



# Stress is inevitable; recovery is conditional: bioenergetic limits of resilience in aging and disease

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**Abstract** Aging, stress-related disorders, and chronic disease are often examined across separate domains—stress physiology, nutrition, psychiatry, and geroscience—despite converging on shared phenotypes of functional decline and reduced resilience. Although adaptive responses to stress are well characterized, why comparable exposures yield sustained resilience in some individuals but progressive dysfunction in others remains insufficiently explained. We propose that the missing unifying constraint is not stress exposure itself, but the bioenergetic capacity to complete recovery. We reframe stress adaptation as a cyclical process comprising response, adaptation, and recovery, emphasizing that recovery is an active, ATP-dependent phase conditionally funded within a finite bioenergetic system. When mitochondrial processing capacity and redox flexibility are constrained,

adaptive programs may persist beyond their functional window, contributing to mitochondrial congestion, epigenetic gridlock, and progressive loss of physiological plasticity—even in the absence of overt pathology. Within this perspective, we introduce Exposure-Related Malnutrition (ERM) as a proposed conceptual model describing a clinically interpretable and potentially reversible phenotype of unresolved bioenergetic triage. ERM is proposed to describe a state of relative undernutrition arising from chronic mismatch between energetic demand and recovery capacity, often occurring despite nominal intake and laboratory values within reference ranges. Distinct from frailty, sarcopenia, cachexia, metabolic syndrome, and classical malnutrition, ERM may reflect an upstream constraint in ATP-dependent recovery rather than structural loss, inflammatory wasting, metabolic thresholds, or inadequate intake. By integrating evolutionary allocation theory, developmental calibration, stress physiology, and mitochondrial mechanics, ERM is proposed to offer a unifying integrative framework for functional decline across aging and chronic disease. Clinically, this perspective shifts risk assessment from isolated thresholds toward coordinated biomarker patterns, trajectories, and recovery kinetics, potentially enabling recognition of vulnerability before incomplete resolution consolidates into irreversible pathology. We further outline translational implications of a recovery-centered approach, positioning mitochondrial processing capacity and

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intercellular bioenergetic support as modifiable determinants of long-term resilience.

**Keywords** Bioenergetic resilience · Stress adaptation and recovery · Mitochondrial capacity · Exposure-Related Malnutrition (ERM) · Aging and chronic disease

## Background

Despite decades of intensive research, stress adaptation, nutrition, psychopathology, and aging continue to be examined largely as separate domains, even though they unfold within a shared bioenergetic economy. Across biological systems, organisms must continuously allocate finite energy and metabolic substrates among competing demands, including neuroendocrine stress responses, immune activation, metabolic regulation, tissue repair, and long-term maintenance. Yet each field has developed its own conceptual language, models, and outcome measures, often interrogating overlapping clinical realities through discipline-specific lenses rather than within a unified framework of bioenergetic allocation and recovery.

Stress biology has traditionally emphasized neuroendocrine and metabolic signaling and the cumulative burden of allostatic load (McEwen 1998; McEwen & Stellar 1993). Nutrition science has focused primarily on intake, absorption, and overt deficiency states, often considered independently of stress physiology and recovery demands (Black et al. 2013; Calder et al. 2020). Psychiatry has centered on symptoms, neural circuitry, and behavior, frequently abstracted from systemic metabolic and energetic constraints (Insel 2014; Miller & Raison 2016). In parallel, geroscience has examined molecular damage, loss of resilience, and the progressive contraction of homeodynamic capacity across the lifespan (Kirkwood 2005; Rattan 2008). Although these disciplines describe overlapping populations and phenotypes, they rarely converge on a shared explanatory model grounded in how bioenergetic substrates are mobilized, consumed, restored, and ultimately depleted during chronic adaptation to everyday exposure.

Across disciplines, conceptual models have progressively shifted away from static and reductionist explanations toward dynamic, adaptive

frameworks—ranging from allostatic regulation in stress biology to functional insufficiency in nutrition, immune-metabolic models in psychiatry, and resilience-based views of aging (Calder et al. 2020; McEwen 1998; McEwen & Wingfield 2003; Miller & Raison 2016; Rattan 2008). Despite these parallel advances, a unifying perspective capable of explaining why comparable stress exposures yield divergent trajectories—sustained resilience in some individuals and progressive dysfunction in others—remains insufficiently articulated.

Clinically, these domains co-manifest as overlapping psychological, metabolic, immune, and functional impairments. A unifying feature across these conditions is sustained adaptation to the cumulative exposome of modern life, occurring in the context of progressively constrained bioenergetic and metabolic substrate availability. Activation of stress responses, immune defenses, tissue remodeling, and adaptive plasticity are intrinsically energy-intensive processes (Picard & McEwen 2018; Straub 2017). While acute stress can be adaptive, repeated or prolonged activation demands effective recovery—an ATP-dependent process requiring intact mitochondrial function, sufficient substrates, and time for re-anabolism. When recovery is incomplete, organisms are forced into energetic prioritization, allocating limited resources toward immediate survival at the expense of repair, maintenance, and long-term resilience (Kirkwood 1977; Shaulson et al. 2024). From this perspective, psychopathology, metabolic inflexibility, immune imbalance, and accelerated aging emerge not primarily from stress exposure itself, but from repeated failure of the recovery phase.

Within this context, *Exposure-Related Malnutrition (ERM)* is introduced as a proposed, clinically interpretable and potentially reversible phenotype that integrates stress adaptation, nutrition, psychopathology, and aging within a shared bioenergetic framework (Tippairote et al. 2025). ERM may reflect preserved adaptive signaling operating under constrained mitochondrial throughput and limited NAD<sup>+</sup> availability—mechanisms supported by broader evidence linking mitochondrial function, redox balance, and stress adaptation (Covarrubias et al. 2021; Picard et al. 2018; Spinelli & Haigis 2018). Unlike classical malnutrition syndromes—such as protein–energy malnutrition, cachexia, or isolated micronutrient deficiency—ERM does not denote inadequate intake or

overt disease. Instead, it describes a bioenergetic vulnerability state that may manifest as emerging functional symptoms and coordinated biomarker trade-offs, even when individual laboratory values remain within reference ranges. By emphasizing recovery kinetics and reversibility, ERM reframes vulnerability not as fixed pathology or inevitable damage accumulation, but as a potentially modifiable failure of adaptive resolution.

Accordingly, this article presents an integrative, hypothesis-generating conceptual model that synthesizes evidence across stress physiology, nutrition, psychopathology, and aging. The aim is not to define a validated clinical entity, but to propose a unifying model that may generate testable hypotheses and guide future empirical and translational research.

### Definitional boundaries: distinguishing ERM from established clinical phenotypes

ERM is not proposed as a replacement for established clinical entities such as frailty, sarcopenia, cachexia, metabolic syndrome, or classical protein–energy malnutrition. These conditions represent structurally or metabolically defined disease states with validated diagnostic criteria (Cederholm & Bosaeus 2024; Cruz-Jentoft et al. 2023; Fearon et al. 2011; Fried et al. 2001). ERM differs in scope and level of abstraction. Whereas frailty captures multisystem vulnerability, sarcopenia reflects loss of muscle mass and function, cachexia denotes inflammatory-driven wasting, and metabolic syndrome represents threshold-defined cardiometabolic dysregulation, ERM refers to a recovery-constrained state at the level of bioenergetic execution. It may precede, coexist with, or contribute to these phenotypes, but it is not defined by their structural, inflammatory, or threshold-based markers. To clarify these distinctions, Table 1 contrasts ERM with established clinical phenotypes.

Rather than being defined by fixed diagnostic cut-offs, ERM is better conceptualized as a vulnerability pattern that may be operationalized through convergent features, including:

- (1) persistent or disproportionate delay in recovery following stress exposure;
- (2) functional decline or physical signs disproportionate to the degree of overt pathology;
- (3) coordinated biomarker deviations suggestive of constrained anabolic or redox capacity; and
- (4) partial reversibility with interventions that restore mitochondrial throughput and recovery support.

Stress adaptation as a cyclical process: respond, adapt, and the energetic cost of recovery

Biological responses to stress are not linear events but cyclical processes comprising coordinated phases of *response, adaptation, and recovery*. Classical stress models—most notably Hans Selye’s *General Adaptation Syndrome*—conceptualized stress as a progression from alarm to resistance and ultimately exhaustion, emphasizing adaptive capacity under sustained demand while offering limited mechanistic treatment of recovery as a distinct biological phase (Selye 1950, 1956).

Within traditional stress frameworks, persistent adaptations are commonly interpreted as manifestations of cumulative stress burden or allostatic load (McEwen & Stellar 1993). What remains comparatively under-articulated, however, is the *recovery phase*—the active biological process through which stress-induced metabolic responses are resolved, adaptive programs are dismantled, and tissues are restored toward baseline functional capacity.

Recovery is neither passive nor automatic. It is an anabolic, reparative, and energetically demanding phase that requires sufficient bioenergetic availability, mitochondrial processing capacity, and coordinated metabolic support (Picard et al. 2018; Picard & McEwen 2018; Ryan & Ryznar 2022). From a bioenergetic perspective, recovery constitutes a highly resource-intensive phase of the stress cycle (Tippairote et al. 2026). It entails replenishment of depleted substrates, repair of macromolecular damage, re-establishment of redox balance, rebuilding of cellular and tissue structures, and restoration of neuroendocrine and immune homeostasis (Hood et al. 2019; Lopez-Otin et al. 2013).

Canonical stress and nutrient-sensing pathways—including mTOR, AMPK, sirtuins, the IGF-1/GH axis, and NAD<sup>+</sup>-dependent regulatory systems—often remain appropriately engaged, functioning as decision layers that suppress growth and prioritize survival under energetic constraint (Nicoletti et al. 2025). Recovery fails when mitochondrial

**Table 1** Conceptual and clinical distinctions between exposure-related malnutrition and established conditions

Feature	Exposure-related malnutrition (ERM)	Protein–energy malnutrition	Frailty	Sarcopenia	Cachexia	Metabolic syndrome
Primary Conceptual Basis	Bioenergetic mismatch between cumulative demand and recovery capacity	Insufficient caloric/protein intake	Multisystem vulnerability with reduced physiological reserve	Loss of skeletal muscle mass and function	Disease-associated catabolic state	Cluster of metabolic risk factors linked to insulin resistance
Dominant Pathophysiological Emphasis	Bioenergetic constraint affecting ATP-dependent recovery processes	Absolute nutrient deficiency	Declining systemic reserve and resilience	Reduced muscle mass, neuromuscular impairment	Inflammation-driven catabolism and anorexia	Substrate oversupply, insulin resistance, adipose dysfunction
Nutritional Intake	May be nominal or adequate	Inadequate	Variable	Variable	Often reduced	Often excessive or dysregulated
Primary Locus of Dysfunction	Recovery phase of stress adaptation	Systemic energy and protein depletion	Global functional capacity	Skeletal muscle	Systemic inflammatory–catabolic axis	Glucose–lipid metabolism
Position in Clinical Trajectory (Typical Presentation)	Often detectable before overt structural pathology	Deficiency state	Established clinical vulnerability phenotype	Clinical phenotype	Advanced disease-associated phenotype	Risk-state phenotype
Reversibility (General Pattern)	Potentially high when identified early	High with refeeding	Variable	Partial	Often limited, disease-dependent	Variable
Primary Diagnostic Approach	Pattern-based, trajectory-informed, integrative interpretation	Anthropometry, biochemical markers	Clinical phenotype criteria (e.g., Fried, Rockwood)	Muscle mass + strength criteria	Weight loss + inflammatory markers	Defined metabolic thresholds
Relationship to ERM	—	Conceptually distinct; ERM may occur despite adequate intake	May overlap with or be influenced by persistent recovery constraint	May share bioenergetic mechanisms related to impaired recovery	May coexist with bioenergetic constraint in chronic disease	May overlap with congestion-related recovery limitation

throughput, NAD<sup>+</sup> regeneration, and redox flexibility are insufficient to execute ATP-dependent repair and resolution. This distinction separates persistent adaptive signaling from failed recovery execution.

These restorative processes are critically dependent on adequate metabolic substrates, sustained ATP availability, and sufficient mitochondrial processing capacity (Willenborg et al. 2021). Recovery is also temporally constrained: compressed recovery windows, recurrent stress exposures, and competing energetic demands can quietly curtail the opportunity for complete biological resolution. Under such conditions, adaptive responses may persist beyond their functional utility, despite the absence of overt disease (Calabrese & Mattson 2017; Picard et al. 2018). Importantly, this mismatch can occur despite nominally adequate caloric intake and the absence of clinically apparent pathology.

Under conditions of chronic or repetitive stress, energetic demand remains persistently elevated while opportunities for complete recovery are progressively curtailed. In this context, sustained stress signaling, altered immune tone, or apparent neuroendocrine “dysregulation” may represent secondary

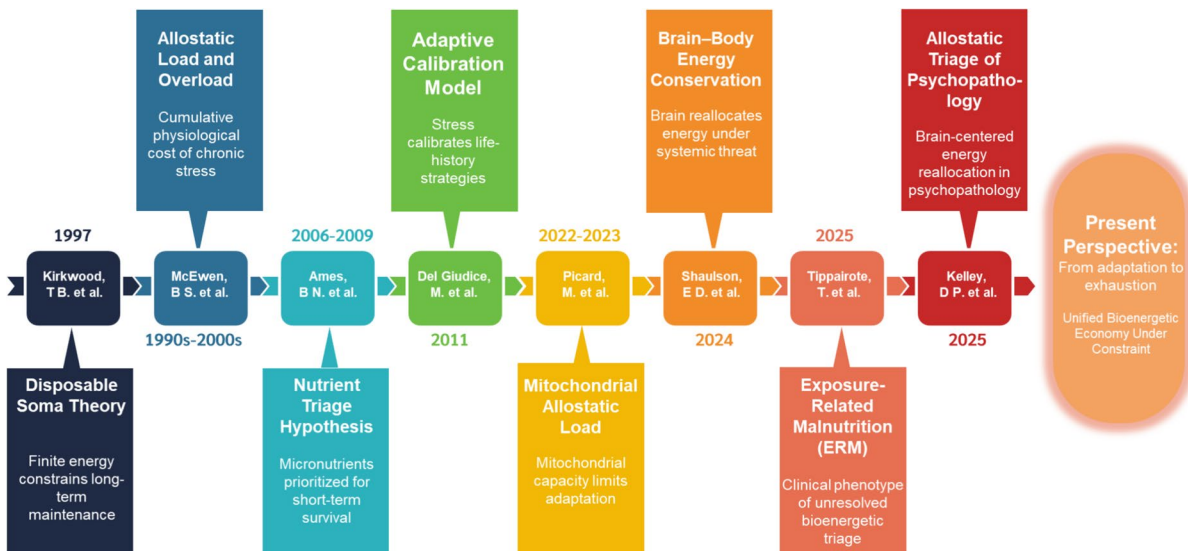
consequences of insufficient bioenergetic support for resolution, rather than primary defects in hormonal control. This interpretation is consistent with emerging models that position mitochondrial capacity as a key rate-limiting determinant of stress resilience (Chen et al. 2023; Picard et al. 2018).

When recovery is repeatedly incomplete, bioenergetic debt accumulates, adaptive programs become biologically entrenched, and physiological resilience progressively erodes (Rattan 2013, 2020; Sterling 2012). In this view, what classical models described as “exhaustion” can be reinterpreted not as an inevitable failure of stress tolerance, but as the downstream expression of a constrained bioenergetic economy.

**The evolutionary logic of bioenergetic triage: from allocation to triage**

Why recovery is not guaranteed

Building on the preceding reframing that shifts vulnerability from stress exposure itself toward recovery capacity, Figure 1 situates the present perspective



**Fig. 1** Evolution of bioenergetic trade-offs toward unresolved triage. This conceptual timeline illustrates how finite energetic resources constrain biological function across disciplines, from evolutionary allocation theories to stress physiology, nutrient prioritization, mitochondrial capacity, and brain–body energy conservation models. Across these frameworks, prioritization under constraint progressively shifts from adaptive, trans-

sient allocation toward persistent bioenergetic triage, in which resources are preferentially directed to immediate survival while recovery and repair are conditionally supported. Exposure-Related Malnutrition (ERM) is positioned as a proposed clinically interpretable phenotype of unresolved triage, reflecting a chronic mismatch between cumulative energetic demand and recovery capacity despite nominal intake

within its broader intellectual lineage. The figure presents a conceptual timeline illustrating how the logic of finite energy and biological prioritization has been progressively articulated across evolutionary biology, stress physiology, nutrition science, neuroscience, and clinical models. Rather than presenting isolated theories, the timeline traces a continuous refinement—from early life-history allocation frameworks to systems-level models of bioenergetic triage—demonstrating how a constrained bioenergetic economy necessitates prioritization, renders recovery conditionally funded, and permits maintenance to be deferred.

A unified evolutionary arc:  
allocation → calibration → triage

Across evolutionary and systems biology, a coherent logic emerges: organisms operate under finite bioenergetic budgets to support survival, reproduction, growth, and somatic maintenance (Stearns 1992). Adaptation across the lifespan is therefore a process of prioritization, in which energy is preferentially allocated to functions that enhance fitness within an expected lifespan rather than to indefinite repair or maximal somatic fidelity.

This logic was formalized by the *Disposable Soma Theory*, which proposed that aging arises not from intrinsic biological failure but from optimized allocation under energetic constraint (Kirkwood 1977; Kirkwood & Holliday 1979). Somatic maintenance and recovery are therefore conditionally funded processes—supported when energetic resources permit, but not evolutionarily guaranteed.

Developmental calibration further embeds these trade-offs within individuals. The *Adaptive Calibration Model* demonstrates that stress-response systems are tuned during early life in response to environmental cues, shaping physiological, neuroendocrine, and behavioral strategies toward anticipated ecological demands (Del Giudice et al. 2011). From a bioenergetic perspective, this implies that investment in recovery is conditionally regulated: environments characterized by persistent threat favor vigilance, rapid mobilization, and stress responsiveness, while energetically costly processes such as growth, reserve accumulation, and long-term repair are deprioritized. As a result, reduced recovery fidelity may

be embedded before adulthood, biasing later stress responses toward prioritization over restoration.

As energetic constraints intensify, allocation transitions into triage. Stress physiology formalized this shift through the concept of *allostatic load*, describing the cumulative cost of sustaining adaptive responses under chronic stress (McEwen & Wingfield 2003). *The nutrient triage hypothesis* further demonstrated that limited substrates are preferentially allocated to immediate survival processes at the expense of long-term repair, even in the absence of overt deficiency (Ames 2006). More recent systems-level models localized this prioritization to energetic infrastructure itself, identifying *mitochondrial processing capacity* and *brain–body energy allocation* as rate-limiting determinants of resilience and adaptive range (Picard et al. 2018; Picard & McEwen 2018; Shaulson et al. 2024).

Together, these perspectives converge on *bioenergetic triage* as a conserved survival strategy: immediate survival functions are preserved, while recovery and restoration are conditionally postponed.

#### Why recovery failure is predictable

From an evolutionary perspective, incomplete recovery is not anomalous but predictable, because:

- *Energetic budgets are finite*, requiring prioritization under constraint
- *The cumulative costs of incomplete recovery* often manifest late in life, beyond periods of strong selective pressure
- *Modern conditions* combine extended lifespan with continuous psychosocial, environmental, and metabolic exposure, promoting persistent rather than transient engagement of *bioenergetic triage*

Under these conditions, prioritization that evolved as a short-term survival strategy becomes chronically engaged, rendering recovery persistently underfunded (Del Giudice et al. 2011; McEwen & Wingfield 2003).

ERM and the allostatic triage of psychopathology: clinical expression of persistent triage

ERM may represent a clinically interpretable consequence of unresolved bioenergetic triage, reflecting

a mismatch between demand and recovery capacity, consistent with broader models of energetic prioritization and stress adaptation, with ERM proposed as a conceptual clinical extension (McEwen & Wingfield 2003; Picard & McEwen 2018; Tippairote et al. 2025). *The Allostatic Triage of Psychopathology (ATP)* model provides a mechanistic framework for how this prioritization is enforced under sustained energetic constraint and expressed as neuropsychological phenotypes. Under energetic scarcity, resources are preferentially allocated to brain systems critical for immediate survival and threat processing—particularly the *Salience Network*—while energetically demanding higher-order functions mediated by the *Central Executive Network*, including executive reasoning, cognitive flexibility, and affect regulation, are downregulated. In parallel, non-immediate processes such as immune resolution and somatic repair are deprioritized (Kelley et al. 2025).

This pattern of triage is adaptive in the short term but becomes maladaptive when persistently engaged, contributing to sustained neuropsychological dysfunction and systemic recovery failure. Together, the ERM and ATP models capture complementary systemic and neural expressions of persistent bioenergetic undersupply.

### Integrative synthesis

The following synthesis integrates established findings with a conceptual interpretation within the proposed ERM framework. Across disciplines, a single evolutionary logic is progressively refined: finite energy constrains long-term maintenance (*Disposable Soma Theory*), prioritization strategies are developmentally embedded (*Adaptive Calibration Model*), and sustained stress formalizes triage under constraint (*allostatic load and nutrient triage*). Systems-level models localize these trade-offs to *mitochondrial processing capacity* and *brain–body energy allocation*, while the ATP model describes their clinical neuropsychological expression (Ames 2006; Del Giudice et al. 2011; Kelley et al. 2025; Kirkwood 1977; McEwen & Wingfield 2003; Picard et al. 2018; Picard & McEwen 2018; Shaulson et al. 2024).

Within this trajectory, ERM is proposed to provide a conceptual clinical bridge, linking evolutionary trade-offs and developmental calibration to

measurable patterns of recovery failure in modern humans. Together, these frameworks suggest a constrained bioenergetic economy, in which recovery may be conditionally supported rather than guaranteed, and aging and chronic disease may emerge as accumulated failures of adaptive resolution rather than abrupt system breakdown (Picard et al. 2018; Rattan 2013).

Mitochondrial mechanics as the bottleneck of recovery.

The following section summarizes empirically supported mitochondrial mechanisms and interprets their relevance within the proposed framework. Multiple stress- and nutrient-sensing pathways operate upstream as adaptive signaling systems whose execution ultimately converges on mitochondrial capacity, with NAD<sup>+</sup> availability serving as a critical coupling variable (Nicoletti et al. 2025). These pathways do not fail under chronic stress; rather, they continue to enforce appropriate bioenergetic prioritization. Recovery fails when mitochondrial throughput and redox flexibility are insufficient to support the ATP-dependent re-anabolic processes that these pathways signal.

### Mitochondria as rate-limiting infrastructure

Mitochondria function as the central information-processing infrastructure of the bioenergetic economy (Picard & Shirihai 2022). Although energetic substrates—glucose, fatty acids, and amino acids—may remain abundant, their biological utility is constrained by mitochondrial throughput: the integrated capacity of the tricarboxylic acid (TCA) cycle, electron transport chain (ETC), redox regeneration, and oxidative phosphorylation (OXPHOS) (Chen et al. 2023; Picard et al. 2018). Declines in any of these components limit not only ATP generation but also the signaling, biosynthetic, and repair processes that depend on mitochondrial integrity.

Across tissues, recovery success is therefore determined not by substrate availability per se, but by mitochondrial processing capacity. Under bioenergetic constraint, stress adaptations—including immune activation, gluconeogenesis, lipolysis, vigilance, and neuroendocrine signaling—can be sustained through compensatory mobilization pathways (Rattan 2013; Sterling 2012). In contrast, recovery processes—protein synthesis,

mitochondrial renewal, membrane repair, synaptic remodeling, and immune resolution—are selectively down-prioritized as mitochondrial efficiency and redox balance decline. Mitochondria therefore may impose a fundamental asymmetry on adaptation, whereby stress responses can proceed under constraint, while recovery processes appear more dependent on sufficient bioenergetic capacity.

#### Cell-to-cell bioenergetic adaptation and compensatory support

Recent experimental evidence provides direct cellular confirmation of this infrastructure-based model of stress adaptation. In peripheral sensory systems, satellite glial cells transfer mitochondria to energetically stressed sensory neurons via tunneling nanotube-like structures in response to neuronal hyperactivity and injury (Xu et al. 2026). This transfer is unidirectional, activity-dependent, and spatially localized, indicating an adaptive response to regional bioenergetic insufficiency rather than generalized metabolic exchange.

When mitochondrial support from neighboring glial cells is intact, neurons maintain functional stability despite ongoing stress exposure. When this support is disrupted—through impairment of nanotube formation, reduced expression of regulators such as myosin-10 (MYO10), a motor protein required for tunneling nanotube formation—neurons develop calcium dysregulation, oxidative stress, axonal degeneration, and pain hypersensitivity (Xu et al. 2026). Notably, these maladaptive outcomes emerge despite preserved short-term ATP levels sufficient for baseline activity, implicating loss of mitochondrial reserve and surplus processing capacity—rather than signaling intensity—as the critical determinant of recovery failure.

Together, these findings demonstrate that mitochondrial adaptation to stress is not exclusively intracellular. When intrinsic mitochondrial capacity becomes limiting, intercellular redistribution can transiently compensate; failure of this adaptive infrastructure exposes latent bioenergetic insufficiency, converting otherwise tolerable stress responses into persistent maladaptation.

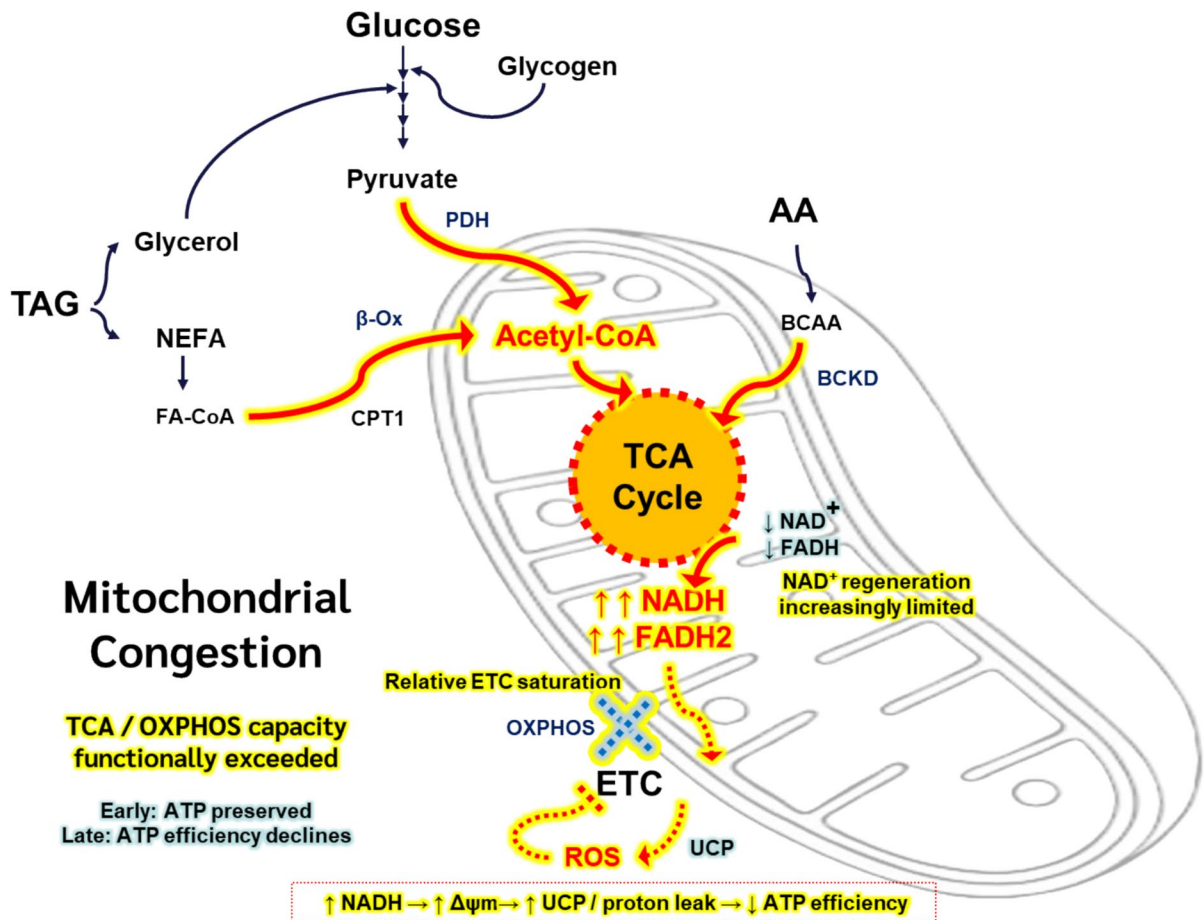
#### Mitochondrial congestion and compensatory ATP maintenance

Figure 2 introduces mitochondrial congestion as the earliest systems-level manifestation of constrained recovery capacity. Congestion arises when substrate inflow into the TCA cycle exceeds downstream ETC and OXPHOS throughput. Under chronic stress, convergent mobilized inputs from glycolysis,  $\beta$ -oxidation, and branched-chain amino acid catabolism markedly increase acetyl-CoA delivery, TCA anaplerosis, and reducing equivalent (NADH, FADH<sub>2</sub>) generation beyond mitochondrial processing limits (Kelley et al. 2025; Picard et al. 2018; Tippairote et al. 2022; Xiao & Loscalzo 2020).

In this state, mitochondrial ATP output may initially appear preserved, masking an underlying loss of bioenergetic efficiency. As ETC capacity becomes functionally saturated, regeneration of oxidized cofactors—particularly NAD<sup>+</sup>—is progressively constrained, leading to redox backlog, elevated mitochondrial membrane potential, and activation of compensatory mechanisms such as partial uncoupling and reactive oxygen species (ROS) production (Tippairote et al. 2022). These adaptations sustain short-term survival but progressively undermine ATP-dependent repair and recovery.

Recent experimental evidence directly supports this dissociation between survival-level ATP maintenance and recovery capacity. In oxidatively stressed human brain microvascular endothelial cells, basal oxygen consumption rate (OCR) remains intact, while maximal respiration and spare respiratory capacity decline sharply—indicating preserved ATP production sufficient for survival but loss of bioenergetic flexibility. Restoration of physiological NAD<sup>+</sup> homeostasis selectively rescues reserve respiratory capacity without altering basal OCR, identifying NAD<sup>+</sup> availability as a constraint on recovery rather than baseline metabolism (Chaubey et al. 2026).

During this early congested phase, compensation involves increased reliance on cytosolic NAD<sup>+</sup> regeneration via glycolytic and lactate dehydrogenase flux, diversion of pyruvate away from mitochondrial oxidation, and partial uncoupling to relieve redox pressure (Murphy 2009; Picard & McEwen 2018). While these mechanisms preserve basal ATP production and stress adaptation, they fail to restore mitochondrial redox flexibility



**Fig. 2** Mitochondrial congestion and compensatory ATP maintenance. This schematic illustrates mitochondrial congestion as an early systems-level consequence of constrained recovery capacity. Under chronic stress, convergent substrate inputs from glycolysis,  $\beta$ -oxidation ( $\beta$ -Ox), and amino acid catabolism increase acetyl-CoA delivery and tricarboxylic acid (TCA) cycle flux beyond downstream electron transport chain (ETC) and oxidative phosphorylation (OXPHOS) throughput. As ETC capacity becomes functionally saturated, regeneration of oxidized cofactors ( $\text{NAD}^+$ ) becomes increasingly limited, leading to redox backlog, increased mitochondrial membrane potential, and activation of compensatory mechanisms such as uncoupling and reactive oxygen species (ROS) production. In early stages, ATP levels may appear preserved;

however, mitochondrial efficiency progressively declines, sustaining short-term survival at the expense of ATP-dependent repair and recovery. Abbreviations: AA, amino acids; BCAA, branched-chain amino acids; BCKD, branched-chain ketoacid dehydrogenase;  $\beta$ -Ox,  $\beta$ -oxidation; CPT1, carnitine palmitoyl-transferase-1; ETC, electron transport chain; FA-CoA, fatty acyl-CoA;  $\text{NAD}^+/\text{NADH}$ , oxidized/reduced nicotinamide adenine dinucleotide; FAD/FADH<sub>2</sub>, oxidized/reduced flavin adenine dinucleotide; NEFA, non-esterified fatty acids; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; TAG, triacylglycerol; TCA, tricarboxylic acid; UCP, uncoupling protein;  $\Delta\psi_m$ , mitochondrial membrane potential

or reserve capacity, thereby promoting oxidative stress, signaling noise, and progressive impairment of ATP-dependent repair processes.

## From congestion to mitochondrial epigenetic gridlock

### From compensatory congestion to regulatory lock-in

Figure 3 extends the congestion framework by illustrating how unresolved mitochondrial congestion progresses toward *mitochondrial epigenetic gridlock* through a growing imbalance between  $\text{NAD}^+$  regeneration and consumption. As OXPHOS throughput remains limiting, mitochondrial redox cycling becomes increasingly constrained. Simultaneously, chronic stress increases  $\text{NAD}^+$  consumption through poly (ADP-ribose) polymerase (PARP) activation and sirtuin-dependent adaptive programs, narrowing the redox buffer and shifting metabolism toward regulatory instability, progressively depleting the available  $\text{NAD}^+$  pool (Chaubey et al. 2026; Picard et al. 2018).

This imbalance initiates a directional shift from flexible metabolic compensation toward regulatory lock-in. Excess reducing equivalents accumulate, reinforcing glycolytic bias and diversion of pyruvate toward lactate production. Meanwhile, continued substrate influx from  $\beta$ -oxidation and branched-chain amino acid catabolism sustains acetyl-CoA generation despite impaired mitochondrial oxidation, decoupling substrate availability from efficient energy processing.

### Mechanistic reinforcement of gridlock

At the regulatory level, this progression reflects a sustained imbalance between excess acetyl-CoA–driven acetylation pressure and impaired  $\text{NAD}^+$ -dependent deacetylation. As mitochondrial  $\text{NAD}^+$  availability declines, citrate export and acetyl-CoA partitioning increasingly favor cytosolic and nuclear compartments, promoting lipid biosynthesis and protein acetylation while mitochondrial reserve capacity remains constrained (Longo et al. 2025; Shi & Tu 2015; Tippairote et al. 2022; Wellen et al. 2009). This shift reflects a redox-driven storage–anabolism bias, in which excess carbon is diverted away from oxidative resolution toward lipid accumulation and acetylation-dependent regulation. Elevated NADH levels further promote conversion of dihydroxyacetone phosphate (DHAP) to glycerol-3-phosphate (Gro3P), providing a redox-coupled glycerol backbone for triglyceride (TAG) synthesis and reinforcing lipid storage

under oxidative constraint (Pan et al. 2026; Yahia & McReynolds 2026).

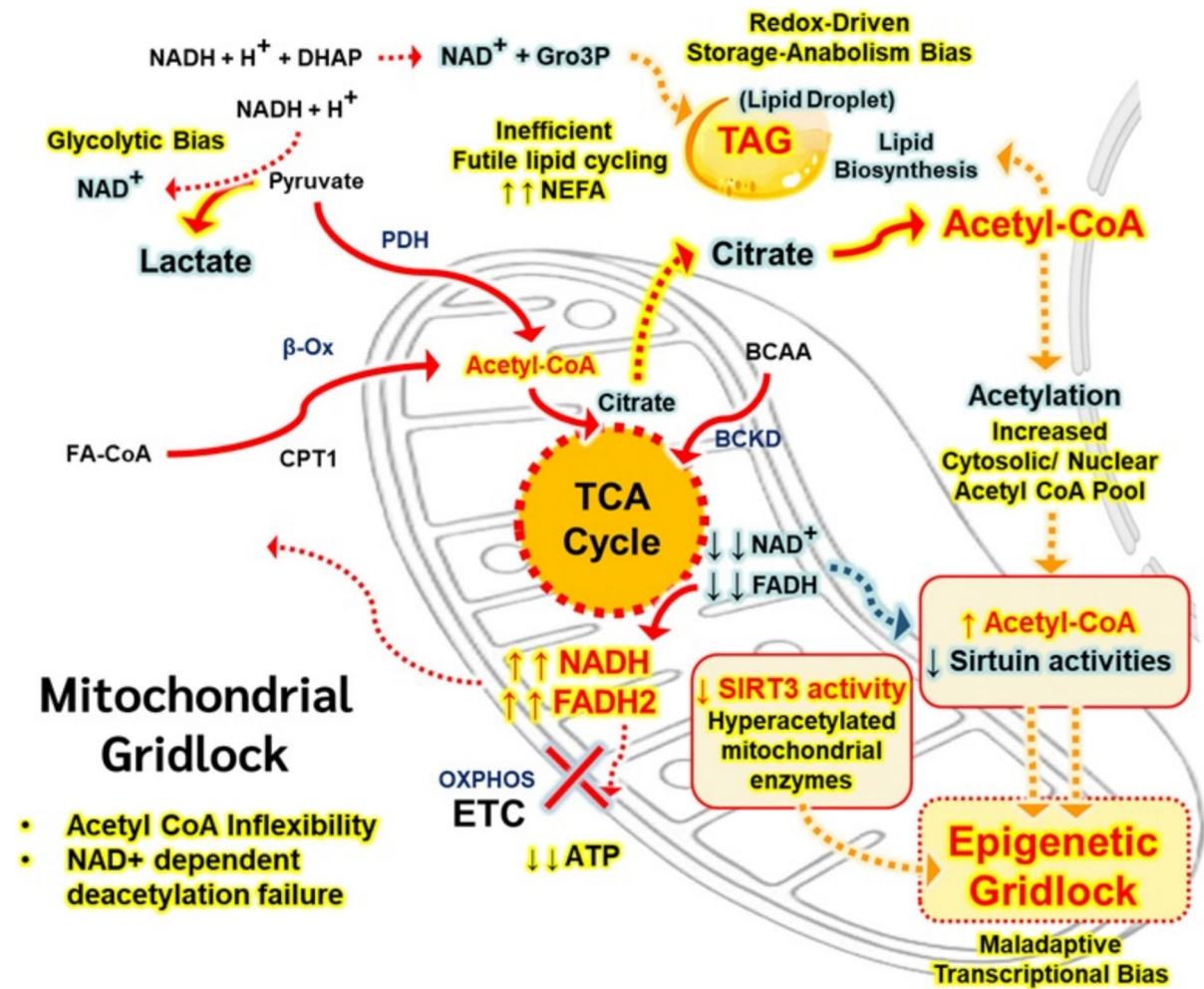
Concurrently, suppression of  $\text{NAD}^+$ -dependent deacetylases—particularly SIRT3—leads to hyperacetylation of mitochondrial enzymes, further impairing oxidative efficiency and redox flexibility (Hirschey et al. 2010; Lombard et al. 2007; Mishra & Kumar 2026). Compensatory reliance on cytosolic  $\text{NAD}^+$  regeneration through enhanced glycolytic flux and lactate dehydrogenase activity preserves basal ATP production and short-term viability, but does not fully restore mitochondrial redox cycling or reserve capacity, stabilizing a low-flexibility, recovery-resistant metabolic configuration (Murphy 2009; Picard et al. 2018).

In this context, *gridlock* can be interpreted as a constrained yet viable survival state rather than acute failure. Bioenergetic continuity is maintained through alternative and anaplerotic pathways, with declining energetic yield, reduced metabolic plasticity, and impaired recovery kinetics. Over time, these metabolic constraints become epigenetically reinforced, biasing transcriptional programs toward glycolytic dependence, lipid accumulation, and reduced energetic efficiency (Picard et al. 2018; Tippairote et al. 2022; Vander Heiden et al. 2009).

### From adaptive gridlock to bioenergetic debt

Mitochondrial congestion and epigenetic gridlock are initially reversible; however, specific mitochondrial–epigenetic thresholds determine whether adaptive resolution remains possible. Persistent  $\text{NAD}^+$  depletion progressively reshapes epigenetic and post-translational regulation, stabilizing stress-adapted programs while suppressing recovery (Chaubey et al. 2026; Picard & McEwen 2018). As a result, the capacity to re-enter a restorative state erodes even when external stressors abate, marking the transition from compensatory adaptation to self-reinforcing *bioenergetic debt* (Mishra & Kumar 2026).

Recent evidence further identifies  $\alpha$ -ketoglutarate (AKG)–dependent mitochondrial–epigenetic coupling as a critical determinant of this transition. Preservation of TCA cycle continuity and AKG availability maintains anaplerotic support and epigenetic buffering, sustaining reversibility. In contrast, disruption of AKG collapses both metabolic and epigenetic flexibility, may limit adaptive flexibility and



**Fig. 3** Mitochondrial epigenetic gridlock arising from persistent bioenergetic congestion. This schematic illustrates the transition from reversible mitochondrial congestion to mitochondrial epigenetic gridlock under sustained bioenergetic constraint. As oxidative phosphorylation (OXPHOS) throughput remains limited, accumulation of reducing equivalents (NADH, FADH<sub>2</sub>) progressively restricts regeneration of oxidized cofactors (NAD<sup>+</sup>, FAD), reinforcing a glycolytic bias and diversion of pyruvate toward lactate production. Under persistent redox backlog, acetyl-CoA becomes metabolically inflexible. Continued substrate influx from β-oxidation and branched-chain amino acid (BCAA) catabolism sustains acetyl-CoA generation despite impaired mitochondrial oxidation. Citrate export expands cytosolic and nuclear acetyl-CoA pools, promoting lipid biosynthesis and acetylation-dependent regulation. Elevated NADH levels further drive the reduction of dihydroxyacetone phosphate (DHAP) to glycerol-3-phosphate (Gro3P), providing a redox-coupled glycerol backbone for triglyceride (TAG) synthesis and reinforcing storage-anabolic bias under oxidative constraint. Declining NAD<sup>+</sup> availability suppresses sirtuin activity—particularly mito-

chondrial SIRT3—leading to hyperacetylation of mitochondrial enzymes, impaired deacetylation-dependent regulation, and further suppression of oxidative efficiency and metabolic flexibility. Together, acetyl-CoA inflexibility, redox backlog, Gro3P-mediated lipid storage, and reduced sirtuin activity stabilize a maladaptive metabolic and transcriptional configuration characterized by reduced ATP reserve capacity and impaired recovery. This epigenetic gridlock limits the capacity to re-enter anabolic, reparative programs even when external stressors diminish. Abbreviations: AA, amino acids; AKG, α-ketoglutarate; BCAA, branched-chain amino acids; BCKD, branched-chain ketoacid dehydrogenase; β-Ox, β-oxidation; CPT1, carnitine palmitoyltransferase-1; DHAP, dihydroxyacetone phosphate; ETC, electron transport chain; FA-CoA, fatty acyl-CoA; FAD/FADH<sub>2</sub>, oxidized/reduced flavin adenine dinucleotide; Gro3P, glycerol-3-phosphate; NAD<sup>+</sup>/NADH, oxidized/reduced nicotinamide adenine dinucleotide; NEFA, non-esterified fatty acids; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; SIRT3, sirtuin-3; TAG, triacylglycerol; TCA, tricarboxylic acid cycle

favor senescence-associated trajectories (Akakura & Tabrizzadeh 2026). In this sense, AKG availability functions as a biochemical boundary between constrained resilience and irreversible loss of recovery capacity.

#### Translational signal: $\alpha$ -Klotho as a marker of recovery investment

Within states of mitochondrial congestion and epigenetic gridlock,  $\alpha$ -Klotho expression declines. In this perspective,  $\alpha$ -Klotho is interpreted not as a passive marker of cumulative damage, but as a bioenergetically expensive maintenance signal reflecting active investment in long-term recovery capacity (Bao et al. 2026). Its downregulation therefore signals constrained energetic allocation, in which survival and stress adaptation are prioritized while maintenance and repair programs are selectively underfunded.

Viewed through this lens,  $\alpha$ -Klotho functions as a translational readout of recovery capacity, integrating mitochondrial throughput,  $\text{NAD}^+$  availability, and epigenetic flexibility into a clinically accessible biomarker. Declining  $\alpha$ -Klotho may reflect not simply aging or damage accumulation, but a system approaching—or having crossed—a bioenergetic threshold beyond which adaptive resolution becomes increasingly unlikely.

#### Downstream phenotypic consequences of recovery failure

Figure 4 summarizes the downstream phenotypic consequences that emerge as recovery failure progresses into a state of chronic mitochondrial epigenetic gridlock. Although these manifestations span diverse clinical and biological domains, they are most coherently understood as adaptive expressions of sustained bioenergetic triage, in which survival is persistently prioritized over successful recovery.

As mitochondrial throughput and  $\text{NAD}^+$  regeneration remain constrained, cytosolic acetyl-CoA is increasingly diverted toward lipid biosynthesis, promoting triglyceride production, lipid droplet formation, and lipid accumulation that contribute to central adiposity (Shi & Tu 2015; Wellen et al. 2009). This lipogenic shift is accompanied by accumulation of bioactive lipid intermediates, including diacylglycerols and ceramides, which impair insulin signaling

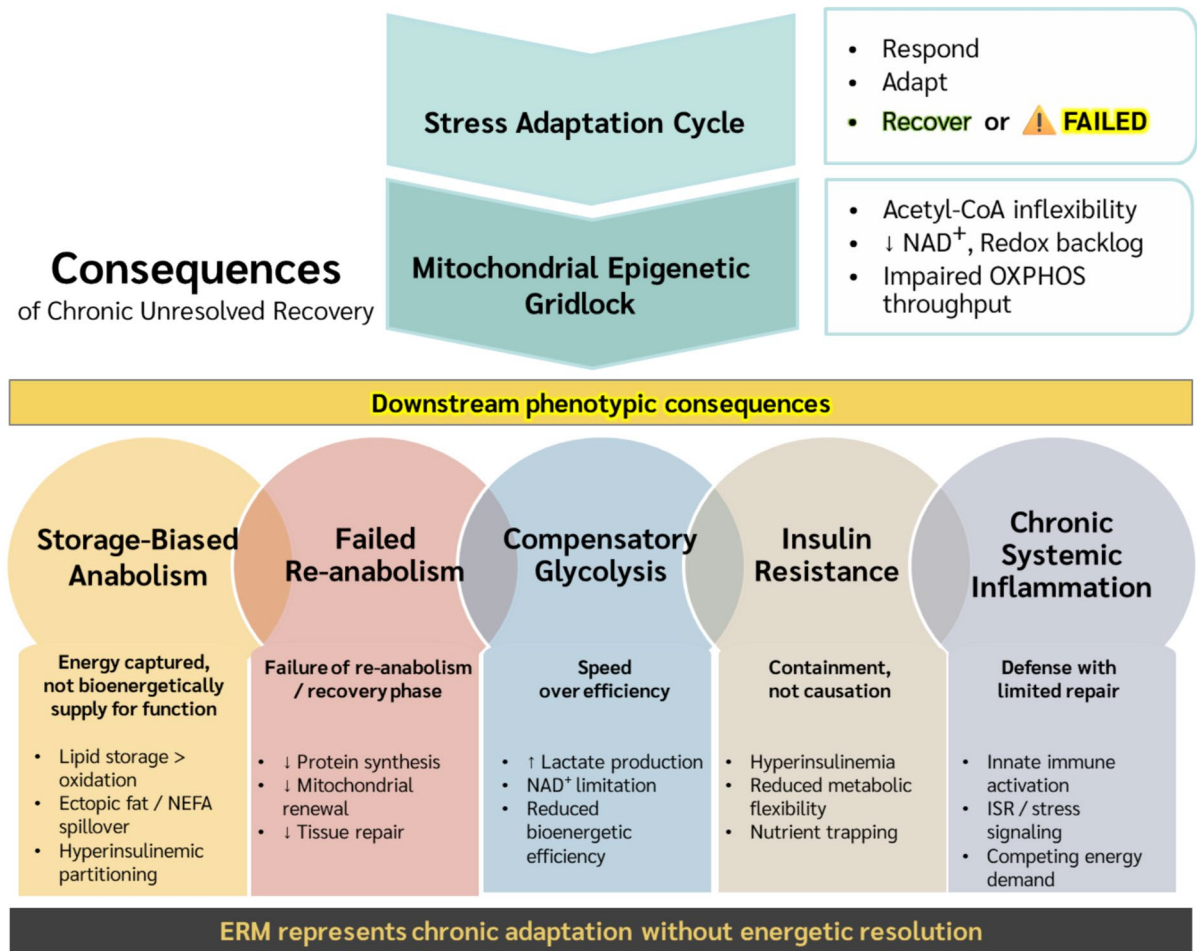
through inhibition of insulin receptor and Akt pathways (Jani et al. 2021). The resulting insulin resistance initially functions as a containment strategy, limiting further substrate inflow into already congested metabolic networks (Samuel & Shulman 2012). However, persistent hyperinsulinemia subsequently promotes central adiposity, reinforcing lipid storage while driving adipocyte hypertrophy, lipotoxicity, and increased release of non-esterified fatty acids (NEFA), thereby further exacerbating systemic inflammation and downstream metabolic consequences (Tippairote et al. 2022).

At the cellular level, sustained bioenergetic stress activates conserved stress-response programs, including the integrated stress response (ISR) and mitochondrial ISR. While acutely adaptive, chronic activation of these pathways becomes maladaptive, promoting inflammasome activation, immune dysregulation, and persistent low-grade inflammation (Hetz et al. 2020; Zhou et al. 2011).

At the organismal level, these bioenergetic and inflammatory constraints manifest as anabolic resistance, muscle loss, immune exhaustion, cognitive symptoms, and chronic pain, linking mitochondrial recovery failure to multisystem functional decline across aging and chronic disease states (Marzetti et al. 2025; Tippairote et al. 2025).

#### Causal reframing: recovery as a mitochondrial constraint

Recent experimental and translational studies support reconsidering recovery failure as potentially arising from *constrained mitochondrial bioenergetic capacity*, rather than being attributable solely to excessive stress signaling or primary dysregulation of upstream pathways. Interventions that modulate downstream immune, neuroendocrine, or inflammatory pathways can improve selected outcomes but have not consistently demonstrated restoration of systemic recovery capacity. For example, combined oxytocin treatment with inhibition of activin receptor–like kinase 5 (ALK5)—the transforming growth factor- $\beta$  (TGF- $\beta$ ) type I receptor mediating pro-fibrotic and inflammatory signaling—suppressed inflammatory and fibrotic programs and extended lifespan and healthspan in very old, frail male mice. However, these effects were sex-specific and occurred without direct evidence of restored mitochondrial bioenergetic function,



**Fig. 4** Downstream phenotypic consequences of chronic recovery failure. This schematic illustrates the system-level phenotypic consequences that arise when stress adaptation persists without energetic resolution. Under conditions of unresolved recovery, the stress adaptation cycle progresses from response and adaptation toward failed recovery, converging on mitochondrial epigenetic gridlock characterized by acetyl-CoA inflexibility, NAD<sup>+</sup> redox backlog, and impaired oxidative phosphorylation (OXPHOS) throughput. Downstream, this unresolved bioenergetic state gives rise to a predictable constellation of maladaptive—but initially protective—phenotypes. These include storage-biased anabolism, in which energy is sequestered as lipid rather than deployed for function; failed re-anabolism, reflecting suppression of protein synthesis, mitochondrial renewal, and tissue repair; compen-

satory glycolysis, prioritizing speed of ATP generation over efficiency; insulin resistance, functioning as a containment strategy to limit further substrate influx; and chronic systemic inflammation, representing sustained immune defense under constrained repair capacity. Collectively, these phenotypes should not be interpreted as independent primary pathologies. Instead, they represent coordinated adaptive responses to persistent bioenergetic constraint, preserving short-term survival while progressively undermining recovery, resilience, and long-term function. Within this framework, Exposure-Related Malnutrition (ERM) may reflect a state of chronic adaptation without energetic resolution. Abbreviations: ERM, Exposure-Related Malnutrition; ISR, integrated stress response; NAD<sup>+</sup>, oxidized nicotinamide adenine dinucleotide; NEFA, non-esterified fatty acids; OXPHOS, oxidative phosphorylation

suggesting that reducing energetic burden may not be equivalent to reactivating ATP-dependent recovery processes (Kato et al. 2025). Notably, the lifespan and healthspan benefits in this model were sex-specific, highlighting biological sex as a modifier of

stress adaptation and recovery efficacy. Mitochondrial function, redox balance, immune responsiveness, and neuroendocrine signaling exhibit sexually dimorphic patterns, which may influence baseline bioenergetic reserve and recovery kinetics (Junker et al. 2022;

Klein & Flanagan 2016). Such variability suggests that bioenergetic constraint is context-dependent rather than uniform across populations.

In contrast, interventions that appear to enhance mitochondrial processing efficiency, redox balance, or substrate-to-ATP conversion have been associated with broader, cross-system improvements that are consistent with ATP-dependent repair capacity (Picard et al. 2018). In oxidatively stressed human brain microvascular endothelial cells, basal mitochondrial respiration sufficient for survival is preserved, whereas maximal respiration and spare respiratory capacity—metrics more closely related to recovery flexibility—are selectively lost. Restoration of physiological NAD<sup>+</sup> homeostasis rescues mitochondrial reserve capacity without altering basal oxygen consumption, identifying mitochondrial redox and processing capacity as potential limiting determinants of recovery (Chaubey et al. 2026).

Consistent with this principle at higher levels of biological organization, administration of small extracellular vesicles from young donor plasma improves physical performance in aged mice, accompanied by upregulation of mitochondrial metabolic and electron transport pathways (Chen et al. 2024). At the cellular level, restoration of satellite glial cell-mediated mitochondrial transfer similarly protects primary sensory neurons against peripheral neuropathy, despite ongoing stress exposure (Xu et al. 2026). Although these findings do not establish singular causality, they are consistent with the interpretation that mitochondrial capacity may be a critical determinant of recovery failure.

Accordingly, strategies that restore mitochondrial capacity—at the organismal, intracellular, or intercellular level—may be necessary to facilitate resolution of accumulated bioenergetic debt and re-establish durable resilience, supporting the proposed framework for ERM as a state of chronic maladaptation.

### **Clinical translation: early recognition, bioenergetic triage, and recovery restoration**

The following clinical considerations are presented as hypothesis-generating implications derived from the proposed model. Translating this perspective into clinical practice requires a shift away from downstream, disease-centered thresholds toward the early

recognition of recovery failure, at a stage when dysfunction remains functional, dynamic, and highly reversible. Within this framework, ERM is not intended to be defined by dietary intake alone or by the presence of established pathology, but by a mismatch between energetic demand and the biological capacity to complete recovery following repeated or sustained stress exposure, consistent with broader evidence linking stress adaptation, bioenergetic constraint, and recovery capacity (Picard et al. 2018; Rattan 2013; Tippairote et al. 2025).

#### **Early recognition: functional signals of recovery failure**

In its earliest stages, ERM may manifest primarily through functional symptoms and signs, rather than fixed disease entities. These include disproportionate or persistent fatigue, delayed recovery after physical or psychological stress, reduced stress tolerance, anabolic resistance, sleep disturbance, and fluctuating immune or inflammatory symptoms (Tippairote et al. 2025). Such features are frequently encountered in clinical practice but are often treated as nonspecific or idiopathic when considered in isolation.

From a bioenergetic perspective, these manifestations reflect stage-dependent impairment of recovery processes, rather than structural failure. Experimental and clinical models of stress physiology demonstrate that adaptation requires not only activation of stress-response pathways but also sufficient energetic capacity to resolve them (Rattan 2020; Sterling 2012; Willenborg et al. 2021). When recovery is repeatedly incomplete, functional impairment accumulates despite the threshold of overt disease is not fulfilled. This approach suggests that ERM recognition may represent a preclinical yet biologically coherent vulnerability state.

#### **Biomarker triage: patterns and trajectories over thresholds**

Clinical recognition of ERM may rely less on isolated abnormal values and more on the integrated interpretation of clinical history and coordinated biomarker patterns across systems, consistent with triage models of energy allocation and adaptive prioritization, with ERM proposed as a conceptual clinical extension (Ames 2006; McEwen & Wingfield 2003;

Tippairote et al. 2025). Alterations in markers of specific nutrient- or stress-sensing pathways may reflect the prevailing adaptive state, but in isolation they cannot determine recovery capacity, as mitochondrial reserve, redox flexibility, and executional throughput required for ATP-dependent resolution are not captured by single molecular readouts. Rather than serving as standalone diagnostics, biomarkers act as context-dependent signals, whose clinical significance emerges only when interpreted alongside exposure history, functional symptom trajectories, and—critically—patterns of recovery over time.

This pattern-based logic is empirically supported by recent longitudinal evidence. In a 20-year prospective cohort study, a composite Physiological Healthy Aging Index (PHAI) derived from five routine clinical biomarkers—systolic blood pressure, fasting glucose, creatinine, forced vital capacity, and C-reactive protein—strongly predicted all-cause, cardiovascular, cancer, and age-related mortality (Lyu et al. 2025). Notably, predictive power did not arise from any single biomarker crossing a pathological threshold, but from the integrated configuration and trajectory of multiple markers, many of which remained within conventional reference ranges.

Within the ERM framework, such subtle yet concordant signals—constrained anabolic capacity, inefficient substrate utilization, persistent low-grade inflammatory tone, or prolonged stress-adaptive signaling—may therefore be detectable well before overt disease emerges. For example, individuals may report adequate protein intake and regular physical activity, yet exhibit low skeletal muscle mass, reduced stamina, or disproportionately low creatinine levels, consistent with limited creatine availability and diminished muscle energy reserves (Groothof et al. 2024; Thongprayoon et al. 2016). In isolation, low creatinine may be dismissed as benign; in a coordinated pattern that includes reduced functional capacity and other subtle markers, it instead signals restricted bioenergetic reserve.

Taken together, these convergent observations support a triage-based interpretation of biomarkers in ERM, in which vulnerability becomes visible through coordinated deviations and longitudinal trajectories rather than isolated threshold violations. When assessed in isolation, such findings are often dismissed as nonspecific variation or laboratory noise. When integrated across systems and followed over

time, however, they reveal a bioenergetic bottleneck at the level of recovery, enabling earlier recognition, staging along a continuum, and intervention before incomplete resolution consolidates into irreversible pathology.

#### Early intervention: reducing mitochondrial congestion

At the intervention level, early ERM management may prioritize reducing sustained energetic congestion to restore mitochondrial throughput and renewable recovery. This process depends not only on lowering energetic load, but on modulating both the volume and the temporal rhythm of energy intake and expenditure. Continuous substrate influx and irregular demand patterns perpetuate metabolic congestion, whereas rhythmic modulation creates defined windows that allow ATP-dependent repair and resolution to proceed.

This principle is consistent with the cyclic metabolic switching framework, which emphasizes that periodic transitions between fed and fasted metabolic states—rather than continuous energy availability—are required to activate cellular stress-resistance, mitochondrial remodeling, and repair pathways (Mattson 2025). Within this model, recovery capacity is flexible but biologically bounded, and its expression depends primarily on timing, spacing, and alignment, rather than maximal intensity or sustained deprivation. Parallel insights from sleep physiology similarly indicate that recovery processes can transiently accrue surplus restorative capacity when temporal conditions are optimized, rather than merely repaying prior debt (Balkin & Rupp 2025).

Accordingly, dietary strategies such as caloric restriction and time-restricted eating reduce persistent substrate oversupply while reintroducing periods of energetic relief, thereby lowering baseline metabolic pressure and improving substrate-handling efficiency (Longo et al. 2021; Longo & Panda 2016; Tippairote et al. 2021). The importance of coordinated rhythm across behaviors is supported by population-level evidence: in a prospective cohort of more than 59,000 UK Biobank participants, modest concurrent improvements in sleep duration, physical activity, and diet quality were associated with meaningful gains in both

lifespan and healthspan, whereas substantially larger changes were required when behaviors were modified in isolation (Koemel et al. 2025).

In parallel, structured physical activity promotes mitochondrial throughput by increasing substrate flux, stimulating mitochondrial biogenesis, and enhancing metabolic flexibility (Holloszy & Booth 1976; Musci et al. 2019; Picard et al. 2014). From a bioenergetic perspective, exercise does not merely add demand; when appropriately dosed and temporally separated from intake, it can functionally relieve congestion by expanding processing capacity.

Importantly, these interventions should not be conceptualized simply as additional stressors. When appropriately timed and scaled, they act as mitohormetic signals, engaging mitochondrial quality-control pathways—including biogenesis, mitophagy, and fusion–fission remodeling—and thereby supporting ATP throughput and recovery capacity (Gorgori-Gonzalez et al. 2025).

#### Supporting resolution: coordinated funding of recovery

Reducing energetic load alone is insufficient if the resources required for recovery remain unavailable. Effective ERM intervention therefore pairs decongestive strategies with active support for resolution, including adequate protein and micronutrient availability, restoration of sleep and circadian regularity, modulation of psychosocial stress, and—critically—sufficient time for recovery to unfold. Anabolic repair, immune resolution, and rebuilding of physiological reserves are fundamentally ATP-dependent and cannot proceed under sustained energetic scarcity or chronic temporal compression (Kirkwood 1977; Mattson 2025; Rattan 2013).

Within the ERM framework, recovery and resolution are governed not by optimization of a single pathway, but by the concurrent availability of time, energy, and substrates across systems. When sleep remains fragmented, physical activity poorly aligned, or nutritional support inadequate, recovery processes compete for limited energetic resources and remain incomplete, allowing adaptive programs to persist beyond their useful window (Picard et al. 2018; Sterling 2012).

#### Reversibility as the central clinical opportunity

A key implication of ERM may be its potential reversibility, particularly when recognized early. Unlike late-stage disease, early ERM reflects functional constraint rather than irreversible damage. By identifying recovery failure before structural breakdown occurs, clinicians can alter trajectories, restore resilience, and prevent progression toward chronic disease and accelerated aging (Rattan 2013; Tippairote et al. 2026).

In this perspective, clinical vulnerability is reframed by a simple but transformative insight: patients are not failing to adapt to stress—they are failing to recover because recovery is energetically underfunded. Early recognition and recovery-centered intervention convert this constraint from an inevitability into a modifiable clinical opportunity.

#### Beyond mitochondrial constraint: genetic, immune, and psychosocial modulators

While this framework emphasizes mitochondrial throughput and NAD<sup>+</sup>-dependent recovery capacity as central constraints in adaptive resolution, resilience and chronic disease trajectories are inherently multifactorial. Genetic heterogeneity influences baseline mitochondrial efficiency, redox handling, inflammatory tone, and substrate utilization, thereby shaping individual recovery capacity and vulnerability (Picard et al. 2018; Wallace 2010). Likewise, immune dysregulation may arise from primary inflammatory or autoimmune processes that are not initially driven by bioenergetic limitation, although sustained immune activation itself imposes substantial energetic demand (Hotamisligil 2017; Medzhitov 2008).

Psychological and social buffering mechanisms further modulate stress exposure and physiological response. Social support, cognitive appraisal, and behavioral flexibility can attenuate neuroendocrine activation and reduce cumulative allostatic load (McEwen & Wingfield 2003; Slavich & Cole 2013; Slavich et al. 2023). Conversely, chronic psychosocial adversity may amplify stress signaling independent of intrinsic mitochondrial mechanics, contributing to sustained physiological activation and altered immune regulation (Esch & Stefano 2025; Esch et al. 2002; Miller & Raison 2016). These moderators influence the magnitude and duration of adaptive activation and therefore shape recovery kinetics.

Accordingly, mitochondrial bioenergetic constraint is not proposed as a singular or exclusive cause of resilience failure. Rather, it may represent a convergent downstream bottleneck through which genetic, immunological, environmental, and psychosocial influences interact to shape recovery capacity. Framed this way, mitochondrial throughput operates within a broader systems context of adaptation, vulnerability, and resilience.

### Conclusion and future perspectives.

Across stress physiology, nutrition science, psychopathology, and aging research, substantial progress has been made in characterizing adaptive responses to challenge. Yet these fields have largely evolved in parallel, leaving unresolved a central clinical paradox: why comparable stress exposures produce sustained resilience in some individuals but progressive dysfunction in others. We propose that the missing unifying constraint is not stress exposure itself, but the bioenergetic capacity to complete recovery.

By reframing stress adaptation as a cyclical process—respond, adapt, and recover—this framework clarifies that recovery is neither passive nor guaranteed. Recovery is an active, ATP-dependent phase that depends on sufficient bioenergetic availability within a finite metabolic economy (Kirkwood 1977; Picard et al. 2018; Rattan 2013). When mitochondrial throughput, redox flexibility, and NAD<sup>+</sup>-dependent execution capacity are constrained, adaptive programs persist beyond their functional window. Over time, this persistence manifests as mitochondrial congestion, epigenetic gridlock, and progressive loss of physiological plasticity, even in the absence of overt pathology (Picard & McEwen 2018; Tippairote et al. 2022).

Within this context, this framework is proposed as a conceptually interpretable pattern of unresolved bioenergetic triage, integrating evolutionary allocation logic, developmental calibration, stress physiology, and mitochondrial mechanics to help explain why functional decline can emerge despite nominal intake, preserved adaptive signaling, and laboratory values within reference ranges (Ames 2006; Del Giudice et al. 2011; Tippairote et al. 2025). By emphasizing recovery failure rather than primary damage or dysregulation, this perspective shifts clinical attention

upstream—toward early vulnerability, staging, and reversibility.

Crucially, this perspective reframes clinical risk assessment away from isolated thresholds and toward coordinated patterns and trajectories across systems. Functional symptoms, longitudinal biomarker configurations, and recovery kinetics become central signals of vulnerability, enabling recognition of ERM before incomplete resolution consolidates into irreversible disease (Lyu et al. 2025; Sterling 2012). In this view, aging and chronic disease emerge not as abrupt system breakdowns, but as accumulated failures of adaptive resolution under sustained energetic constraint.

The clinical implications may be significant. Early interventions that reduce mitochondrial congestion, restore temporal alignment, and actively fund recovery—through coordinated modulation of intake, activity, sleep, stress exposure, and nutrient availability—can re-establish the energetic conditions required for resolution (Longo & Panda 2016; Mattson 2025; Picard et al. 2014). Such strategies do not merely suppress downstream consequences of stress; they restore the capacity to recover. This distinction helps explain why rhythm, spacing, and throughput consistently outperform isolated optimization of individual pathways (Koemel et al. 2025).

Looking forward, this framework provides a scaffold for mitochondrial-centered translational strategies that prioritize restoration of recovery capacity rather than downstream symptom control. Converging experimental and translational evidence indicates that improving mitochondrial processing efficiency, redox balance, substrate handling, and intercellular energy support can partially restore function even in aging and chronically stressed systems (Chen et al. 2024; Picard et al. 2016). In this context, mitochondria emerge not as passive energy producers, but as active gatekeepers of recovery, resilience, and aging trajectories.

Two complementary lines of evidence reinforce this shift. First, studies of small extracellular vesicles demonstrate that vesicle-mediated signaling constitutes a systemic metabolic communication network capable of modulating inflammation, insulin sensitivity, and mitochondrial function across tissue (Rohm et al. 2025; Safaei et al. 2025). Second, emerging evidence of direct intercellular mitochondrial support—including mitochondrial transfer between cells under energetic stress—suggests that recovery failure

reflects not only intracellular limitations, but also impaired network-level energy redistribution (Xu et al. 2026). Together, these findings reframe resilience and aging as properties of coordinated bioenergetic systems rather than isolated cellular defects.

The central insight of this perspective is simple but transformative: *patients may not be failing to adapt to stress—they may be failing to recover* because recovery is energetically underfunded. Recognizing and addressing this constraint early converts vulnerability from an inevitability into a modifiable clinical opportunity, with ERM providing a conceptual framework for interpreting recovery failure under bioenergetic constraint (Rattan 2013; Tippairote et al. 2026).

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**Data availability** No datasets were generated or analysed during the current study.

#### Declarations

**Competing Interests** The authors declare no competing interests.

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