reported in the machine-readable data.

A machine-readable evidence and assumption ledger is provided in Supplementary File S1, with a readable companion in Supplementary File S2. The ledger records exact manuscript anchors, source identifiers, exact excerpts, source-version hashes, actual quotation-check outcomes and unresolved assumptions; it does not establish biological truth, clinical efficacy or a Lean proof.

Each source was coded for model system, contact-site perturbation or measurement, endpoint class, observed evidence, interpretive limitation and role in the competing-model analysis. The analysis did not pool effect sizes because the sources differ by tissue,

species, contact perturbation, disease/stress context, substrate exposure, time window and endpoint. Information gain was defined as whether a source changed the rule for assigning lactate/pyruvate outcomes to direct monocarboxylate-ratio control versus contact-site-first pyruvate-oxidation control.

The prespecified discriminator was same-condition temporal separation. The contact-site-first account predicts that perturbing or rescuing GRP75/IP3R/VDAC, PDK4/PACS2 or MAM state

changes mitochondrial calcium, PDH/PDK state, pyruvate oxidation, OCR and only then lactate/pyruvate or glucose/lactate readouts. The ratio-first account predicts that lactate/pyruvate ratio changes alter MERC abundance, calcium transfer and pyruvate oxidation even when contact-site machinery, pH, substrate supply, fatty-acid exposure and stress timing are held constant.

3 Results

3.1 Evidence synthesis

Table 1 summarizes the five archived primary sources. The table preserves source-specific endpoint classes so that molecular contact evidence, T-cell pyruvate oxidation, skeletal-muscle PDK4/MAM coupling, hepatic calcium flux and ALS pyruvate-use failure are not collapsed into a generic lactate mechanism.

3.2 Evidence-coded sensitivity analysis

Three sensitivity checks were prespecified and labeled by role. The decision-changing check removed Larrea 2025. Without the ALS pyruvate-use source, the synthesis still supports contact-site control over respiration and calcium, but the direct statement that high lactate can be downstream of impaired pyruvate use becomes weaker. The robustness check removed Bantug 2018. The remaining sources still support contact-site machinery and tissue metabolic consequences, but the explicit memory T-cell pyruvate oxidation bridge is lost. The exploratory check added current adjacent mitochondrial lactate-import literature as context only; it strengthens the need to separate lactate handling from pyruvate transport, but it does not change the central decision because it does not test MERC remodeling by lactate/pyruvate ratio under matched contact-site state.

The sensitivity results support a conservative conclusion. The paper is ready as a source-coded discriminability rule and experimental-design synthesis, not as proof that contact sites always precede lactate/pyruvate changes or that lactate/pyruvate ratio never directly affects MERCs.

4 Discussion

This synthesis separates three claims that are often conflated. First, ER-mitochondria contact machinery can directly organize calcium transfer [1]. Second, contact-site perturbation can alter respiration and pyruvate oxidation or pyruvate use in specific immune and neuronal systems [2,5]. Third, lactate or lactate/pyruvate readouts can be consequences of altered pyruvate use rather than the initiating MERC signal [5]. The available source set does not prove the inverse proposition that monocarboxylate ratio directly remodels MERCs.

The contribution beyond the closest primary work is a same-condition measurement rule. Direct lactate/pyruvate-ratio MERC language should require pH-neutral ratio manipulation,

Table 1. Primary-source evidence matrix for contact-site state, calcium transfer, pyruvate oxidation and lactate/readout interpretation.

ID	Model and perturbation	Key finding	Interpretive limitation
[1]	IP3R/GRP75/VDAC contact-site machinery; VDAC1 bait, co-immunoprecipitation, IP3R ligand-binding-domain targeting and grp75 knockdown	VDAC1 was physically linked to IP3R through GRP75, and grp75 knockdown abolished the stimulatory effect on mitochondrial calcium uptake.	Defines the contact-site calcium machinery, but it does not test pyruvate oxidation, lactate/pyruvate ratio or direct monocarboxylate effects on MERCs.

ID	Model and perturbation	Key finding	Interpretive limitation
[2]	Mitochondria-ER junction control of glucose-derived mitochondrial respiration; Nocodazole, 4-PBA and GRP75 knockdown with PLA, respiration, glycolysis and glucose tracing	Memory CD8 T cells had enriched mitochondria-ER contacts; GRP75 depletion reduced contacts and mitochondrial respiration while glycolysis was unchanged, and glucose tracing pinpointed mitochondrial pyruvate oxidation.	The system is immune-cell recall, not direct lactate/pyruvate-ratio perturbation of contact abundance.
[3]	PDK4 stabilization of IP3R1-GRP75-VDAC1 at MAM; PDK4 knockout, PDK4 knockdown, palmitate, DCA and synthetic ER-mitochondria linker	PDK4 interacted with and stabilized the IP3R1-GRP75-VDAC1 complex; PDK4 inhibition dampened MAM formation, mitochondrial calcium accumulation, mitochondrial dysfunction and insulin-signaling defects.	Links a pyruvate dehydrogenase kinase to MAM state but does not establish lactate/pyruvate ratio as an upstream MERC ligand.
[4]	Excessive hepatic MAM and calcium flux in metabolic dysfunction; Genetic and diet-induced obesity, induced ER-mitochondria interactions, PACS2 or IP3R1 down-regulation	Obesity increased hepatic MAM formation and calcium flux from ER to mitochondria; reducing tethering or calcium transport improved mitochondrial oxidative capacity and insulin sensitivity in obese animals.	Shows contact-state directionality in liver glucose homeostasis, but the direction of MAM change is context-specific and not a monocarboxylate-ratio experiment.
[5]	MAM dysfunction shifts mitochondrial fuel use away from glucose-derived pyruvate; SOD1-mutant cellular and mouse ALS models with MAM proteomics, respiration and pyruvate/glucose metabolism assays	MAM dysfunction impeded use of glucose-derived pyruvate as mitochondrial fuel and caused a shift toward fatty acids; decreased pyruvate production and use were proposed to explain high lactate and glucose in ALS patients.	Disease-specific stress and ALS metabolic remodeling limit generalization, and the study does not manipulate lactate/pyruvate ratio as a direct MERC input.



Figure 1. Source-bound workflow for MERC/contact-state versus monocarboxylate-ratio model discrimination. Numbered nodes denote: 1 selected question, 2 public full texts, 3 endpoint coding, 4 model contrast and 5 research rule; the workflow verifies five primary sources, codes endpoint classes, contrasts temporal models, runs sensitivity checks and binds review artifacts.

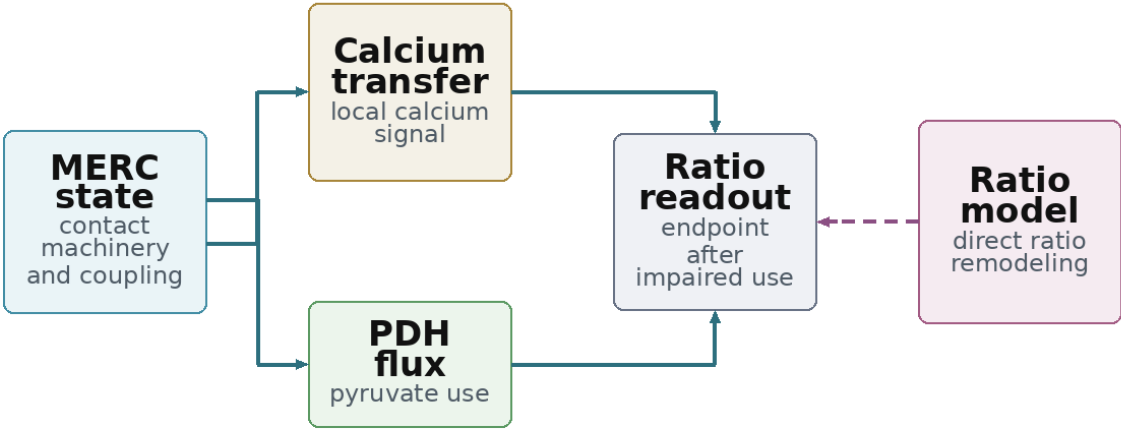


Figure 2. Competing mechanism map for lactate/pyruvate interpretation in contact-perturbed systems. Solid links show the source-supported contact-state path through calcium transfer and pyruvate oxidation to readouts; the dashed link shows the direct ratio-first alternative requiring future same-condition testing.

matched glucose and fatty-acid supply, viability, time-resolved MERC proximity, calcium transfer, PDH/PDK state, pyruvate oxidation, OCR and lactate/pyruvate readouts in the same system. A contact-site-first interpretation is strengthened when restoring MERC formation or PDH flux normalizes oxidation and lactate/pyruvate readouts without changing the external monocarboxylate ratio. A ratio-first interpretation is strengthened when ratio manipulation remodels MERCs before contact-site protein, pH or stress changes and when contact-site rescue fails.

The negative result is valuable. If direct ratio perturbation changes MERC abundance, calcium transfer and pyruvate oxidation under matched contact-site state, future Mito Map work should prioritize monocarboxylate-ratio sensors, pH/redox mechanisms and mitochondrial lactate handling. If ratio perturbation fails while contact-site rescue normalizes oxidation and downstream lactate/pyruvate readouts, ratio-only causal language should be avoided.

5 Limitations

This working paper is a public full-text reanalysis and measurement-rule synthesis. It does not include raw image quantification, raw metabolomics, unpublished data, new wet-lab experiments, patient-level analysis, clinical outcomes, clinical efficacy claims or a pooled effect-size meta-analysis. Cross-system comparison across T cells, skeletal muscle, liver and ALS models is used for discriminability logic, not for a universal biological mechanism.

Current primary-literature searching found adjacent lactate-import and MERC-modulation studies, but no archived central source established direct lactate/pyruvate-ratio remodeling of MERCs under matched contact-site state. Absence of that source is a limitation, not evidence against all ratio-first biology. Contradictory evidence was searched by combining lactate or lactate/pyruvate ratio with MERC, MAM, ER-mitochondria contact, contact-site abundance, calcium transfer and pyruvate oxidation; the strongest competing account remains experimentally open.

6 Conclusions

Current public primary evidence supports a cautious rule for mitochondrial adaptation interpretation. In contact-perturbed systems, lactate/pyruvate-ratio changes should be treated as downstream readouts unless the same condition shows ratio-driven MERC remodeling before changes in contact-site machinery, calcium transfer or PDH/pyruvate-oxidation flux. This rule changes research design: ratio claims require temporal MERC, calcium, PDH/PDK, OCR and lactate/pyruvate panels rather than endpoint-only lactate interpretation.

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.

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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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