

Redox-signal gating constrains antioxidant interpretation in exercise mitochondrial adaptation

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Abstract

Exercise-induced mitochondrial adaptation is often described through energy-stress and calcium-signaling pathways, yet primary studies also support a redox-sensitive control layer. This working paper evaluates whether exercise-derived redox signals behave as a permissive gate for mitochondrial adaptation and whether antioxidant intervention studies justify a generalized anti-antioxidant conclusion. A structured evidence synthesis was performed across eight primary-study records spanning human biopsy studies, randomized antioxidant-training interventions, mouse NFE2L2/Nrf2 perturbation studies, and exercise proteomics. Studies were coded by endpoint class, perturbation type, direction of evidence, and interpretive limitation. The evidence supports a bounded model: transient exercise redox signaling participates in mitochondrial-biogenesis and endogenous-defense responses, while high-dose antioxidant supplementation can blunt selected cellular adaptations. However, cellular markers, insulin-sensitivity outcomes, and whole-body performance endpoints diverge across studies. The defensible conclusion is therefore not that antioxidants are uniformly harmful, but that exogenous antioxidant exposure can mask or reroute redox-dependent training signals under specific dose, timing, and endpoint conditions.

Keywords: exercise; redox signaling; Nrf2; PGC-1alpha; mitochondrial biogenesis; antioxidants

1 Introduction

Skeletal muscle adapts to endurance exercise through coordinated changes in substrate flux, calcium signaling, transcriptional coactivation, antioxidant defense, and mitochondrial remodeling. Early human biopsy work established that exercise can rapidly induce PGC-1 α transcription in skeletal muscle, positioning mitochondrial biogenesis as a dynamic post-exercise response rather than a slow structural afterthought [1]. That finding created a measurement anchor for later intervention studies that asked whether oxidant signals are merely damaging by-products or necessary information carriers.

The redox question is important because the same molecules can be framed in opposite ways. Reactive oxygen and nitrogen species can damage macromolecules when sustained or excessive, yet transient oxidant and electrophile signals can activate stress-response pathways. Trials that administer vitamin C or vitamin E during training are therefore not simple wellness tests. They are perturbation experiments against a signaling system. If antioxidant exposure attenuates mitochondrial or metabolic adaptation, the result supports redox participation; if performance remains unchanged, the result also constrains how far marker-level findings may be generalized [2-4].

This paper examines the central concept that exercise mitochondrial adaptation is redox gated. The term redox gate is used here as a constrained construct: transient exercise-derived redox change is treated as one permissive signal among several, not as the sole causal driver of training adaptation. The analysis asks three questions. First, do primary human and mechanistic studies support a redox-responsive layer linked to mitochondrial adaptation? Second, do antioxidant interventions alter cellular or physiological endpoints consistently enough to justify broad claims? Third, what falsifiers and boundary conditions should govern future mitochondrial-exercise interpretation?

2 Methods

Primary studies were selected when they directly tested exercise, antioxidant perturbation, NFE2L2/Nrf2 signaling, or mitochondrial adaptation in skeletal muscle. PubMed and publisher records were used to verify DOI, PMID, population or model, intervention, and endpoint interpretation for each included record. Reviews and commentary were used only to identify candidate primary sources and were not counted as evidence rows. The final evidence set included eight primary-study records: one early human exercise-transcription study, four human antioxidant or Nrf2-associated studies, two mouse genetic or proteomic Nrf2 studies, and one mixed human-preclinical antioxidant study [1-8].

Each study was coded in evidence_table.csv for model, perturbation, endpoint class, observed evidence, interpretive limitation, and direction. Endpoint classes separated exercise signal, antioxidant perturbation, mitochondrial-biogenesis marker, insulin-sensitivity or performance outcome, genetic perturbation, human Nrf2 association, and proteomic support. A claim-boundary rule was applied before synthesis: marker movement could support pathway engagement, but it could not be converted into generalized clinical or performance benefit without matching functional evidence. Sensitivity checks then removed preclinical-only support, separated cellular from performance outcomes, and treated divergent antioxidant trial results as boundary evidence rather than noise.

3 Results

3.1 Evidence synthesis

The eight evidence records form a coherent but bounded signal map. Human exercise-biopsy evidence places PGC-1 α activation early after exercise [1]. Antioxidant perturbation studies

then show that high-dose vitamin C, with or without vitamin E, can attenuate selected exercise-induced cellular or metabolic responses [2-4,7]. This supports the idea that some adaptation signals are redox sensitive. It does not support the stronger claim that every antioxidant exposure blocks training benefit.

NFE2L2/Nrf2 evidence strengthens the mechanistic interpretation. In mice, disruption of NFE2L2 impaired normal increases in mitochondrial-biogenesis markers and antioxidant-response genes after exercise [5]. A later muscle-specific inducible Nrf2 knockout and proteomics study added functional and pathway-level support by showing impaired training capacity and altered redox, respiration, and adaptation pathways in knockout animals [8]. Human data are directionally consistent: acute exercise increased Nrf2-linked transcripts, four weeks of interval training increased citrate synthase activity and Nrf2, NRF-1, and TFAM protein, and training-induced Nrf2 change correlated with NRF-1 [6].

The key result is a boundary rather than a slogan. Vitamin C/E exposure can blunt cellular adaptation, but performance outcomes may remain neutral or less consistently affected [4,7]. Therefore, the redox-gate model is strongest for pathway engagement and cellular mitochondrial adaptation. It is weaker for predicting immediate performance changes, supplement harm, or clinical outcomes.

3.2 Evidence-coded sensitivity analysis

Removing the mouse-only Nrf2 studies leaves a human evidence set that still supports redox sensitivity through antioxidant perturbation and Nrf2-associated biopsy responses [2-4,6,7]. Removing antioxidant trials leaves a weaker but still plausible mechanistic model based on exercise transcription, Nrf2 association, and genetic/proteomic perturbation [1,5,6,8]. The most important falsifier is endpoint discordance: if future trials repeatedly show preserved mitochondrial proteins, preserved endogenous antioxidant induction, and preserved insulin-sensitivity responses despite verified redox attenuation, the gate model should be downgraded. A second falsifier is timing specificity. If antioxidant exposure far from training sessions has the same effect as exposure near the exercise signal, the model must shift away from an acute redox-gate explanation and toward chronic nutritional or systemic confounding.

4 Discussion

The synthesis supports a mechanistic interpretation in which transient exercise redox signals operate as part of the adaptive information system of skeletal muscle. This interpretation aligns with human exercise-transcription data, human antioxidant perturbation trials, and Nrf2-linked mouse and human findings [1-8]. It is also appropriately narrower than common public claims. A redox gate does not mean reactive species are always beneficial or antioxidant strategies are always harmful. It means that suppressing the signal during an adaptation-relevant window can alter downstream cellular remodeling.

Competing explanations remain credible. Antioxidant supplements may change training adaptation through redox-independent pharmacology, differences in baseline diet, altered inflammation, adherence, or measurement timing. Whole-body performance may be buffered by cardiovascular, neural, behavioral, and substrate adaptations even when mitochondrial proteins or transcripts shift. Conversely, marker changes can be statistically detectable without reaching a meaningful functional threshold. These alternatives are not defects in the model; they are the boundaries that prevent overinterpretation.

The most useful next experiment would randomize participants by baseline redox and dietary status, separate peri-exercise from non-exercise antioxidant timing, and measure matched acute redox markers, Nrf2 activity, PGC-1 α -linked transcription, mitochondrial proteins, citrate synthase or respiration, insulin

Table 1. Primary-study evidence matrix for redox gating of exercise mitochondrial adaptation.

Study	Model and perturbation	Key finding	Interpretive limitation
[1]	Human skeletal-muscle biopsy study after prolonged exercise; Single prolonged knee-extensor exercise bout in trained and untrained legs	Exercise transiently increased PGC-1alpha transcription and mRNA in human skeletal muscle, supporting a rapid adaptive transcription layer.	The study established timing of transcriptional activation, not a causal requirement for oxidant signaling.
[2]	Randomized human training study with supporting rat experiments; Vitamin C supplementation during endurance training	Vitamin C reduced training efficiency and blunted some exercise-induced mitochondrial-biogenesis signals, with rat data supporting reduced PGC-1alpha and cytochrome c responses.	The human arm was modest in size and vitamin C alone cannot represent all antioxidant exposures, doses, or timing strategies.
[3]	Human exercise-training intervention; Vitamin C plus vitamin E supplementation during exercise training	Exercise improved insulin-sensitivity measures and induced PGC-1 family and antioxidant-defense transcripts in unsupplemented participants; antioxidant supplementation attenuated these responses.	The work supports redox-sensitive signaling but should not be generalized to every antioxidant molecule or all clinical contexts.
[4]	Double-blind randomized human endurance-training trial; Vitamin C plus vitamin E during endurance training	Vitamin C and E hampered increases in selected mitochondrial proteins after endurance training while endurance-performance gains were not clearly blocked.	Cellular adaptation and whole-body performance diverged, creating a boundary against claims that antioxidant blunting always impairs performance.
[5]	Mouse acute exercise and training with NFE2L2/Nrf2 deficiency; NFE2L2 disruption, acute exercise, and training	NFE2L2 deficiency prevented normal exercise-induced increases in several mitochondrial-biogenesis and antioxidant-response markers in skeletal muscle.	Mouse genetic evidence identifies a necessary redox-responsive layer but does not define the complete human training response.
[6]	Human skeletal-muscle biopsy study of acute and chronic exercise; Submaximal endurance exercise, supramaximal interval exercise, and four weeks of Tabata training	Acute exercise increased Nrf2, NRF-1, and HO-1 mRNA; training increased citrate synthase activity and Nrf2, NRF-1, and TFAM protein, with Nrf2 changes correlated with NRF-1.	Associations support a role for Nrf2 but do not prove that Nrf2 alone gates adaptation.
[7]	Human endurance-training intervention; Vitamin C plus vitamin E supplementation	Supplementation did not attenuate acute oxidative-stress or gene-expression responses but prevented some cellular adaptations to endurance training.	This partly discordant pattern argues for endpoint-specific rather than binary antioxidant interpretation.
[8]	Muscle-specific inducible Nrf2 knockout mice after treadmill exercise training; Nrf2 deletion plus three weeks of treadmill training	Wild-type trained mice improved running distance, whereas knockout trained mice showed impaired capacity and altered proteomic pathways related to redox homeostasis, mitochondrial respiration, and muscle adaptation.	Proteomic and mouse functional data should be treated as mechanistic support, not direct human supplementation guidance.

Redox-gating synthesis workflow

Executed steps and audit path for this bundle

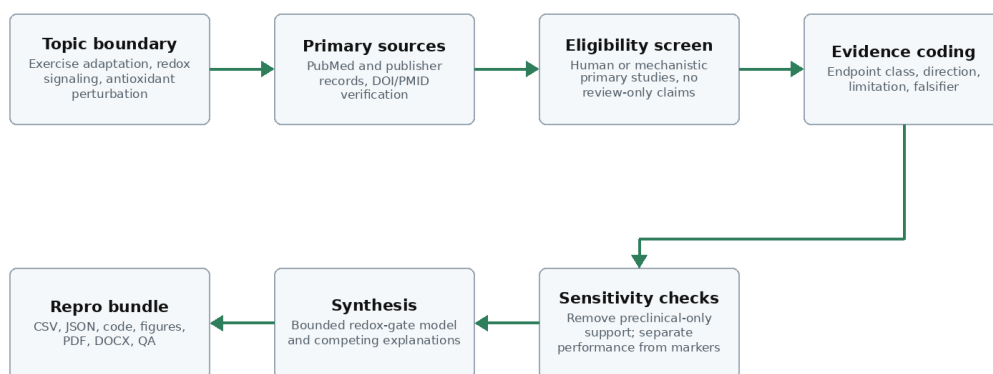


Figure 1. Analysis process. The workflow moved from topic boundary and primary-source verification through eligibility screening, evidence coding, sensitivity checks, synthesis, and reproducible bundle assembly. Solid connectors indicate executed analysis steps.

Conceptual model: a redox signal gate, not an antioxidant rule

Solid links are evidence-supported; dashed links are bounded competing explanations or falsifiers

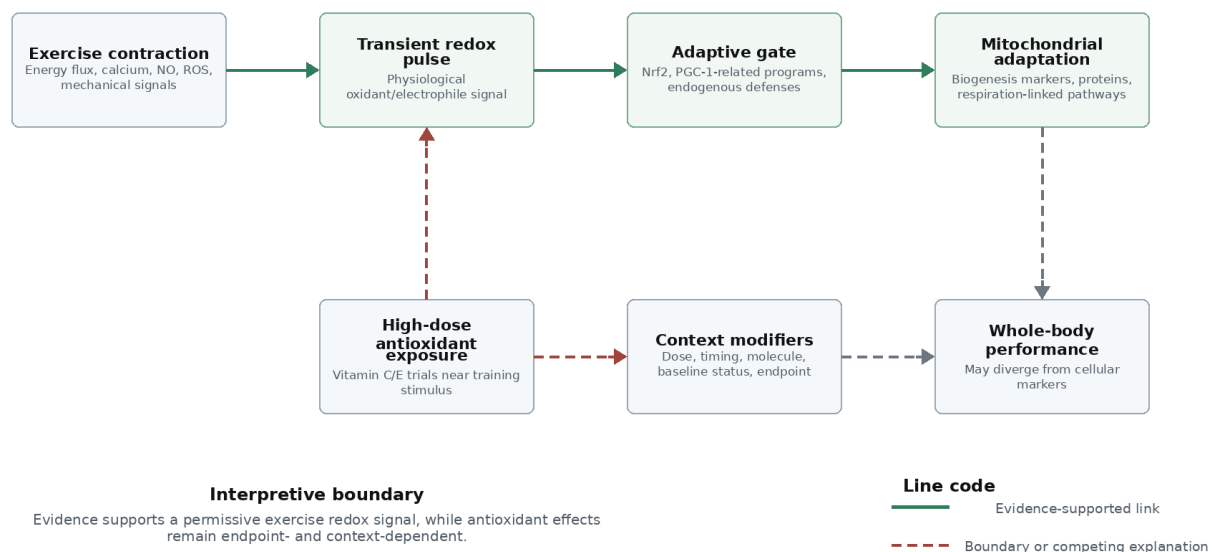


Figure 2. Redox-gate concept summary. Solid connectors show evidence-supported links from exercise contraction to transient redox signaling, adaptive-gate pathways, and mitochondrial adaptation. Dashed connectors show antioxidant perturbation, context modifiers, and the boundary between cellular markers and whole-body performance.

sensitivity, and performance outcomes. Such a design would discriminate between an acute redox-gate hypothesis, a chronic nutrient-status hypothesis, and a nonspecific supplement-adherence explanation.

5 Limitations

This synthesis is intentionally small and mechanistic. It is not a systematic review or meta-analysis, and the included interventions, doses, populations, and endpoints are heterogeneous. Several records use molecular markers that are informative for pathway engagement but are not clinical outcomes. Mouse Nrf2 perturbation studies improve causal inference but do not transfer directly to human supplement decisions. All eight included records were verified against primary-study reports and PubMed or publisher metadata; bibliographic identifiers do not remove the underlying population and endpoint limitations.

6 Conclusions

Primary evidence supports a bounded redox-gate model for exercise mitochondrial adaptation. Transient exercise redox signaling contributes to mitochondrial-biogenesis and endogenous-defense responses, and high-dose antioxidant exposure can blunt selected cellular adaptations. The model should be applied with endpoint discipline: it supports redox-sensitive pathway interpretation, not a universal claim that antioxidants block exercise benefit.

Declarations

Data and code availability. The evidence table, machine-readable data, analysis code, figures, and QA record accompany this repository deposit.

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

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