
Metabolic Overdrive in Elite Sport: A Mechanistic Review on AMPK–mTOR Oscillation, NAD⁺ Economy, and Epigenetic Drift

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Review

Metabolic Overdrive in Elite Sport: A Mechanistic Review on AMPK–mTOR Oscillation, NAD⁺ Economy, and Epigenetic Drift

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Abstract

Elite performance relies on a rhythmic alternation between catabolic and anabolic states orchestrated by AMPK and mTOR. We propose that chronic nutrient or hormonal stimulation can flatten this oscillation and induce a metabolic overdrive state characterized by sustained mTORC1 activation, suppressed autophagy, redox imbalance, and NAD⁺-dependent silencing of SIRT1 via PARP overactivation, with downstream epigenetic drift. We present a conceptual mechanistic narrative review integrating evidence from molecular nutrition, exercise physiology, and cancer biology into a systems framework linking AMPK–mTOR dynamics, the SIRT1–PARP NAD⁺ economy, and chromatin regulation (DNMT/TET, HAT/HDAC, miRNAs). Using elite sport as a natural model of maximal adaptation, we outline mechanistic parallels—not causal equivalence—between performance enhancement and pro-proliferative signaling. We define testable predictions: (1) prolonged mTORC1 activation (>24 h post-exercise) associates with ↓AMPK Thr172-P, ↓NAD⁺ and ↓SIRT1 activity; (2) overreaching with high anabolic load increases PARylation and H3K9ac while reducing TET activity; (3) interventions that periodically restore AMPK (fasted endurance, time-restricted feeding, polyphenol-mediated AMPK activation) re-establish oscillation and reduce redox/epigenetic noise. The Metabolic Overdrive Model provides a mechanistic language for the molecular limits of exercise adaptation and a basis for biomarker-guided periodization that preserves resilience. No causal inference is claimed.

Keywords: AMPK; mTOR; NAD⁺/SIRT1; PARP; redox signaling; DNA methylation; histone acetylation; microRNA; elite sport; exercise adaptation

1. Introduction

Elite sport offers a unique experimental model for studying the adaptive limits of human physiology. Through rigorous training, specialized nutrition, and—in some cases—the use of pharmacological agents, athletes continuously push cellular systems to optimize energy flux, recovery, and performance. These strategies rely on the dynamic regulation of energy-sensing

pathways, particularly the AMP-activated protein kinase (AMPK) and the mechanistic target of rapamycin (mTOR), which together orchestrate the balance between catabolic and anabolic metabolism [1–4]. Under normal conditions, this oscillation ensures efficient substrate use, mitochondrial quality control, and tissue repair. However, chronic stimulation of anabolic pathways by nutrient overload, supplementation, or doping may lead to a loss of regulatory balance—a state of *metabolic overdrive* [5,6].

Recent advances in molecular physiology and nutrition research have revealed that nutrient-sensitive signaling cascades not only control energy metabolism but also influence the epigenetic landscape of the cell. Modifications such as DNA methylation, histone acetylation, and noncoding RNA expression act as metabolic sensors, translating nutritional and redox states into gene-regulatory outcomes [7–9]. This has profound implications for both performance enhancement and disease risk, as dysregulated AMPK–mTOR activity and oxidative stress can promote aberrant DNA methylation, genomic instability, and tumorigenic signaling [10–12].

While exercise is broadly recognized as protective against metabolic and oncologic disorders, the extremes of performance physiology may blur the boundary between adaptation and pathology. The overlap between anabolic signaling in hypertrophying muscle and in proliferating cancer cells raises an important question: can the biological mechanisms that drive elite performance also predispose to molecular instability when chronically overstimulated? This issue is particularly relevant in the context of nutritional excess and ergogenic aids, which can amplify both anabolic and oxidative stress pathways [13,14].

The present review aims to synthesize current evidence on the interactions between nutritional signaling, AMPK–mTOR regulation, oxidative stress, and epigenetic drift, using elite sport as a conceptual framework for exploring the limits of human adaptation. By integrating findings from molecular nutrition, exercise physiology, and cancer biology, this work proposes a mechanistic model of *metabolic overdrive* that may help clarify how chronic anabolic stimulation affects both performance optimization and long-term cellular stability.

2. Materials and Methods

The methodological approach adopted in this review reflects the nature of the question addressed rather than adherence to a predefined review protocol. Because the aim is to elucidate how recurrent molecular patterns emerge across nutrition, exercise, redox biology, and epigenetic regulation, emphasis is placed on mechanistic coherence, directional signaling relationships, and temporal context. Evidence is therefore integrated in a manner that privileges explanatory depth and translational relevance, allowing disparate findings to be interpreted within a unified physiological framework.

2.1. Aim and Review Type

This work is a conceptual mechanistic narrative review employing structured evidence mapping. The primary aim was not exhaustive literature coverage or quantitative effect-size estimation, but the integration of directional mechanistic evidence across molecular nutrition, exercise physiology, redox biology, and epigenetic regulation into a coherent systems-level framework relevant to elite sport. Accordingly, the review is hypothesis-generating and does not claim to meet the criteria of a systematic review or meta-analysis.

2.2. Conceptual Framework

Evidence integration was guided a priori by a mechanistic framework organized along three interconnected regulatory axes:

- (1) Nutrient and energy sensing (AMPK–mTOR signaling),
- (2) Redox regulation and NAD⁺ economy (SIRT1–PARP balance), and
- (3) Epigenetic control mechanisms (DNA methylation, histone modifications, and microRNAs).

Across all axes, particular emphasis was placed on upstream–downstream relationships, feedback topology (negative vs. positive feedback), and temporal dynamics, especially within 0–48 h post-exercise or post-nutritional stimulus recovery windows. Priority was given to mechanisms that could be operationalized using human-assayable biomarkers (e.g., skeletal muscle biopsies, PBMCs, circulating metabolites or miRNAs).

2.3. Literature Identification

A nonsystematic literature search was conducted using PubMed, Scopus, and Web of Science. The search focused primarily on studies published within the last 15 years, complemented by seminal earlier publications fundamental to the understanding of the targeted pathways. Representative search terms included combinations of:

- “AMPK and mTOR and exercise”,
- “NAD⁺ and SIRT1 and PARP”,
- “exercise and redox signaling and autophagy”,
- “exercise epigenetics and DNA methylation”,
- “overtraining and oxidative stress”.

Additional relevant studies were identified through backward and forward citation tracking of key articles. The search strategy was designed to capture mechanistic depth rather than exhaustive breadth.

2.4. Eligibility Criteria

Studies were considered eligible if they fulfilled at least one of the following criteria:

- provided directional mechanistic evidence (e.g., pathway activation/inhibition, cofactor dependence);
- included temporal resolution relevant to exercise, nutritional intervention, or recovery dynamics;
- involved human data or demonstrated clear translational relevance (e.g., skeletal muscle tissue, PBMCs, or validated human biomarkers).

Excluded were:

- purely descriptive associations lacking mechanistic interpretation;
- single time-point studies without temporal context;
- studies unrelated to the predefined mechanistic axes or performance physiology.

2.5. Qualitative Appraisal of Evidence

Consistent with the narrative mechanistic nature of the review, no formal risk-of-bias scoring or quantitative quality grading was applied. Instead, evidence was qualitatively appraised based on:

- (1) internal mechanistic coherence,
- (2) consistency across experimental models (cellular, animal, and human), and
- (3) concordance among multiple molecular readouts within the same signaling pathway (e.g., AMPK phosphorylation alongside autophagy markers).

2.6. Synthesis Strategy

Eligible evidence was mapped onto the three predefined mechanistic axes and integrated through conceptual synthesis, emphasizing oscillatory versus sustained activation patterns, feedback polarity, and cross-axis convergence. This integrative process resulted in the formulation of the Metabolic Overdrive Model, which conceptualizes the loss of adaptive oscillation as a systems-level transition. The model is intended to guide future experimental testing and biomarker-driven investigation rather than to establish causal inference.

3. Mechanistic Synthesis

This section integrates existing molecular evidence into a mechanistic synthesis rather than reporting new experimental results; emphasis is placed on feedback topology (AMPK–mTOR antagonism, SIRT1–PARP NAD⁺ economy) and energetic context.

3.1. Nutritional Signaling and the AMPK–mTOR Axis

Energy and nutrient availability act as master regulators of metabolic homeostasis, governing the balance between catabolism and anabolism in virtually all eukaryotic cells. The AMP-activated protein kinase (AMPK) and the mechanistic target of rapamycin (mTOR) represent the two central signaling nodes coordinating this metabolic dialogue. AMPK acts as a low-energy sensor activated by an increased AMP/ATP ratio through the upstream kinase LKB1 and the calcium/calmodulin-dependent kinase kinase β (CaMKK β). Once activated, AMPK phosphorylates multiple downstream targets, including acetyl-CoA carboxylase (ACC) and peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α), thereby enhancing glucose uptake, fatty-acid oxidation, and mitochondrial biogenesis [15,16].

mTOR, in contrast, serves as a nutrient and growth sensor, existing in two complexes—mTORC1 and mTORC2—with distinct regulatory roles. mTORC1 responds primarily to amino-acid sufficiency, insulin, and growth factors to promote ribosomal biogenesis, protein synthesis, and lipid production via activation of p70S6 kinase (S6K1) and inhibition of the eukaryotic initiation factor 4E-binding protein (4E-BP1). mTORC2, conversely, modulates cell survival and cytoskeletal organization through AKT and SGK1 signaling. This bidirectional interplay ensures metabolic flexibility, where AMPK activation under energy stress suppresses mTORC1 through phosphorylation of tuberous sclerosis complex 2 (TSC2) and raptor, whereas sufficient energy and amino acids reverse the inhibition, restoring anabolic signaling [17–19].

In skeletal muscle, this AMPK–mTOR oscillation underpins the molecular basis of *training–fuel coupling*. During exercise, AMPK activation favors catabolic fluxes—autophagy, lipid oxidation, and mitochondrial turnover—essential for energetic recovery. Following exercise, nutrient repletion and growth signals transiently reactivate mTOR to promote hypertrophy and protein synthesis. Such rhythmic alternation maintains *metabolic flexibility*, defined as the capacity to efficiently switch between oxidative and glycolytic metabolism depending on substrate availability [20,21].

The time-domain behavior of the adaptive AMPK–mTOR rhythm is illustrated in Figure 1 below, showing the expected out-of-phase dynamics across the training–feeding cycle.

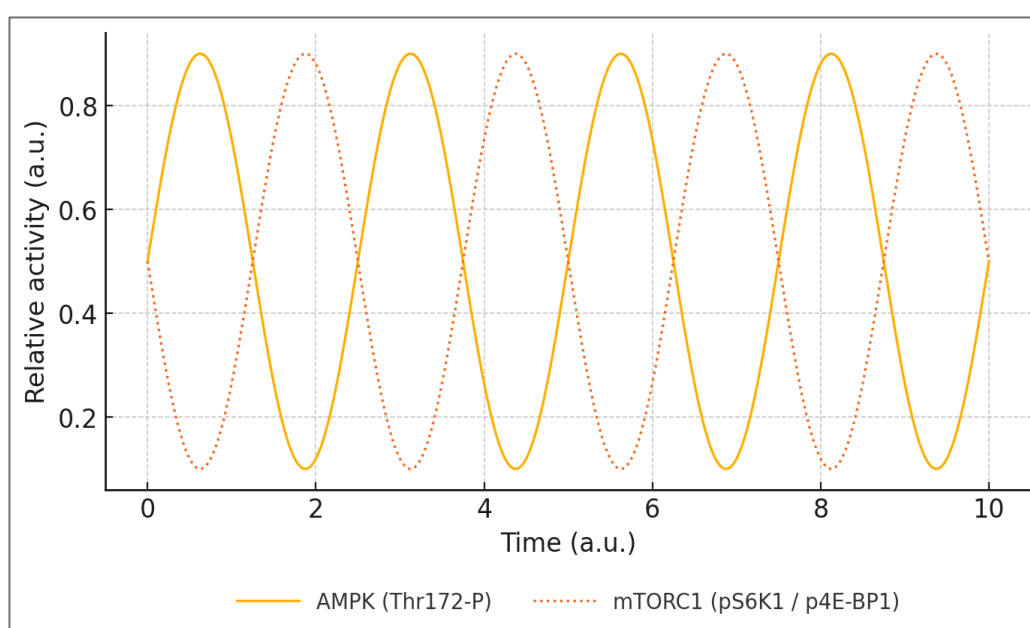


Figure 1. AMPK–mTOR oscillation in the adaptive state. Out-of-phase time-course of AMPK (Thr172-P; solid line) and mTORC1 readouts (pS6K1/p4E-BP1; dotted line) during sequential exercise–refeeding cycles. The adaptive signature is the antiphase between catabolic (AMPK) and anabolic (mTORC1) peaks; axes are in arbitrary units; legend placed below panel to avoid overlap.

This time-resolved view clarifies why adaptive recovery windows matter: as long as AMPK and mTORC1 remain antiphased, autophagic turnover and synthesis are temporally decoupled, limiting ROS spillover and protecting chromatin integrity. When nutrient or hormonal input compresses this phase separation, the oscillation flattens and the system drifts toward sustained anabolism—an entry point into the lock-in regime.

However, chronic nutrient oversupply or pharmacologic stimulation can flatten this oscillatory pattern. High-protein or high-carbohydrate diets with constant amino-acid and insulin stimulation maintain mTORC1 activation and suppress AMPK-mediated checkpoints [10,11,22]. The resulting anabolic “lock-in” diminishes autophagy, impairs mitophagy, and exacerbates mitochondrial reactive oxygen species (ROS) production [23]. This oxidative burden promotes endoplasmic reticulum (ER) stress, unfolded protein response (UPR) activation, and redox imbalance, compromising mitochondrial quality control [24,25]. In the long term, these processes may contribute to insulin resistance, inflammation, and epigenetic dysregulation, mirroring several molecular hallmarks of tumorigenesis [26].

The loss-of-oscillation pattern is illustrated in Figure 2 where AMPK activity decays while mTORC1 remains persistently high—an anabolic lock-in consistent with the overload context described above.

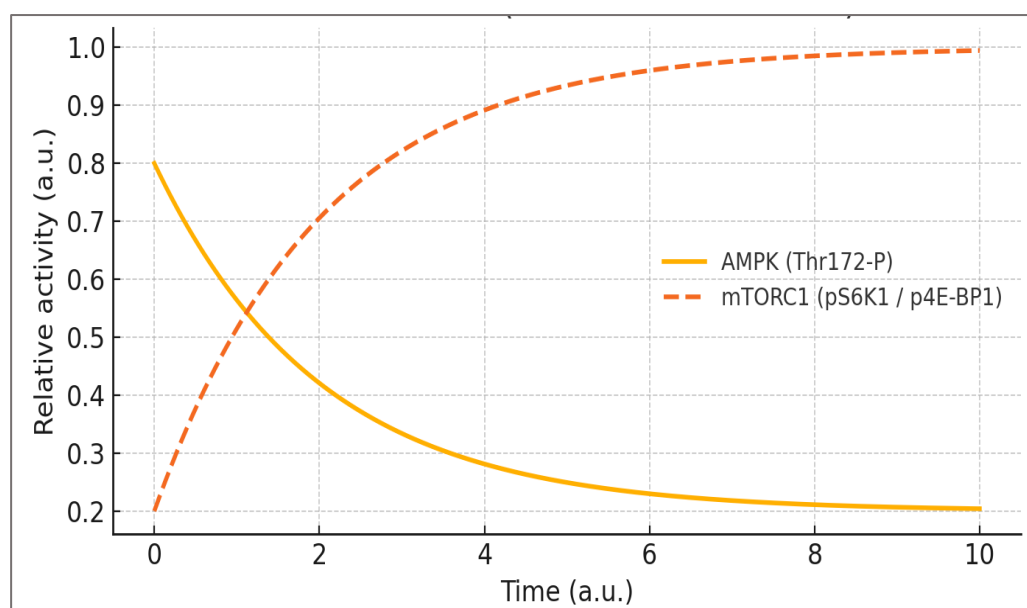


Figure 2. Lock-in (Metabolic Overdrive): loss of oscillation and sustained mTORC1. Time-domain collapse from the adaptive antiphase to a fixed state with depressed AMPK (Thr172-P; solid line) and persistently elevated mTORC1 readouts (pS6K1/p4E-BP1; dotted/segmented). Curves are schematic (a.u.) and depict the convergence to a high-anabolic steady state; legend is placed within the panel without obscuring the traces.

This collapse explains why constant amino-acid and insulin exposure keeps mTORC1 tonically active while AMPK checkpoints fade, reducing autophagy and mitophagy and increasing ROS/ER-stress. In practice, the absence of a 24–48 h AMPK–mTOR antiphase window signals reduced metabolic flexibility. Operationally, lock-in is suspected when pS6K1 (Thr389) and p4E-BP1 (Ser65) remain elevated >24 h with low AMPK Thr172-P and reduced LC3-II turnover.

Nutritional factors can either exacerbate or mitigate this imbalance. Amino acids such as leucine and methionine are potent mTORC1 activators through Rag GTPase signaling [27], whereas bioactive

compounds like resveratrol, curcumin, and epigallocatechin gallate (EGCG) stimulate AMPK and restore redox equilibrium [28–30]. Caloric restriction, intermittent fasting, and endurance training represent physiological strategies that periodically reactivate AMPK and improve mitochondrial efficiency [31,32]. Conversely, chronic overfeeding or supplementation-driven anabolic excess perpetuates mTOR dominance, driving *metabolic overdrive*—a state of sustained anabolism, suppressed autophagy, and cumulative oxidative and epigenetic stress [33].

To make this construct actionable in human studies, we define an operational set of criteria for the metabolic overdrive state (Box 1).

Box 1. Operational definition of the Metabolic Overdrive state

Concept - *Metabolic overdrive* is a measurable state of sustained anabolic activation in which the adaptive AMPK–mTOR oscillation collapses into a fixed, high-energy steady state.

Core measurable features (human-assayable):

1. Persistent mTORC1 activation — \uparrow p-S6K1 (Thr389) and \uparrow p-4E-BP1 (Ser65) persisting >24 h after training/feeding.
2. Suppressed AMPK signaling — \downarrow AMPK Thr172-P, \downarrow ULK1 Ser555-P, reduced LC3-II turnover and \uparrow p62 under lysosomal inhibition.
3. Redox imbalance — \uparrow 8-oxo-dG / TBARS, \downarrow GSH/GSSG, \uparrow inflammatory redox tone.
4. NAD⁺ economy shift — \uparrow PARylation, \downarrow NAD⁺, \downarrow SIRT1 activity, \downarrow NAMPT.
5. Epigenetic drift — \uparrow H3K9ac, \uparrow DNMT1, \downarrow TET activity / 5hmC; promoter-level changes at FOXO3 / SOD2 (oxidative-stress loci).
6. Functional correlates — reduced metabolic flexibility, delayed HRV recovery, impaired fat oxidation at submaximal workloads.

Threshold (operational) - Presence of ≥ 3 criteria above persisting ≥ 24 h after a metabolic challenge (training \pm nutritional load).

Reversibility window - Normalization of AMPK Thr172-P and NAD⁺ within 48–72 h indicates adaptive oscillation; failure indicates lock-in.

At the systems level, the AMPK–mTOR axis acts as a molecular interface between nutrition, metabolism, and growth signaling. Understanding how dietary and pharmacological interventions modulate this crosstalk is crucial for defining the threshold between adaptive remodeling and pathological overload in elite performance contexts. In this review, the AMPK–mTOR regulatory dyad serves as the central mechanistic framework through which nutritional signaling connects energy balance, redox homeostasis, and epigenetic stability. Together, these signaling nodes form an adaptive triad that integrates energetic demand, substrate availability, and anabolic drive. Their dynamic cross-regulation ensures that catabolic and anabolic fluxes oscillate in harmony, preserving mitochondrial integrity and metabolic flexibility across varying nutritional states. The principal components and interactions of this network are summarized in Table 1, which integrates upstream regulators, downstream targets, and physiological outcomes of AMPK–mTOR–SIRT1 coordination.

Table 1. Nutritional signaling pathways and their integrated roles in metabolic adaptation.

| Pathway / Component | Nutritional or Energetic Trigger | Upstream Regulator(s) | Primary Molecular Effect | Downstream Target(s) | Adaptive Role (Physiological Context) | Potential Dysregulation (Overdrive State) |
|---------------------|-----------------------------------|-----------------------|---|---------------------------|---|--|
| AMPK | Energy deficit, exercise, fasting | AMP/ATP ratio, LKB1 | Activates catabolic fluxes; inhibits mTORC1 | ACC, ULK1, PGC-1 α | Enhances mitochondrial biogenesis, endurance, autophagy | Chronic suppression \rightarrow anabolic dominance, insulin resistance |

| | | | | | | |
|-------------------------------------|--|-----------------------------|---|--------------------------------------|--|--|
| mTORC1 | Amino acids (leucine), insulin, IGF-1 | PI3K–AKT, Rheb, Rag GTPases | Stimulates protein synthesis via p70S6K and 4E-BP1 | Ribosomal proteins, eIF4E | Promotes muscle growth and recovery | Persistent activation → oxidative stress, epigenetic drift |
| SIRT1 | NAD ⁺ levels, caloric restriction | AMPK, NAMPT | Deacetylates transcriptional regulators (PGC-1 α , FOXO) | PGC-1 α , p53, NF- κ B | Increases oxidative metabolism and stress resistance | NAD ⁺ depletion → loss of redox control and mitochondrial decline |
| IGF-1/AKT axis | Protein intake, GH, insulin | GH/IGF-1 signaling | Activates mTORC1, inhibits AMPK | FOXO, TSC2, GSK3 β | Supports hypertrophy and tissue regeneration | Chronic activation → reduced autophagy, oncogenic signaling |
| Leucine–AMPK–mTOR crosstalk | Branched-chain amino acids | Ragulator complex | Coordinates anabolism–catabolism balance | mTORC1, AMPK | Fine-tunes training–fuel coupling, metabolic flexibility | Excess BCAA intake → insulin desensitization, ROS accumulation |
| NAD⁺/PARP balance | Oxidative load, DNA repair demand | PARP1, SIRT1 | Competes for NAD ⁺ substrate | SIRT1, PGC-1 α | Links redox balance to mitochondrial maintenance | PARP hyperactivation → NAD ⁺ depletion, energy collapse |
| FOXO transcription factors | Energy deficit, oxidative stress | AMPK, SIRT1, AKT | Regulate autophagy, antioxidant enzymes | Catalase, MnSOD, LC3 | Antioxidant defense and longevity | AKT-mediated inhibition → reduced oxidative protection |

Notes: Nutritional signaling integrates energetic and anabolic cues through AMPK–mTOR–SIRT1 coordination, maintaining metabolic flexibility and cellular homeostasis.

Following this integrative overview, it becomes evident that sustained nutrient stimulation or pharmacological enhancement may disturb this oscillatory equilibrium, driving metabolic overdrive and initiating downstream redox and epigenetic consequences.

3.2. Molecular Parallels Between Performance Enhancement and Tumorigenesis

The molecular architecture of performance adaptation shares striking similarities with the signaling networks that drive oncogenic growth. Both rely on sustained anabolic activation, redox modulation, and metabolic reprogramming to support energy-intensive biosynthesis. Central to this overlap is the insulin/IGF-1–PI3K–AKT–mTOR cascade, which governs nutrient sensing and cell growth. In skeletal muscle, transient activation of this pathway stimulates protein synthesis and hypertrophy following training or nutritional stimuli. However, chronic hyperactivation through excessive caloric intake, anabolic steroids, or exogenous insulin-like factors may disrupt the homeostatic balance between growth and repair [34,35]. Continuous mTORC1 stimulation bypasses AMPK checkpoints, promoting unrestrained anabolism and attenuated autophagy—features that closely parallel those of neoplastic proliferation [36,37]. Detailed analysis of neuromuscular adaptations to strength and plyometric training has further clarified how anabolic drive interacts with adaptive signaling cascades at the molecular level, highlighting the fine boundary between beneficial remodeling and pathological overactivation [38].

Insulin and IGF-1 signaling are among the most studied molecular links between nutrition, muscle hypertrophy, and cancer biology. Both ligands activate receptor tyrosine kinases, leading to

PI3K–AKT phosphorylation cascades that enhance glucose uptake, inhibit FOXO-dependent catabolic genes, and suppress apoptosis [39]. While beneficial for short-term adaptation, persistent activation of this axis contributes to insulin resistance and tumorigenic potential by stabilizing mTORC1 activity and driving oxidative and ER stress [38]. Epidemiological data support this duality: hyperinsulinemic states and high circulating IGF-1 are associated with increased cancer risk in metabolic diseases and overnutrition [41,42].

Another converging mechanism involves the hypoxia-inducible factor 1 α (HIF-1 α) pathway, which is upregulated both during intense exercise and in the hypoxic microenvironment of tumors. In athletes, HIF-1 α activation promotes angiogenesis, mitochondrial remodeling, and erythropoietin (EPO) production to improve oxygen delivery [43]. In tumors, the same transcriptional program drives vascularization, glycolytic enzyme expression, and cell survival under hypoxia [42]. Exogenous EPO administration—a doping practice in endurance sports—mimics this pathway, further elevating HIF-1 α and VEGF signaling, a pattern that resembles oxidative and genomic stress responses observed in other high-drive systems. [45,46]. Although EPO doping in athletes differs mechanistically from tumor hypoxia, the shared molecular endpoints—ROS generation, mitochondrial remodeling, and DNA repair stress—highlight a conserved bioenergetic logic across physiological and pathological adaptation.

Oxidative stress represents another axis of convergence. Both exercise and cancer involve transient ROS production; however, chronic oxidative overload shifts ROS from signaling intermediates to damaging agents. In skeletal muscle, ROS act as secondary messengers activating AMPK, PGC-1 α , and MAPK cascades, mediating adaptation to endurance training [47]. Yet under sustained nutrient excess or pharmacologic overstimulation, antioxidant defenses become insufficient, leading to lipid peroxidation, mitochondrial DNA damage, and redox-dependent epigenetic drift [48]. This imbalance recapitulates the oxidative phenotype of cancer cells, where mitochondrial dysfunction, NADPH oxidase upregulation, and impaired mitophagy promote genomic instability [49,50].

Finally, both hypertrophying muscle and proliferating cancer cells display a metabolic preference for aerobic glycolysis—a phenomenon akin to the *Warburg effect* [51]. During high-intensity training or anabolic stimulation, increased glycolytic flux provides rapid ATP and biosynthetic precursors (e.g., serine, glycine, acetyl-CoA) for protein and nucleotide synthesis. In cancer, this same metabolic configuration supports biomass accumulation and redox control. The intersection of glycolytic metabolism, one-carbon flux, and methyl donor availability also affects epigenetic regulation, as enzymes in the methionine and folate cycles are tightly coupled to cellular redox and energy status [52,53]. Persistent activation of these nutrient–signaling circuits, particularly when combined with exogenous ergogenic aids, may therefore shift the metabolic landscape from adaptive remodeling toward oncogenic instability.

Understanding these parallels does not imply causality between performance enhancement and cancer but rather underscores the shared molecular economy underlying growth, repair, and survival. Both systems exploit nutrient-driven signaling to optimize function—one physiologic, the other pathologic. Distinguishing where adaptation ends and instability begins remains a key challenge in deciphering the limits of metabolic plasticity in elite athletes.

The mechanistic parallels between anabolic adaptation and oncogenic signaling are summarized in Table 2, which integrates key physiological drivers, molecular mediators, and pathological counterparts that illustrate the shared architecture of metabolic overdrive across sport and cancer biology.

Table 2. Molecular parallels between performance enhancement and tumorigenesis.

| Mechanistic domain | Representative trigger or intervention | Physiological driver (Elite sport) | Oncogenic analogue (Cancer biology) | Key molecular mediator(s) | Adaptive outcome | Pathological counterpart (Overdrive state) |
|--------------------|--|------------------------------------|-------------------------------------|---------------------------|------------------|--|
|--------------------|--|------------------------------------|-------------------------------------|---------------------------|------------------|--|

| | | | | | | |
|--|---|--|---|--|---|---|
| Anabolic signaling (mTOR/AKT) | Resistance training, growth hormone, anabolic steroids | Transient anabolic activation for muscle hypertrophy and recovery | PI3K-AKT-mTOR hyperactivation promoting uncontrolled cell proliferation | mTORC1, AKT, S6K1, 4E-BP1, TSC2 | Enhanced protein synthesis and tissue remodeling | Persistent anabolic signaling, autophagy suppression, tumor-like growth |
| Hypoxia and angiogenesis | Altitude exposure, EPO doping, hypoxic training | HIF-1 α activation and VEGF upregulation for capillary and mitochondrial biogenesis | Tumor hypoxia, neovascularization | HIF-1 α , VEGF, EPO, PGC-1 α | Improved oxygen transport and energy efficiency | Pathological angiogenesis, oxidative stress, DNA instability |
| Oxidative stress and redox signaling | Intense endurance training, overreaching, nutrient excess | ROS-mediated activation of antioxidant defense and mitochondrial adaptation | Chronic ROS accumulation and oxidative DNA damage | NRF2, NF- κ B, SIRT1, p53 | Adaptive hormesis, redox-dependent signaling plasticity | Genomic instability, lipid peroxidation, mitochondrial dysfunction |
| Autophagy-UPR balance | Caloric restriction, intermittent fasting, recovery phases | Controlled proteostasis and organelle turnover | Autophagy dysregulation and ER stress adaptation | AMPK, LC3, ATF4, GRP78 | Protein quality control and metabolic recycling | Proteotoxic stress, ER overload, resistance to apoptosis |
| Epigenetic reprogramming | Nutrient timing, methyl donor availability, supplementation | Transient changes in DNA methylation and histone acetylation for gene regulation | Stable oncogenic methylation, miRNA dysregulation | DNMT1, HDACs, TETs, miR-21 | Flexible gene expression, adaptive remodeling | Epigenetic drift, transcriptional instability, dedifferentiation |
| Hormonal and growth factor signaling | GH/IGF-1 therapy, insulin use, anabolic stacking | Enhanced recovery, anabolic sensitivity | Endocrine-driven tumor growth, hyperinsulinemia | IGF-1R, STAT5, ERK1/2 | Accelerated regeneration, anabolic drive | Endocrine disruption, persistent proliferative signaling |
| Metabolic reprogramming (Warburg-like effect) | High-intensity training, glucose or amino acid loading | Glycolytic shift for ATP and biosynthetic precursor supply | Aerobic glycolysis in tumors (Warburg effect) | HK2, PKM2, LDHA, MYC | Efficient energy flux for adaptation | Persistent glycolysis, one-carbon imbalance, redox exhaustion |

Notes: Shared molecular pathways regulate both physiological adaptation and oncogenic proliferation, differing mainly in degree and duration of activation. *Representative measurable endpoints for the hypoxia/angiogenesis domain include VEGF (ELISA), GLUT1 (mRNA/protein), plasma EPO, resting lactate, and HIF-1 α stabilization (WB/flow cytometry).*

This convergence underscores how anabolic, oxidative, and epigenetic pathways form a common biochemical language between adaptation and disease. When sustained beyond physiological thresholds, the same nutrient-sensing mechanisms that promote recovery and

remodeling can drive instability, genomic stress, and redox imbalance. These transitions define the mechanistic foundation for the next section, which explores how metabolic stress reshapes the epigenetic landscape through redox-dependent signaling and NAD⁺-linked regulation.

3.3. Epigenetic Modulation Under Metabolic Stress

The interface between metabolism and epigenetics has emerged as one of the defining discoveries of modern molecular physiology. Cellular energy flux dictates the availability of cofactors that directly modify chromatin, making metabolism not merely a supplier of energy but an active governor of gene expression. Enzymes responsible for DNA and histone modifications depend on metabolites such as S-adenosylmethionine (SAM), acetyl-CoA, α -ketoglutarate (α -KG), and nicotinamide adenine dinucleotide (NAD⁺) [54]. These metabolites serve as dynamic reporters of the nutritional and redox environment: changes in diet, exercise load, or mitochondrial efficiency immediately reverberate in the epigenome.

In low-energy states, AMPK activation promotes NAD⁺ synthesis through the salvage enzyme NAMPT, which in turn enhances SIRT1 activity. SIRT1 deacetylates histones H3 and H4 and transcriptional regulators such as PGC-1 α , FOXO, and p53, thereby promoting oxidative metabolism, autophagy, and stress resistance [55]. This AMPK–SIRT1–PGC-1 α axis epitomizes a nutrient-sensing feedback that maintains chromatin compactness and genomic integrity during caloric scarcity. In contrast, nutrient oversupply generates abundant acetyl-CoA and SAM, driving histone hyperacetylation and DNA hypermethylation at promoters of oxidative and stress-response genes [56,57]. The chromatin thus “remembers” energy abundance through an anabolic epigenetic imprint.

DNA Methylation and Histone Acetylation in Exercise and Overload - exercise transiently remodels the skeletal muscle methylome. Acute endurance sessions induce hypomethylation at promoter CpG sites of metabolic regulators such as *PGC-1 α* , *PDK4*, and *TFAM*, facilitating transcriptional activation and mitochondrial biogenesis [58]. Over repeated training cycles, this hypomethylated pattern stabilizes, giving rise to the so-called *epigenetic memory* of exercise, which persists even after detraining [59,60]. Such “memory” reflects a primed chromatin state that accelerates re-adaptation upon retraining — a beneficial example of epigenetic plasticity.

However, this flexibility has limits. When nutrient intake, supplementation, or anabolic pharmacology impose chronic mTOR activation, the methylome drifts toward hypermethylation of catabolic and antioxidant genes (*FOXO3*, *SOD2*, *CAT*) and hypomethylation of anabolic and proliferative loci (*IGF1*, *MYC*, *mTOR*) [61,62]. The resulting transcriptional asymmetry mirrors the epigenetic architecture of many cancers, in which DNA methylation suppresses checkpoints and reinforces growth signaling [63]. Histone acetylation patterns behave analogously: during caloric restriction or endurance training, reduced acetyl-CoA levels and increased SIRT activity condense chromatin and favor repair pathways, whereas chronic nutrient overload expands chromatin through HAT activation (notably p300/CBP and GCN5) and enhances transcription of biosynthetic programs [64,65].

The Sirtuin–PARP Axis: NAD⁺ Competition and Redox Imbalance - a less visible but crucial intersection between metabolism and the epigenome lies in NAD⁺ partitioning between sirtuins and poly(ADP-ribose) polymerases (PARPs). Both enzyme families consume NAD⁺, but for divergent purposes: sirtuins preserve mitochondrial function and genomic stability via deacetylation, while PARPs respond to DNA damage by poly-ADP-ribosylation, a repair signal [65]. Under chronic oxidative stress, excessive PARP activation depletes NAD⁺, silencing sirtuin activity and collapsing the AMPK–SIRT1 axis [66]. This shift diverts energy from repair and metabolic regulation toward futile cycles of DNA damage and inflammatory signaling — a mechanism shared by overtrained muscle and tumor cells. Nutritional or pharmacological activation of AMPK (via resveratrol, berberine, or caloric restriction) can rebalance this NAD⁺ economy, restoring redox homeostasis and chromatin fidelity [28,31].

MicroRNAs and Translational Noise - microRNAs (miRNAs) represent an additional, fast-acting mechanism through which metabolic stress reshapes the adaptive landscape. Several miRNAs —

notably miR-1, miR-133a, miR-206, and miR-378 — coordinate muscle differentiation, mitochondrial turnover, and oxidative defense [66–68]. Endurance training typically upregulates oxidative miRNAs (miR-494, miR-181a) that enhance PGC-1 α signaling, whereas resistance or overload training preferentially increases miR-378 and miR-486, which promote hypertrophy [69]. Chronic nutrient and redox stress, however, destabilize this regulatory network, producing aberrant miRNA expression such as persistent miR-21 or miR-34a overexpression, both associated with fibrotic remodeling and oncogenic pathways [70,71]. In this context, miRNAs act as both messengers and memory traces of metabolic experience — biomarkers that reflect whether adaptation remains reversible or slides toward pathology.

From Metabolic Flexibility to Epigenetic Drift - epigenetic mechanisms are inherently reversible, yet their reversibility is time- and context-dependent. Prolonged oxidative overload exhausts α -KG and NAD⁺ pools, while accumulating succinate and fumarate — competitive inhibitors of TET and Jumonji demethylases [72]. This inhibition stabilizes aberrant histone and DNA methylation, anchoring the chromatin in maladaptive configurations. Mitochondrial dysfunction amplifies this process through disrupted one-carbon flux and altered SAM/SAH ratios, leading to global methylation instability [73,74].

The term *epigenetic drift* describes this cumulative loss of methylation precision across the genome. In cancer and aging, drift manifests as hypervariable methylation, local hypomethylation, and transposon reactivation. In the context of high-performance sport, analogous processes might underlie the progressive reduction in adaptive potential observed in chronically overloaded athletes. Methylation noise could blunt the genomic responsiveness to training stimuli, a molecular correlate of the overtraining syndrome [75].

Such convergence of redox imbalance, NAD⁺ depletion, and methylation drift reveals a unifying framework: the same biochemical plasticity that enables human adaptation also contains the seeds of instability. The oscillation between anabolic expansion and catabolic renewal—between acetylation and deacetylation, methylation and demethylation—is the molecular rhythm of life. When that rhythm is flattened by nutritional excess or pharmacologic drive, the epigenome ceases to dance to the music of adaptation and begins to echo the static of disease.

The principal metabolic–epigenetic mechanisms are summarized in Table 3, which integrates molecular cofactors, enzymatic regulators, and evidence from elite sport to illustrate how nutrient-driven signaling shapes the reversible—or progressive—nature of epigenetic remodeling.

Table 3. Epigenetic regulation under metabolic stress: mechanisms linking redox imbalance, nutrient flux, and adaptive instability.

| Epigenetic layer | Primary metabolic cofactor or pathway | Key enzyme s/ regulators | Physiological role (adaptive) | Pathological outcome (overdrive state) | Representative molecular targets | Evidence from elite sport | Potential interventions/modulators |
|---------------------|---------------------------------------|---------------------------|-------------------------------|--|---|--|---|
| DNA methylation | SAM / one-carbon metabolism | DNMT1, TET1–3, MTHFR, MTR | | Hypermethylation of antioxidant genes; hypomethylation of anabolic/proliferative loci; methylation drift | PGC-1 α , PDK4, TFAM, FOXO3, MYC | Endurance athletes show promoter hypomethylation of PGC-1 α and TFAM after repeated training cycles | Folate and methionine balance, caloric restriction, AMPK activation |
| Histone acetylation | Acetyl-CoA, NAD ⁺ / AMPK– | SIRT1, p300/CBP, P, | Chromatin compaction under | Hyperacetylation and persistent transcription | H3K9ac, H4K16ac, PGC-1 α , p53 | Training fasted or under caloric | Resveratrol, curcumin, |

| | | | | | | | |
|---|---|--|--|---|---|--|---|
| | SIRT1 axis | GCN5, HDACs | energy deficit; regulation of repair and mitochondrial genes | of anabolic programs | | restriction enhances SIRT1 activity and deacetylation | exercise-fasting cycles |
| Histone and DNA demethylation | α -KG / TCA flux | TETs, Jumonji demethylases | Removal of repressive marks; mitochondrial-nuclear communication | α -KG depletion, succinate/fumarate inhibition of demethylases | <i>H3K27me3</i> , <i>H3K9me3</i> , <i>IDH2</i> , <i>SDH</i> | Overreaching phases show transient TET up-regulation linked to oxidative flux | Endurance exercise, antioxidant restoration |
| NAD⁺-dependent regulation | NAD ⁺ salvage, PARP vs. sirtuins | PARP1, SIRT1, NAMPT | Balanced DNA repair and mitochondrial biogenesis | PARP overactivation \rightarrow NAD ⁺ depletion, SIRT1 silencing, redox collapse | <i>PGC-1α</i> , <i>FOXO</i> , <i>PARP1</i> , <i>SIRT1</i> | Overtraining decreases muscle NAD ⁺ and SIRT1, paralleling redox fatigue | Caloric restriction, AMPK activators, NAD ⁺ precursors |
| MicroRNA regulation | Energy/redox-dependent transcription | miR-1, miR-21, miR-34a, miR-486, miR-494 | Fine-tuning of hypertrophy, oxidative capacity, stress defense | Aberrant miRNA expression driving fibrosis and oncogenic signaling | <i>miR-21</i> , <i>miR-34a</i> , <i>miR-133a</i> , <i>miR-206</i> | Endurance \uparrow miR-181a, miR-494; resistance \uparrow miR-378, miR-486; overtraining \uparrow miR-21 | Training modulation, antioxidant support |
| One-carbon and methyl donor flux | Methionine-folate cycle | MAT2A, BHMT, SHMT1/2 | Maintenance of methyl balance for DNA/histone regulation | SAM/SAH imbalance, global hypermethylation, redox-linked drift | <i>DNMT3A</i> , <i>HMTs</i> , <i>MTHFD1L</i> | High-protein diets alter plasma methionine and SAM/SAH ratios in athletes | Controlled protein intake, B-vitamin support |

Notes: Metabolic stress remodels chromatin through energy-derived cofactors that couple redox status to gene regulation. In elite sport, these same epigenetic pathways mediate both resilience and exhaustion, defining the molecular border between adaptation and drift.

These findings consolidate the concept that metabolism and chromatin function as two interlocked systems, each continuously rewriting the state of the other. In elite athletes, periodic metabolic stress through training and recovery fosters a reversible form of epigenetic plasticity, allowing performance optimization without molecular instability. Yet, when this oscillation is flattened by chronic overnutrition, excessive supplementation, or pharmacological drive, the same adaptive machinery turns against itself.

Redox imbalance, NAD⁺ depletion, and one-carbon overload jointly erode the fidelity of chromatin signaling, promoting transcriptional noise and cumulative methylation drift. This progression defines a redox-epigenetic continuum that bridges adaptive exhaustion in sport with genomic instability in disease.

3.4. Case Contexts: Elite Sport and Doping Paradigms

This section describes molecular parallels and health risks associated with performance-enhancing practices; it does not imply causation or endorsement of such interventions.

Elite sport represents an unparalleled natural laboratory for studying the extremes of human adaptation — and, occasionally, its pathologies. The metabolic ambition to optimize performance often blurs into a gray zone where physiology meets pharmacology. Recent advances in artificial intelligence now assist in identifying performance determinants in elite team sports, offering data-driven perspectives on training load, nutritional status and adaptive physiology [76]. Big-data analytical frameworks further enhance such decision-making processes by integrating multivariate performance, physiological, and contextual metrics [77]. The interplay between *training, nutrition, and doping* creates an environment of sustained metabolic stimulation rarely encountered in any other context [78]. This section examines how performance-enhancing practices recapitulate the molecular features of *metabolic overdrive* and *epigenetic destabilization* described earlier.

Endurance Sports and the Hypoxic–Erythropoietic Axis - endurance sports such as professional cycling provide the most emblematic example of physiological adaptation pushed to its biochemical edge. Chronic endurance training induces a hypoxia-like signaling pattern characterized by transient stabilization of HIF-1 α , activation of erythropoietin (EPO), angiogenic remodeling, and mitochondrial biogenesis [79,80]. These responses are adaptive under normal conditions, improving oxygen transport and aerobic metabolism. However, exogenous EPO administration and blood transfusions — practices widely documented in professional cycling during the 1990s and early 2000s — exaggerated this system far beyond physiological boundaries [81].

Artificially elevated hematocrit increases oxygen-carrying capacity but imposes hemodynamic strain, oxidative load, and erythroid proliferation. Sustained HIF-1 α activity amplifies ROS generation and promotes a metabolic shift toward glycolysis and lactate accumulation even at rest [82]. In the long term, such *pseudo-hypoxic* signaling profiles are indistinguishable, at the molecular level, from tumor hypoxia responses, featuring upregulation of VEGF, GLUT1, and glycolytic enzymes [44,83]. Moreover, EPO itself acts as a growth and survival factor beyond erythroid cells, activating JAK2–STAT5 and PI3K–AKT pathways implicated in cancer progression [84]. While no causal link exists between EPO doping and malignancy, its signaling footprint overlaps substantially with pro-oncogenic pathways, illustrating how chronic stimulation of adaptive systems can drift toward dysregulation.

Strength Sports and the Anabolic–Epigenetic Axis - bodybuilding and other strength disciplines push the opposite side of the metabolic spectrum: sustained activation of the IGF-1–AKT–mTOR axis through resistance training, high-protein diets, and anabolic–androgenic steroids (AAS). Supraphysiological androgen exposure amplifies protein synthesis and suppresses catabolic genes via AR–mTORC1 crosstalk, while exogenous growth hormone (GH) and insulin potentiate this effect through the IGF-1 receptor [85–87]. In muscle tissue, these stimuli enlarge fiber cross-sectional area but also suppress autophagy, reduce mitochondrial density, and generate oxidative stress [88].

Recent molecular profiling of long-term AAS users revealed persistent epigenetic modifications, including hypomethylation of hypertrophy-related genes and hypermethylation of stress-response pathways, consistent with the “epigenetic memory” of drug-induced adaptation [89]. Moreover, chronic AAS exposure alters liver methylation and acetylation profiles, induces gene-expression signatures that overlap with hepatocellular carcinoma profiles, without implying causal progression. [90]. Case studies of elite bodybuilders who developed cardiac hypertrophy, hepatic adenomas, or renal neoplasms suggest that these effects appear molecularly traceable, though no causal inference can be drawn [91].

Nutritionally, high-protein intakes exceeding 3 g·kg⁻¹·day⁻¹, coupled with insulinotropic supplements and carbohydrate overfeeding, sustain mTOR activation while suppressing AMPK and SIRT1 activity [92]. The resulting anabolic lock-in mirrors the metabolic rigidity described in cancer cells: persistent mTORC1 signaling, reduced autophagic flux, and redox imbalance [10,33]. This creates a cellular environment favoring DNA damage and aberrant methylation. When compounded

with androgen-driven oxidative metabolism, the milieu becomes one of *metabolic overdrive* – high energy throughput but low regulatory elasticity.

Hormonal Manipulation and “Metabolic Doping” - beyond classical anabolic agents, a new frontier of *metabolic doping* targets pathways originally intended for therapeutic modulation. Thyroid hormones, β 2-agonists (e.g., clenbuterol), insulin, and selective AMPK modulators (AICAR, metformin) have been misused by athletes to alter substrate utilization or enhance endurance [93,94]. These agents interfere directly with metabolic sensors and cofactor pools, producing unpredictable downstream effects on the epigenome. For instance, AICAR activates AMPK pharmacologically and can mimic the transcriptional signature of endurance training, whereas clenbuterol overstimulates adrenergic pathways and induces mitochondrial uncoupling [95,96]. Chronic manipulation of these sensors may uncouple the finely tuned oscillation between AMPK and mTOR, destabilizing redox balance and epigenetic control.

Ethical and Biomedical Implications - the molecular parallels between performance optimization and disease raise ethical and medical questions that transcend doping control. Current anti-doping frameworks focus on detection and fairness, yet the long-term health consequences of chronic metabolic stimulation remain insufficiently understood. Persistent alterations in DNA methylation, histone acetylation, and microRNA networks could represent a form of *molecular scarring* that outlasts pharmacological exposure. This concept reframes the notion of “clean recovery”: molecular homeostasis may take years to restore, and in some cases, residual epigenetic instability could persist indefinitely [97].

The cases of high-profile endurance and strength athletes – from those involved in EPO-era cycling to long-term steroid users in bodybuilding – exemplify how human physiology can be optimized to the edge of self-destruction. Their bodies serve as extreme testbeds where metabolic and epigenetic mechanisms of adaptation, plasticity, and degeneration converge. Understanding these processes is not merely an exercise in moral scrutiny but an opportunity to learn how the same molecular programs that sustain elite performance can, under persistent drive, erode the genomic architecture they were meant to enhance.

The integrated dynamics of oxidative metabolism and chromatin remodeling are summarized in Table 4, illustrating how redox flux and epigenetic regulation form a unified feedback architecture that defines the physiological and pathological boundaries of adaptation.

Table 4. The redox–epigenetic feedback loop: a systems model linking oxidative metabolism, chromatin regulation, and adaptive limits.

| System component | Primary molecular driver | Key sensors or enzymes | Physiological feedback (adaptive) | Pathological feedback (overdrive state) | Representative molecular signature | Potential modulators / countermeasures |
|------------------------------|--|--------------------------|--|--|--|---|
| Mitochondrial ROS generation | Electron transport flux, NADH/NAD ⁺ ratio | Complex I–III, NOX, SOD2 | ROS act as signaling molecules activating AMPK and antioxidant genes | Chronic ROS accumulation leads to mtDNA damage, lipid peroxidation, and nuclear stress signaling | ↑ ROS, ↑ SOD2, ↑ NRF2 | Endurance training, antioxidant periodization, redox-adaptive nutrition |
| NAD ⁺ metabolism | NAMPT salvage pathway, PARP activity | NAMPT, PARP1, SIRT1 | Balanced NAD ⁺ use supports DNA repair and mitochondrial biogenesis | PARP overactivation depletes NAD ⁺ , silencing SIRT1 and | ↓ NAD ⁺ , ↓ SIRT1, ↑ PARylation | Caloric restriction, resveratrol, niacinamide, AMPK activation |

| | | | | | | |
|--------------------------------------|---|--|---|---|--|--|
| AMPK–SIRT1–PGC-1α axis | Energy sensing, NAD ⁺ /AMP ratio | AMPK, SIRT1, PGC-1α | Enhances oxidative metabolism, mitophagy, and chromatin integrity | impairing repair Collapse of AMPK–SIRT1 feedback causes autophagy failure and metabolic rigidity | ↑ PGC-1α, ↑ LC3-II, ↓ FOXO | Exercise-induced AMPK activation, fasting cycles |
| DNA and histone modifications | SAM/SAH ratio, α-KG availability | DNMTs, TETs, HDACs, HATs | Dynamic methylation/acetylation maintains gene expression flexibility | Methylation drift and histone hyperacetylation stabilize maladaptive transcription | ↑ H3K9ac, ↓ TET activity, ↑ DNMT1 | Balanced methyl donor intake, one-carbon flux restoration |
| Inflammatory redox signaling | NF-κB, NLRP3, cytokine ROS loops | NF-κB, IL-6, TNF-α | Transient activation supports repair and immune remodeling | Chronic activation sustains oxidative stress and metabolic block | ↑ NF-κB, ↑ IL-6, ↑ TNF-α | Polyphenols, omega-3s, anti-inflammatory recovery |
| Epigenetic memory and drift | ROS/NAD ⁺ -dependent enzyme regulation | SIRT1, PARP1, DNMT1, miRNAs | Transient chromatin remodeling encodes adaptive responses | Persistent oxidative stress leads to irreversible epigenetic drift | Hypomethylated oncogenes, hyperacetylated histones | Controlled recovery, antioxidant therapy, NAD ⁺ support |
| System-level outcome | Redox–epigenetic coupling | Integrated signaling through AMPK–mTOR–SIRT1 | Self-limiting oscillation ensures resilience | Feedback saturation locks system in pathological anabolism | ↓ AMPK, ↑ mTOR, ↑ ROS | Nutritional periodization, training load modulation |

Notes: Redox flux and chromatin dynamics form a self-reinforcing circuit that determines the trajectory of cellular adaptation. When balanced, this loop promotes renewal; when sustained beyond control, it accelerates molecular entropy and epigenetic drift.

Together, these findings delineate a dynamic equilibrium in which oxidative metabolism and chromatin architecture continually inform one another. Within this circuit, redox flux is not simply a by-product of energy turnover but a transcriptional signal that encodes the metabolic state into chromatin memory. As long as this feedback remains oscillatory—alternating between activation and recovery—the system preserves its resilience. When that oscillation collapses under continuous anabolic or oxidative drive, the feedback loop loses its corrective power, locking the cell into a state of sustained activation.

At this point, adaptation ceases to be reversible. The biochemical symphony that once synchronized energy use, redox balance, and gene regulation turns into a self-perpetuating echo of stress. What begins as performance optimization thus converges, mechanistically, toward the molecular grammar of instability.

3.5. The Metabolic Overdrive Model

Across the spectrum of elite performance, metabolic adaptation is characterized by oscillations between catabolic and anabolic states — a rhythmic negotiation between energy depletion and restoration. In physiological balance, this oscillation forms a *closed adaptive loop* governed by reciprocal activation of AMPK and mTOR, periodic fluctuations in redox tone, and reversible epigenetic remodeling. The loop functions as an information-processing system: metabolic cues are encoded as transient chemical modifications on chromatin, which in turn regulate the next cycle of energy flux.

From Oscillation to Lock-In - in the adaptive state, AMPK activation during energetic stress initiates autophagy, mitochondrial renewal, and chromatin deacetylation through SIRT1. During recovery, nutrient abundance and growth signals transiently activate mTORC1, promoting protein synthesis and tissue repair. This rhythmic succession of AMPK–mTOR–SIRT1 signaling maintains metabolic flexibility, minimizes oxidative stress, and preserves epigenetic plasticity.

Metabolic overdrive arises when this rhythm collapses into a static state of chronic anabolism. Persistent nutrient or hormonal stimulation suppresses AMPK checkpoints, silences sirtuins, and locks mTORC1 in constitutive activation. The system transitions from oscillation to saturation — energy continues to flow, but regulatory feedback weakens. Elevated acetyl-CoA, NADH/NAD⁺ imbalance, and ROS accumulation feed forward into histone hyperacetylation and aberrant DNA methylation [98]. The epigenome, once adaptive, becomes entrained to a pathological steady state: hypertranscriptional but inflexible.

Formal view - The dynamics can be approximated as a loss-of-oscillation (Hopf-like) bifurcation: as energetic input (nutrient/hormonal drive) increases, the amplitude of the AMPK–mTOR oscillation diminishes toward zero; beyond a critical input threshold, the oscillatory attractor disappears and the system converges to a single high-anabolic steady state (mTORC1-dominant “lock-in”).

For conceptual clarity, the oscillatory behavior of the AMPK–mTOR system can be represented by a minimal three-variable model:

$$\begin{aligned}\partial A/\partial t &= k_1 - k_2A - k_3M + \eta_1 \\ \partial M/\partial t &= k_4N - k_5A - k_6M + \eta_2 \\ \partial N/\partial t &= k_7A - k_8N + \eta_3\end{aligned}$$

where A = AMPK activity, M = mTORC1 activation, and N = NAD⁺ pool, while η_i represent stochastic fluctuations. Increasing energetic or hormonal input raises k_4 and suppresses k_5 , weakening negative feedback from AMPK to mTOR. Numerical simulation under these constraints yields a Hopf-like transition: oscillation amplitude decreases until the system collapses to a high-M steady state. This simplified structure captures the loss-of-oscillation threshold illustrated in Figure 3.

Bridge to architecture - Operationally, the threshold in figure maps onto the Box 1 criteria: persistence >24 h of \uparrow p-S6K1/4E-BP1 with \downarrow AMPK Thr172-P, accompanied by NAD⁺ depletion / \uparrow PARylation and redox/epigenetic drift. This is the measurement logic summarized in Table 6.

The Closed-Loop Architecture of Adaptation - Figure 4 (conceptual diagram) illustrates the dual-loop control underpinning these dynamics: an outer AMPK–mTOR oscillator across training/feeding and an inner redox–epigenetic loop via the SIRT1–PARP NAD⁺ economy. When negative feedback is intact, the loops remain antiphased and resilient; under chronic drive, feedback polarity shifts toward positive, predisposing to lock-in.

Together, the outer AMPK–mTOR and inner redox–epigenetic circuits form a closed-loop system in which metabolic sensing and chromatin remodeling are dynamically coupled.

Redox-Epigenetic Coupling and Systemic Instability - at the biochemical level, overdrive couples redox imbalance to epigenetic drift. Excess ROS oxidize 5-methylcytosine and histone residues, impairing TET- and Jumonji-mediated demethylation [98]. NAD⁺ depletion through PARP overactivation reduces SIRT-dependent chromatin silencing, compounding transcriptional noise. As feedback fidelity deteriorates, the epigenome begins to store the metabolic history of stress — a

persistent “memory” of overload. Biomechanical asymmetry during repetitive effort may further amplify local metabolic load and redox stress, providing a physical correlate of systemic overdrive [99]. Such molecular scars explain the lingering performance decrements and altered recovery profiles seen in chronically overtrained athletes [100].

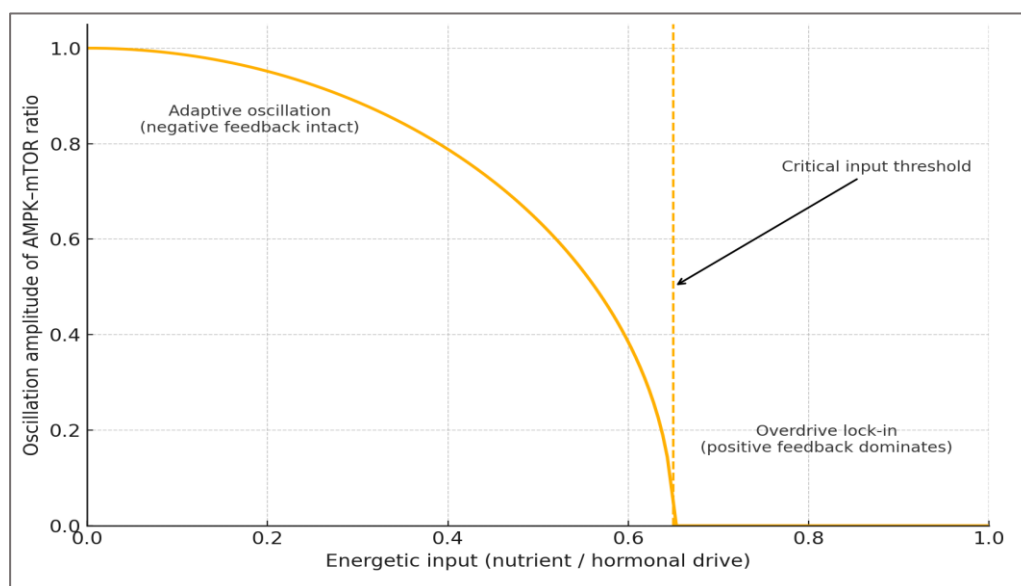


Figure 3. Bifurcation schematic of the Metabolic Overdrive Model. Increasing energetic or hormonal input reduces the oscillation amplitude of the AMPK–mTOR ratio. Beyond the critical input threshold (dashed line), the system collapses to a high-anabolic steady state (“lock-in”).

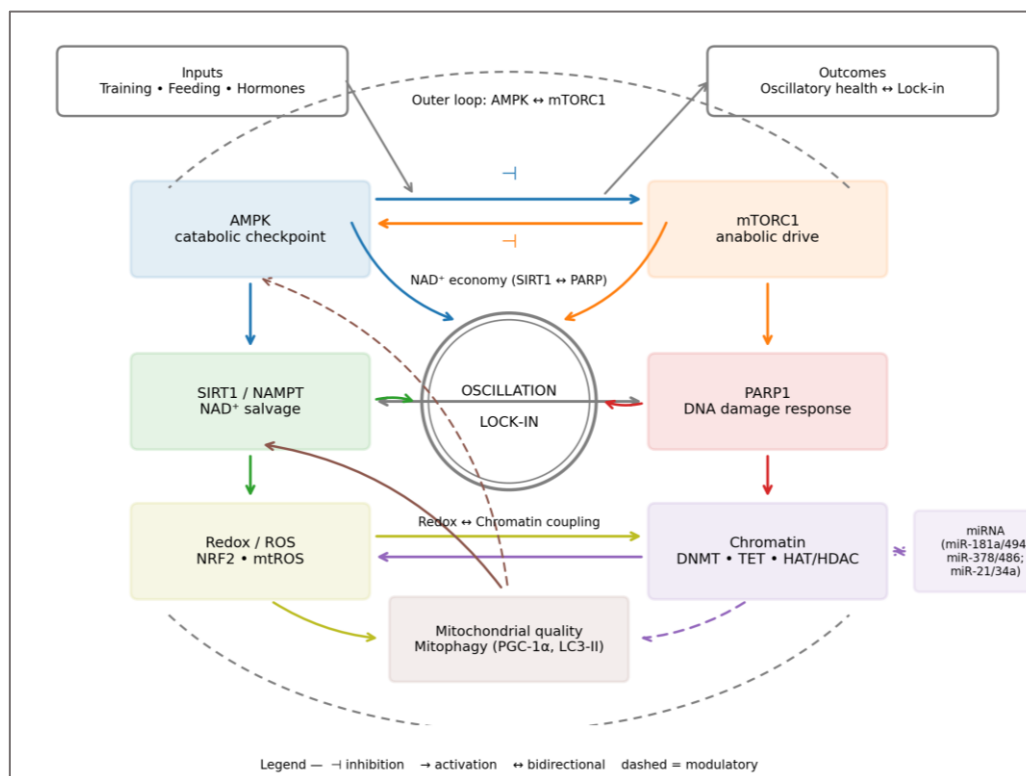


Figure 4. Dual-loop architecture of the Metabolic Overdrive Model. Outer loop: AMPK–mTORC1 oscillator across training/feeding. Inner loop: redox–chromatin coupling via SIRT1–PARP (NAD⁺ economy) and DNMT/TET/HAT/HDAC/miRNAs. Top banner: Inputs (training, feeding, hormones) and Outcomes (oscillatory health → lock-in). Dashed lines = modulatory interactions; bidirectional; ⊖ inhibition.

From Adaptation to Pathology - in its terminal form, *metabolic overdrive* recapitulates the molecular hallmarks of tumorigenesis: constitutive mTOR signaling, defective autophagy, mitochondrial hyperpolarization, and aberrant methylation [101,102]. Yet the model is not a statement of equivalence between athletic performance and cancer, but of shared architecture — both are systems pushed beyond adaptive elasticity. The lesson is systemic: human performance is limited not by energy supply, but by the capacity to restore homeostatic oscillation after each perturbation.

Implications - the *Metabolic Overdrive Model* redefines performance physiology as a dynamic equilibrium rather than a linear progression. It integrates nutrient sensing, redox homeostasis, and epigenetic regulation into one mechanistic continuum, uniting the biology of adaptation, aging, and disease. By identifying the molecular inflection point between beneficial stress and chronic overload, this framework offers a language to discuss both the promise and the peril of metabolic enhancement. In elite sport — and perhaps in life itself — resilience may depend less on how much energy we can generate than on how gracefully we can oscillate between expenditure and renewal.

To operationalize the Metabolic Overdrive Model, the key regulatory axes—nutritional, redox, and epigenetic—can be compared between adaptive and pathological configurations. This framework summarizes how oscillatory control across these domains sustains performance resilience, whereas persistent activation transforms feedback into self-reinforcing instability.

Table 5 presents a comparative synthesis of molecular, functional, and systemic features characterizing the transition from physiological adaptation to metabolic lock-in, integrating evidence from elite sport contexts.

Table 5. The Metabolic Overdrive Framework: comparative features of adaptive and pathological states across metabolic axes.

| Regulatory axis | Adaptive (oscillatory) state | Overdrive (lock-in) state | Representative molecular indicators | Functional outcome (physiological/clinical) | Evidence or relevance in elite sport | Reversibility potential |
|--|--|---|--|--|---|--|
| Nutritional signaling (AMPK–mTOR) | Alternating activation maintains energy balance and anabolic–catabolic cycling; mTOR activity transient and self-limiting. | Chronic nutrient or hormonal stimulation suppresses AMPK; mTORC1 locked in constitutive activation. | Adaptive: ↑ AMPK (Thr172-P), oscillatory ↑ mTOR (Ser2448-P); Overdrive: ↑ S6K1, ↓ AMPK. | Efficient recovery, balanced hypertrophy, metabolic flexibility. | Observed in endurance vs. bulking athletes; chronic protein or insulin use suppresses AMPK signaling. | High — restored through fasting, caloric periodization, AMPK activators. |
| Redox homeostasis (ROS–NAD⁺ balance) | Controlled ROS pulses activate NRF2–SIRT1 defense; NAD ⁺ recycling sustains redox tone. | ROS accumulation exceeds detox capacity; PARP activation depletes NAD ⁺ , silencing SIRT1. | Adaptive: ↑ NRF2, ↑ SIRT1, stable NAD ⁺ /NADH; Overdrive: ↑ PARP1, ↓ NAD ⁺ , ↑ oxidative adducts. | Enhanced mitochondrial efficiency and repair capacity. | Seen in overtraining and altitude exposure; redox imbalance linked to delayed recovery and fatigue. | Moderate — restored with NAD ⁺ boosters, antioxidant periodization. |
| Epigenetic regulation (chromatin) | Reversible histone deacetylation and | Hyperacetylation and aberrant methylation | Adaptive: ↑ TET1–3, ↑ HDACs; Overdrive: | Improved adaptation memory, | Exercise-induced hypomethylation of | Variable — reversible early, lost |

| | | | | | | |
|-------------------------------|--|--|---|--|---|---|
| remodeling) | DNA demethylation maintain transcriptional flexibility; stress memory remains functional. | fix anabolic programs; transcriptional noise accumulates. | ↑ DNMT1, ↑ HATs, ↑ H3K9ac. | genomic stability. | <i>PGC-1α</i> and <i>TFAM</i> vs. hypermethylation under chronic overload. | under prolonged overload. |
| Mitochondrial dynamics | Balanced fusion–fission and autophagic recycling sustain bioenergetic quality. | Hyperpolarization, impaired mitophagy, ROS leakage disrupt energy homeostasis. | Adaptive: ↑ <i>PGC-1α</i> , ↑ <i>MFN2</i> , ↑ <i>LC3-II</i> ; Overdrive: ↑ <i>DRP1</i> , ↑ ROS. | Optimal endurance and energy turnover. | Endurance training enhances mitophagy; chronic supplementation or doping impairs mitochondrial turnover. | Moderate — restored through recovery and redox normalization. |
| System-level behavior | Oscillatory negative feedback ensures renewal after stress; system remains dynamically stable. | Positive feedback loops reinforce anabolic and oxidative stress; system enters chaotic saturation. | Adaptive: oscillatory AMPK/mTOR ratio; Overdrive: flattened rhythm, ↑ entropy. | Resilient adaptation, sustained performance. | Elite athletes under chronic load exhibit reduced HRV and hormonal adaptability — biomarkers of systemic lock-in. | Low — requires full metabolic reset through deloading and restoration cycles. |

Notes: The final form of the Metabolic Overdrive Framework integrates molecular dynamics with evidence from elite performance physiology. The collapse of oscillatory regulation—observable in both molecular biomarkers and functional markers such as fatigue, hormonal rigidity, and impaired recovery—defines the biochemical signature of adaptive exhaustion.

Together, these patterns reveal that high performance and molecular fragility are separated not by intensity but by rhythm. When oscillatory checkpoints fail, systems designed for renewal become trapped in activation. The restoration of resilience, therefore, lies not in suppressing energy flux, but in reestablishing periodicity—the cellular capacity to alternate between catabolic repair and anabolic growth without losing feedback integrity.

3.6. Testable Predictions and Biomarkers

Based on the AMPK–mTOR antagonism, the SIRT1–PARP NAD⁺ economy, and redox–epigenetic coupling described in Sections 2.1–2.5, we propose the following falsifiable predictions:

P1. Persistent anabolic drive flattens the AMPK–mTOR rhythm. After heavy training plus high nutrient/hormonal load, p-S6K1/4E-BP1 remain elevated >24 h while AMPK Thr172-P is depressed, indicating a shift toward sustained mTORC1 dominance and reduced autophagy. Readouts: AMPK Thr172-P, p-S6K1, p-4E-BP1, LC3-II, p62. *Rationale:* Sections 2.1 and 2.5.

P2. Redox stress drives an NAD⁺ sink and epigenetic drift. Overreaching under anabolic excess increases PARP activity (PARylation), lowers NAD⁺ and SIRT1 activity, and biases chromatin toward ↑H3K9ac with ↓TET activity/5hmC. Readouts: NAD⁺/NADH, PARylation, SIRT1 activity, H3K9ac, 5hmC. *Rationale:* Sections 2.3 and 2.5.

P3. Periodic AMPK restoration re-establishes oscillation. Interventions that intermittently activate AMPK (e.g., fasted endurance, time-restricted feeding, polyphenol-driven AMPK activation)

normalize NAD⁺, reduce PARYlation/ROS, and reverse acetylation/methylation drift. Readouts: AMPK Thr172-P, NAD⁺, PARYlation, H3K9ac, LC3-II. *Rationale*: Sections 2.1, 2.3, 2.5.

Measurement window: 24–48 h post-stimulus phase used to distinguish adaptive oscillation from lock-in dynamics. These hypotheses are non-causal claims but operational tests of the Metabolic Overdrive Model.

To operationalize predictions P1–P3, we map human-assayable readouts onto the 0–48 h recovery window, separating fast redox/NAD⁺ shifts from slower structural signals. This clarifies which endpoints are expected to move immediately (T_0 – T_1) versus those that resolve or diverge at T_2 – T_3 , where oscillation versus lock-in becomes distinguishable.

Preferred sampling windows across T_0 – T_3 are visualized in Figure 5, aligning predictions P1–P3 with assay timing.

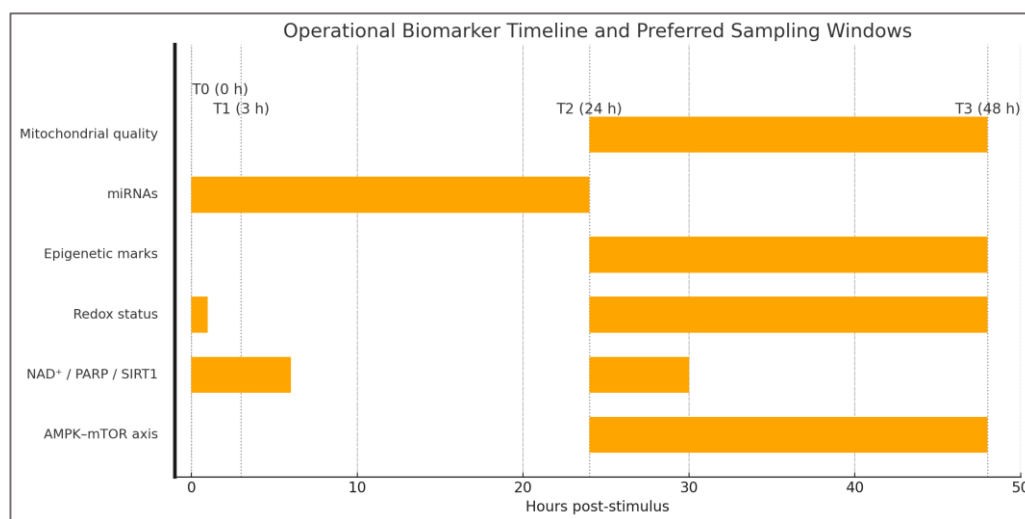


Figure 5. Operational biomarker timeline (0–48 h) and preferred sampling windows. Bars denote recommended collection windows: AMPK–mTOR axis (24–48 h), NAD⁺/PARP/SIRT1 (0–6 h and ~24–30 h), Redox status (0–1 h and 24–48 h), Epigenetic marks (24–48 h), miRNAs (0–24 h), Mitochondrial quality (24–48 h). Vertical markers indicate T_0 (0 h), T_1 (3 h), T_2 (24 h), T_3 (48 h). Windows are conceptual and harmonized with Table 6 and the protocol in Box 2.

Operational biomarkers, preferred sampling windows and the strength of evidence supporting each axis are summarized in Table 6.

Table 6. Level of evidence and operational biomarkers for the Metabolic Overdrive Model.

| Mechanistic axis | Primary human readouts (assay & specimen) | Predicted direction in overdrive | Evidence base (cell/animal/human) | Reversibility signal (periodic AMPK) | Preferred sampling window |
|-------------------|--|---|--|--|---|
| AMPK–mTOR balance | AMPK Thr172-P (WB/ELISA; muscle or PBMCs), p-S6K1 (Thr389) / p-4E-BP1 (Ser65) (WB), LC3-II/p62 (autophagic flux with lysosomal inhibition) | ↓ AMPK Thr172-P; ↑ p-S6K1/4E-BP1; ↓ autophagic flux | Strong (cells/rodents) + human acute & training blocks | ↑ AMPK Thr172-P; normalization of p-S6K1; ↑ LC3-II | 24–48 h post-stimulus, spanning feeding |

| | | | | | |
|---|--|--|--|--|------------------------------|
| NAD⁺ economy (SIRT1–PARP) | NAD ⁺ /NADH (enzymatic cycling; muscle/PBMCs), PARylation (WB), SIRT1 activity (fluor./ELISA) | ↓ NAD ⁺ ; ↑ PARylation; ↓ SIRT1 activity | Moderate–strong (cells/rodents) + human acute (exercise/irradiation) | ↑ NAD ⁺ ; ↓ PARylation; ↑ SIRT1 | 0–6 h and 24 h post-stimulus |
| Redox status | 8-oxo-dG (DNA damage), GSH/GSSG, TBARS/MDA, SOD2/Catalase (WB/activity) | ↑ oxidative adducts; ↑ inflammatory redox tone | Strong across models; robust human acute | ↓ adducts; normalization of GSH/GSSG | Immediately post + 24–48 h |
| Epigenetic layer | H3K9ac (ChIP-WB), 5mC/5hmC (LC-MS/MS; targeted bisulfite), TET activity, DNMT1; target loci: <i>PGC-1α</i> , <i>TFAM</i> , <i>PDK4</i> | ↑ H3K9ac; ↓ TET/5hmC at oxidative loci; ↑ DNMT1; methylation drift | Moderate (cells/rodents) + human acute/longitudinal | ↓ H3K9ac; ↑ 5hmC/TET upon AMPK restoration | 24–72 h (miRNAs earlier) |
| miRNA remodeling | Plasma/serum miR-181a/494 (oxidative), miR-378/486 (hypertrophic), miR-21/34a (fibro-oncogenic) | ↑ miR-21/34a; rigidified profile | Human: acute + training periods | Shift back toward oxidative profile (miR-181a/494) | 0–24 h |
| Mitochondrial quality | <i>PGC-1α</i> , MFN2, DRP1, mtDNA damage, LC3-II | ↓ mitophagy; ↑ DRP1; ↑ mtROS | Robust experimental; emerging human data | ↑ mitophagy; ↑ <i>PGC-1α</i> ; reduced mtROS | 24–72 h |

Notes: PBMC, peripheral blood mononuclear cells; WB, Western blot; ELISA, enzyme-linked immunosorbent assay; ChIP, chromatin immunoprecipitation; TRF, time-restricted feeding.

This synthesis prioritizes operationalization over exhaustiveness. When feasible, **muscle biopsy** allows direct quantification of AMPK Thr172-P and autophagy markers; otherwise, **PBMCs and plasma** provide translational surrogates for **NAD⁺/NADH**, **PARylation**, and **circulating miRNAs**. Arrows in **Table 6** denote the **expected deviation under metabolic overdrive**, whereas the “Reversibility signal” column summarizes the direction of change when **oscillatory control is restored** by AMPK-centric strategies (e.g., fasted endurance, time-restricted feeding, polyphenol-mediated AMPK activation). The **sampling windows (0–6 h; 24–72 h)** are chosen to distinguish **transient adaptive oscillations** from **pathological lock-in**. Together with **Figure 1-2** and Sections **2.1–2.5**, **Table 6** anchors the Metabolic Overdrive Model in **measurable outcomes**, closing the loop between mechanism and application. These operational choices define a biomarker panel and timing strategy that can be prospectively tested in elite athletes, informing periodization and health monitoring.

Pre-Analytical Considerations - translational application of the proposed biomarker panel requires strict pre-analytical control. NAD⁺, PARylation, and oxidative adducts are labile and sensitive to handling delays. PBMC isolation should occur within two hours of venipuncture in EDTA tubes kept on ice, followed by immediate centrifugation and quenching in methanol or –80 °C storage. Plasma redox assays (GSH/GSSG, TBARS) need rapid deproteinization to prevent artifactual oxidation. Whenever feasible, paired muscle biopsies remain the reference for AMPK Thr172-P and

autophagic flux, but PBMCs are acceptable translational proxies if standardized processing is ensured. Inconsistent handling can mask oscillatory signatures and inflate inter-subject variability.

To illustrate how these biomarker axes can be empirically tested in human settings, an example protocol is outlined in Box 2.

Box 2. Illustrative protocol for testing the Metabolic Overdrive Model in humans

Design: within-subject repeated-measures study in trained athletes.

Stimulus: combined endurance + resistance session under high-nutrient load (post-exercise refeeding + amino-acid/protein supplementation).

Sampling windows:

- T₀ – baseline (fasted)
- T₁ = 3 h – early recovery (catabolic → anabolic transition)
- T₂ = 24 h – post-feeding steady state
- T₃ = 48 h – delayed recovery (oscillation vs. lock-in check)

Assays:

AMPK–mTOR axis (p-AMPK Thr172, p-S6K1 Thr389, p-4E-BP1 Ser65, LC3-II/p62 ± bafilomycin);

NAD⁺ economy (NAD⁺/NADH, PARylation, SIRT1 activity);

Redox/epigenetic layer (H3K9ac, 5hmC, TET activity, miR-21/181a/494).

Outcome: restoration of AMPK phosphorylation and NAD⁺ within 48–72 h = adaptive oscillation; persistence of low AMPK/high S6K1 = lock-in signature.

Optional interventions: fasted endurance bout, time-restricted feeding, or polyphenol supplementation to probe reversibility (P3).

4. Discussion

Elite sport represents the most concentrated form of physiological adaptation. Training, recovery, and nutrition interact through molecular pathways that sustain a delicate balance between energy demand and cellular renewal. This review integrated evidence from molecular physiology, redox biology, and epigenetic regulation to propose a unified view of exercise adaptation—the *Metabolic Overdrive Model*. At its core, this model frames the oscillatory interplay between AMPK and mTOR as the molecular rhythm that governs energy homeostasis and cellular remodeling. When this rhythm is maintained, performance optimization and cellular resilience coexist; when it collapses, chronic anabolic signaling, oxidative imbalance, and epigenetic drift emerge as markers of metabolic saturation [103–106].

Molecular Integration and Adaptive Oscillation - Exercise imposes alternating metabolic states—energy depletion followed by nutrient restoration—that naturally activate AMPK and mTOR in sequence. AMPK responds to energetic stress by promoting catabolic fluxes, mitochondrial biogenesis, and NAD⁺ regeneration, while mTOR reactivates during recovery to stimulate protein synthesis and hypertrophy. This rhythmic succession underlies training adaptation: muscle repair, metabolic flexibility, and efficient redox management. Such periodicity prevents the accumulation of reactive oxygen species and preserves genomic stability through the coupling of energy and chromatin regulation [107].

However, excessive training load, hypercaloric intake, or anabolic enhancement may flatten this oscillation. Constant nutrient abundance maintains mTORC1 activation, suppressing AMPK and silencing sirtuin signaling. The system enters a quasi-steady state of “metabolic overdrive,” in which feedback loops become feedforward, energy consumption continues without renewal, and oxidative stress amplifies [108]. The same molecular mechanisms that drive adaptation under transient activation can, under persistent stimulation, erode the balance between synthesis and repair.

Redox–Epigenetic Coupling and Molecular Memory - Redox signaling provides a bridge between metabolic flux and long-term gene regulation. ROS generated during exercise act as transient messengers that activate AMPK, PGC-1 α , and MAPK cascades—promoting antioxidant defense and mitochondrial turnover. When recovery is adequate, these signals resolve, leaving behind an adaptive chromatin imprint. Epigenetic mechanisms such as DNA demethylation at *PGC-1 α* , *TFAM*, and *PDK4* loci or histone deacetylation via SIRT1 enhance oxidative capacity and metabolic resilience [109,110].

In contrast, chronic anabolic activation alters this balance. Persistent nutrient supply increases acetyl-CoA and SAM availability, favoring histone hyperacetylation and DNA hypermethylation at antioxidant and catabolic genes while maintaining open chromatin at anabolic loci (*IGF1*, *MYC*, *mTOR*). Combined with NAD⁺ depletion through PARP overactivation, this state stabilizes transcriptional noise and accelerates epigenetic drift [111]. These findings suggest that redox imbalance and methylation instability are not side effects of exercise overload but integral components of its molecular ceiling—the point where adaptability reaches saturation.

From Adaptive Drive to Overdrive - The boundaries of adaptation become most visible in elite contexts where metabolic pathways are chronically stressed. In endurance athletes, repeated hypoxic stimuli amplify HIF-1 α signaling and erythropoietic drive, enhancing oxygen delivery but simultaneously elevating oxidative load. In strength and hypertrophy sports, sustained nutrient signaling and high protein or supplement intake reinforce mTOR dominance, suppressing autophagy and narrowing metabolic flexibility. Both scenarios reflect the duality of exercise as a molecular amplifier—capable of generating resilience or instability depending on rhythm and recovery [112].

These parallels indicate that exercise, while fundamentally beneficial, shares with pathological systems the same feedback architecture: oscillatory when adaptive, rigid when overstimulated. Recognizing this continuum can help refine nutritional and training periodization strategies aimed at maintaining oscillatory fidelity—the biochemical equivalent of recovery capacity. Periodic activation of AMPK through endurance work, caloric modulation, or redox-based interventions (polyphenols, fasting, mitochondrial uncouplers) may restore flexibility and counteract chronic mTOR saturation [113].

Integrative Implications and Conceptual Outlook - The *Metabolic Overdrive Model* thus provides a mechanistic language to describe how exercise-induced molecular rhythms sustain or lose coherence under stress. It reconciles findings from performance physiology, sports nutrition [114], and redox biology, showing that metabolic resilience depends less on the magnitude of energy flux than on the precision of feedback control. In practice, maintaining rhythmic transitions between activation and renewal—training and recovery, feeding and fasting—may be the most fundamental determinant of long-term performance stability [115,116].

Beyond sport, the same logic applies to broader contexts of human adaptation: aging, metabolic disease, and tissue regeneration all depend on the fidelity of oscillatory control. Exercise serves here as both model and metaphor—a living system that teaches how biological renewal is sustained through periodic imbalance.

Limitations and Future Directions - While this review offers a mechanistic synthesis grounded in established molecular principles, it remains a conceptual construct requiring empirical validation. Most data supporting the oscillatory model derive from indirect or cross-sectional evidence. Future studies should employ longitudinal multi-omics approaches—integrating transcriptomic, metabolomic, and methylomic time-series—to track molecular cycles of AMPK–mTOR activation, NAD⁺ flux, and redox oscillation during structured training interventions. Computational modeling

could further identify energetic thresholds or “bifurcation points” marking the transition from adaptive to maladaptive states.

Elite performance provides an ideal setting for this inquiry. The same interventions used to maximize adaptation—nutritional periodization, recovery modulation, and exercise dosing—can serve as experimental tools for testing system stability. Integrating molecular assays with performance metrics may reveal biomarkers of oscillatory health, guiding safer performance enhancement and long-term metabolic preservation.

5. Conclusions

Human performance emerges from a dynamic equilibrium between energy generation and molecular repair. The *Metabolic Overdrive Model* proposed here reframes this equilibrium as an oscillatory dialogue between nutrient sensing, redox regulation, and epigenetic plasticity. Within this loop, AMPK and mTOR act not as antagonists but as temporal partners, orchestrating periodic cycles of depletion and renewal that sustain adaptation. When this rhythm collapses—through nutritional excess, pharmacologic stimulation, or chronic overload—the system enters metabolic overdrive: an energetically amplified but informationally unstable state.

This framework unites the physiology of performance with the biology of instability. The same molecular circuits that enable hypertrophy, angiogenesis, and resilience under stress can, when persistently activated, erode redox homeostasis, silence autophagy, and imprint maladaptive epigenetic marks. The border between adaptation and pathology is therefore not structural but rhythmic—defined by whether the organism can restore oscillation after each pulse of stress.

Understanding performance through this lens moves the field beyond simple narratives of training load or nutrient intake toward a systems view of resilience. It invites a future in which athlete health is monitored not only through hormonal or metabolic markers but also through signatures of epigenetic flexibility and redox rhythm. Protecting the capacity to oscillate—to alternate between anabolism and repair—may prove to be the true foundation of both longevity and excellence.

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