

Mitochondrial Dynamics and TCA-Cycle Claims Require Same-Condition Flux Evidence

Andrew Friedl

Precision Mito, Florida, USA

Correspondence: afriedl@precisionmito.com

Abstract

Background: Mitochondrial fusion, fission, oxygen-consumption and metabolomics readouts are often interpreted together as evidence that mitochondrial shape directly controls TCA-cycle efficiency. That interpretation can overrun the assays when morphology, respiration and TCA endpoints were not measured under the same dynamics perturbation.

Objective: This working paper asks whether public primary morphology/dynamics studies support direct fusion/fission control of TCA-cycle efficiency, or whether they currently justify only an assay boundary requiring same-condition TCA flux or metabolite measurement.

Methods: PubMed, PubMed Central, publisher records and the frozen concept-evidence archive were checked on 2026-10-11. Five complete public primary records were source-coded: propionic-aciduria kidney, residual triple-negative breast cancer, TM4SF5 mitochondria-lysosome contact sites, hypertrophic-cardiomyopathy energetics and Newcastle disease virus mitophagy. Endpoint classes were mitochondrial morphology/dynamics or structure, direct TCA flux, quantified TCA/metabolite evidence, respiration/OXPHOS and same-condition dynamics-to-TCA support. The analysis was a source-level evidence synthesis with no pooling, no effect-size estimation and no biological validation.

Results: The coded set contained 5 primary records. Four records contained explicit mitochondrial morphology/dynamics language, five contained TCA/metabolite or metabolic-endpoint language, four contained respiration/OXPHOS or energetics language, two contained direct TCA-flux language and one contained same-condition dynamics perturbation plus direct TCA-flux support. The strongest partial contradiction was the TNBC OPA1 study, which measured morphology, OXPHOS and isotope TCA flux; however, the same source also reported that Mdivi-1-induced elongation was insufficient to alter glycolytic or TCA flux. The remaining records supported an assay boundary by showing disease-context co-measurement, OXPHOS/TCA decoupling, flux measurement without fusion/fission causality, or viral-stress dynamics without matched TCA flux.

Conclusions: Public primary evidence supports a cautious assay-boundary claim rather than a broad direct-control claim. Dynamics-to-TCA language is licensed only when the same experimental condition includes an explicit morphology/fusion/fission perturbation and direct isotope-resolved TCA flux or quantified TCA-intermediate evidence. This synthesis is exploratory, non-causal and non-pooled; it does not estimate clinical benefit or validate a mitochondrial intervention.

Keywords: mitochondrial dynamics; fission; fusion; TCA cycle; OPA1; DRP1; metabolomics; isotope tracing; assay boundary

1 Introduction

Mitochondrial shape is biologically meaningful, but it is not itself a TCA-cycle flux assay. Fusion, fission, cristae remodeling, mitophagy, oxygen consumption, metabolomics and isotope tracing can move in related directions while answering different questions. A paper that measures mitochondrial elongation and OCR has not necessarily measured TCA-cycle efficiency, and a paper that measures TCA metabolites has not necessarily shown that fission or fusion caused the metabolic change.

The selected question is therefore a measurement and causal-identification problem: Do public primary morphology/dynamics studies support direct fusion/fission control of TCA-cycle efficiency, or do they currently justify only an assay-boundary requiring same-condition TCA flux measurement? The competing account is stronger than a straw claim. It states that fusion or fission state directly controls TCA-cycle efficiency in these systems, so co-measured OCR, OXPHOS, metabolomics or TCA-cycle intermediate changes are adequate evidence of a causal dynamics-to-TCA mechanism. Under the boundary account, the same literature should instead show heterogeneous endpoint coverage, with direct flux evidence concentrated in a subset and ordinary disease, stress, substrate or treatment context remaining plausible.

The closest prior Mito Map monocarboxylate-routing paper separated fuel routing, PGC-1-family signaling and mitochondrial content or respiratory-quality endpoints using primary-source coding [6]. The present paper extends that measurement discipline to a different scientific object. It does not ask whether lactate or pyruvate route carbon through mitochondria. It asks when morphology and dynamics evidence can support direct TCA-cycle control.

2 Methods

The search and verification date was 2026-10-11. The frozen selection already archived five complete public primary texts from PubMed Central or publisher-accessible records. Current searches used combinations of mitochondrial fission, fusion, OPA1, DRP1, morphology, TCA cycle, isotope tracing, flux, OXPHOS, kidney, triple-negative breast cancer, mitochondria-lysosome contact sites, hypertrophic cardiomyopathy and Newcastle disease virus. The search identified the selected TNBC OPA1 paper as the strongest direct comparator and did not identify a reason to replace the frozen selected question.

Eligible records for the analysis were the five selected complete public primary texts. Reviews and news records were used only for orientation and were not coded as evidence. The coding unit was the public article record, not a biological replicate, cell line, mouse, patient, tumor or experiment. No raw participant data, patient-derived private input, proprietary source archive or product-score information was used.

Each source was coded for five endpoint classes: mitochondrial morphology/dynamics or structure language, direct TCA-flux language, quantified TCA/metabolite language, respiration/OXPHOS or energetic language, and same-condition dynamics-to-TCA support. A same-condition support code required an explicit morphology, fusion or fission perturbation plus direct TCA flux or quantified TCA-intermediate evidence in the relevant experimental window. The code was deliberately stricter than a general metabolism code.

Three sensitivity analyses were specified by role before interpretation. Strict same-condition flux was decision-changing because it determines whether direct-control language is licensed. Closest-three-only was a robustness check because Baek, Schumann and Kim are the most direct comparators. Removal of cardiac and infection comparators was exploratory because those records test assay taxonomy and stress transfer rather than direct

dynamics-to-TCA causality.

The evidence table is rendered as a native table and is also included as CSV. Machine-readable source coding, analysis counts, sensitivity roles, figure source data and measured diagram geometry are included in the public bundle. A supplementary biological-audit ledger records exact manuscript anchors, source identifiers, exact excerpts and unresolved assumptions; it checks quotation integrity and manuscript anchoring only, and it does not establish biological truth, clinical validity or intervention efficacy.

3 Results

The Results section follows the coding order used in the analysis: endpoint inventory, source-level contrasts, sensitivity checks and claim boundary.

3.1 Evidence synthesis

The first evidence step separated assays before considering mechanism. The five-record set contained four records with explicit mitochondrial morphology, dynamics or structure language; five with TCA/metabolite or metabolic-endpoint language; four with respiration/OXPHOS or energetic language; two with direct TCA-flux language; and one with same-condition dynamics perturbation plus direct TCA-flux support. These are article-level counts, not biological independent units.

Schumann et al. measured a renal propionic-aciduria mouse model and reported altered mitochondrial networks shifted toward fission together with LC-MS/MS evidence of TCA-cycle energy-generation disturbance [1]. The same source is informative for co-measurement, but the disease genotype did not directly perturb DRP1, OPA1 or MFN to test whether the network shift caused TCA disturbance. Baka et al. supplied a methodological comparator because ¹³C MRS and related energetics can measure metabolic efficiency and substrate flux, but the cardiac paper did not make fusion or fission the causal object [4].

Baek et al. provided the strongest partial contradiction to a pure assay-warning account. In residual TNBC models, DNA-damaging chemotherapy increased mitochondrial elongation, mitochondrial content, glucose flux through the TCA cycle and OXPHOS; OPA1 inhibition reduced glucose-driven TCA flux, and genetic or pharmacologic dynamics perturbation altered OCR [2]. This source justifies treating OPA1-linked morphology as potentially causal in its TNBC chemotherapy context.

The same record also prevents a broad morphology-equals-TCA rule. The authors reported that Mdivi-1 did not significantly alter glycolytic or TCA-cycle flux, indicating that drug-induced elongation was insufficient to drive those pathways [2]. The direct-control account therefore cannot rely on morphology alone. It requires the more specific OPA1, treatment, substrate and same-condition flux context.

Kim et al. supplied a decoupling comparator. TM4SF5-enriched mitochondria-lysosome contact sites clustered DRP1 and mitophagy receptors, leading to mitochondrial fission/autophagy, while the same abstract-level result stated impaired oxidative phosphorylation with intact TCA-cycle and beta-oxidation language [3]. That pattern is compatible with dynamics or contact-site control of some mitochondrial outputs, but it is not sufficient evidence that fission directly reduces TCA-cycle efficiency.

Qu et al. added a viral-stress boundary. NDV infection disrupted mitochondrial spatial distribution and imbalanced fusion and fission, leading to structural damage and PRKN-dependent mitophagy [5]. The paper also described amino-acid metabolic reprogramming and TCA-replenishment logic, but it did not provide a same-condition isotope TCA-flux test of a controlled fission/fusion perturbation. This source therefore supports a stress-context caution rather than a general dynamics-to-TCA mechanism.

Table 1. Primary-study evidence matrix

ID	Model and perturbation	Key finding	Interpretive limitation
Schumann 2024	female Pcca-/- (A138T) propionic-aciduria mouse kidney across ages; disease genotype and renal aging; no direct fission or fusion perturbation	Kidney tissue combined altered mitochondrial ultrastructure and networks shifted toward fission with LC-MS/MS evidence of TCA-cycle energy-generation disturbance.	The record supports co-measurement and disease-context association, but it does not perturb DRP1, OPA1 or MFN to test whether dynamics cause TCA changes.
Baek 2023	residual triple-negative breast cancer cells and patient-derived xenograft models after chemotherapy; DNA-damaging chemotherapy, taxanes, MYLS22 OPA1 inhibition, Mdivi-1 and siRNA dynamics perturbations	DNA-damaging chemotherapy increased elongation, mitochondrial content, glucose flux through the TCA cycle and OXPHOS; MYLS22 reduced glucose-driven TCA flux while Mdivi-1 elongation did not significantly alter TCA flux.	This is the strongest direct comparator, but it is a TNBC chemotherapy-survival context and it shows fusion/OPA1 can be necessary without simple elongation being sufficient.
Kim 2023	hepatocellular-carcinoma and hepatocyte systems with TM4SF5-enriched mitochondria-lysosome contact sites; glucose starvation/repletion, TM4SF5 manipulation, cholesterol-contact-site assays	TM4SF5 contact-site enrichment clustered DRP1 and mitophagy receptors, promoting fission/autophagy while impairing OXPHOS with intact TCA-cycle and beta-oxidation language.	This decouples dynamics/contact-site reprogramming from a simple TCA-cycle-control claim; it does not provide isotope TCA flux under a direct fission/fusion perturbation.
Baka 2025	R403Q hypertrophic-cardiomyopathy mouse heart treated with empagliflozin; 16-week empagliflozin treatment in a sarcomere-mutation mouse model	The cardiac record used multinuclear MRS and multi-omics to measure metabolic efficiency and substrate flux without making fusion/fission the causal object.	It is a metabolic-efficiency comparator, not a mitochondrial dynamics paper; it supports assay taxonomy and flux-measurement standards rather than direct dynamics-to-TCA inference.
Qu 2026	Newcastle disease virus infection in A549 and related tumor-cell models; NDV infection, PRKN/SQSTM1 genetic backgrounds and amino-acid supplementation	NDV infection disrupted mitochondrial distribution and fusion-fission balance, with mitophagy and amino-acid metabolic reprogramming that can feed TCA-related biosynthesis.	The viral-stress model supports dynamics and metabolism co-occurrence, but it does not measure isotope-resolved TCA flux from a controlled fission/fusion perturbation.

3.2 Evidence-coded sensitivity analysis

The strict same-condition flux sensitivity analysis was decision-changing. Only one of five records met the strict criterion for direct dynamics-to-TCA support. The result favors an assay boundary: direct-control language should be restricted to cases resembling the TNBC OPA1 design, not generalized from morphology plus OCR or broad metabolomics alone.

The closest-three-only robustness check retained the same interpretation. Baek et al. supplied direct flux and OPA1 evidence, Schumann et al. supplied disease-context morphology plus

quantified metabolic disturbance without a dynamics perturbation, and Kim et al. supplied OXPHOS/TCA decoupling [1-3]. Removing the cardiac and infection comparators narrowed scope but did not remove the boundary.

The exploratory comparator-removal check also preserved the decision. Without Baka et al. and Qu et al., the manuscript no longer uses cardiac MRS or viral mitophagy as auxiliary examples; however, the remaining source set still contains one strong direct comparator, one disease co-measurement source and one decoupling source. The conclusion therefore does not depend on cross-tissue topic rotation.

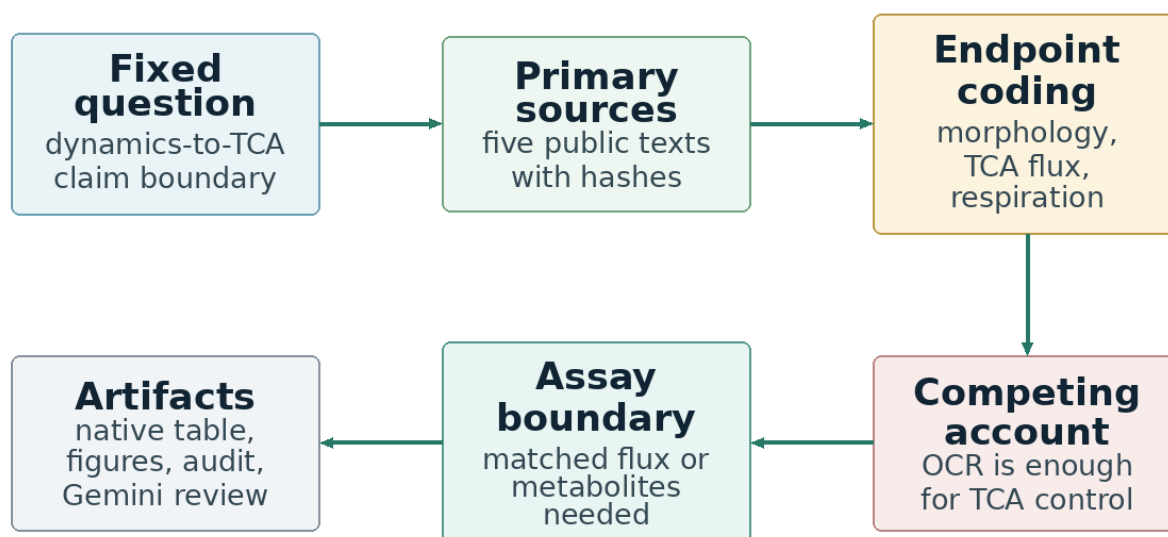


Figure 1. Analysis process for the mitochondrial dynamics-to-TCA assay-boundary synthesis. Solid connectors show the workflow from fixed question through archived public sources, endpoint coding, competing-model contrast, claim-boundary synthesis and artifact QA.

4 Discussion

The analysis supports a bounded, useful claim. Mitochondrial dynamics can plausibly influence TCA-cycle use in some contexts, and the TNBC OPA1 paper shows why the direct-control alternative deserves respect. But the broader literature reviewed

here does not license a default rule that morphology, OCR or metabolomics is equivalent to direct TCA-cycle efficiency. The evidentiary threshold must be the same condition, the same perturbation window and a direct flux or quantified metabolite endpoint.

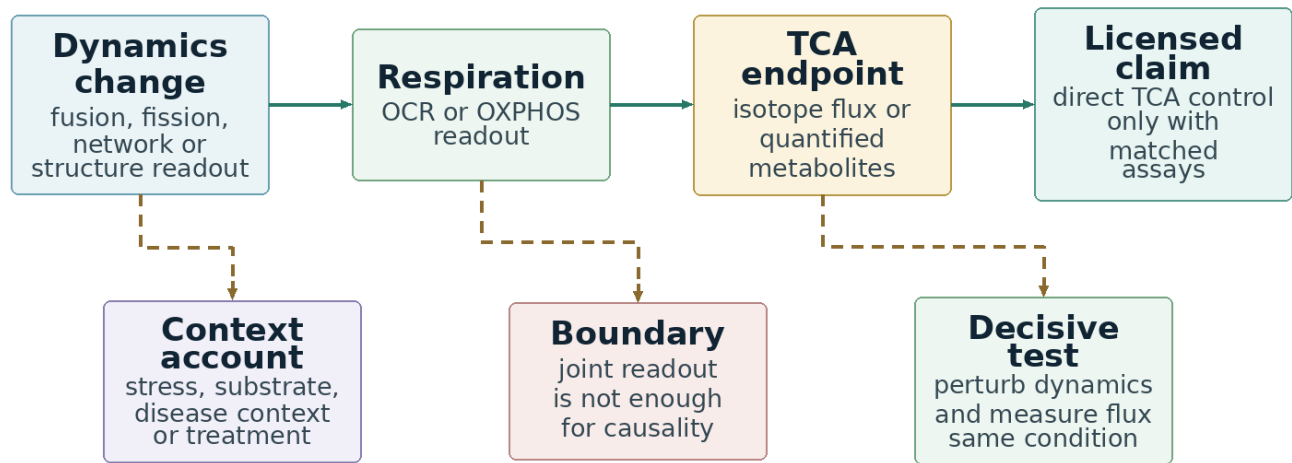


Figure 2. Conceptual summary of the morphology/dynamics-to-TCA assay boundary. Solid links identify observed co-measured endpoint classes; dashed links mark alternative stress or substrate context and the decisive same-condition flux test needed before direct TCA-control claims are licensed.

Figure 1 summarizes the workflow from fixed question through archived public sources, endpoint coding, competing-model contrast, boundary synthesis and artifact QA. Figure 2 summarizes the concept. Solid links show evidence-supported co-measurement classes. Dashed links mark the ordinary alternative: shared stress, substrate, disease context or treatment effects can move morphology, respiration and metabolites without proving that fission or fusion directly controls TCA-cycle efficiency.

The strongest competing account predicts routine direct TCA evidence tightly linked to morphology perturbation across the closest primary works. The observed source set was more heterogeneous. The direct-control account is plausible in the TNBC OPA1 context, but it weakens when applied to renal PA disease context, TM4SF5 contact-site decoupling, cardiac empagliflozin energetics or viral infection stress. The boundary account predicts exactly that pattern.

Confirmation changes a concrete research decision. Future dynamics-to-metabolism manuscripts should demand same-condition morphology perturbation plus isotope TCA flux or quantitative TCA-intermediate evidence before stating direct TCA-cycle control. OCR, OXPHOS protein, mitochondrial content, mitochondrial network shape and broad metabolomics should remain separate endpoint classes unless a source directly links them.

A contrary result would also be informative. If an expanded primary-source screen found that most closest morphology/dynamics papers already contain same-condition isotope-resolved TCA flux or quantified TCA intermediates tied to the dynamics perturbation, the assay-boundary synthesis would no longer be the right contribution. The next paper should instead build a narrower causal model comparing OPA1, DRP1, substrate entry, cristae structure and disease context.

5 Limitations

This was a structured source comparison, not a systematic review, meta-analysis or biological validation. The sample was selected through a frozen concept-selection process and contains five complete public primary texts. The source count is small, tissues differ, and article-level endpoint counts are not biological independent units. No effect sizes were extracted, no raw isotope traces were reanalyzed, and no clinical or therapeutic claim follows from the synthesis.

Tissue transfer is especially limited. TNBC chemotherapy survival, PA kidney disease, hepatocellular contact-site biology, HCM cardiac energetics and NDV infection are not interchangeable systems. The direct OPA1-to-TCA evidence in TNBC should not be treated as kidney, heart or infection evidence. Conversely,

decoupling in TM4SF5 contact sites or viral stress does not refute the TNBC mechanism.

The biological audit is an integrity ledger for exact source excerpts and manuscript anchors. Its automated statuses do not represent accountable biological interpretation, reviewer approval, clinical efficacy or a Lean proof. UNKNOWN and NOT_RUN statuses remain part of the evidence boundary.

6 Conclusions

Public primary evidence supports a disciplined assay boundary. Mitochondrial fusion/fission and TCA-cycle endpoints can be connected, but the connection is identifiable only when dynamics perturbation and direct flux or quantified metabolite evidence occur under the same condition. The most useful next investigation is a same-condition OPA1 or DRP1 perturbation crossed with ¹³C glucose, glutamine and lactate tracing, live morphology measurement, OCR, TCA-intermediate quantification and stress-matched controls across a defined tissue context.

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. Manuscript-quality and concept-impact grades are available at <https://precisionmito.com/paper-grades>.

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 when

artifact-bound review was available. Andrew Friedl remains solely responsible for the content and is the sole author.

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