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Opinion

Rethinking frailty as a disorder of mitochondrial adaptability, from energetic congestion to systemic vulnerability

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ABSTRACT

Frailty is a clinical syndrome of reduced physiological reserve in older adults for which no pharmacological treatment exists and whose cellular basis remains incompletely defined. As life expectancy rises without a comparable extension of healthspan, the absence of a mechanistic account able to guide targeted intervention is a growing clinical problem. The dominant model of primary mitochondrial bioenergetic insufficiency does not accommodate several features of the phenotype. Among the conditions most strongly associated with frailty in aging, obesity, particularly when coupled with sarcopenia, stands out for its rising prevalence and the depth of its systemic metabolic consequences. Drawing on a recent multi-omics characterisation of skeletal muscle in sarcopenic obesity and on the convergent literature in aging metabolism, organelle communication, and redox biology, we propose a complementary framework in which the proximate cellular abnormality of frailty is energetic congestion, a chronic mismatch between substrate input, energetic demand, and the capacity to dispatch the resulting flux through demand-driven oxidative metabolism. In this view the mitochondrion is not failing because fuel is scarce, but because energetic demand declines below the rate at which substrate continues to be delivered, so that substrate persists in relative rather than absolute excess, while mitochondrial adaptability is progressively impaired. The resulting cycle is self-amplifying, anchored in reverse electron transport, and generalises across skeletal muscle, adipose tissue, liver, heart and brain. Strategies that re-engage demand-driven metabolic flux through AMPK activation, substrate restriction, mild mitochondrial uncoupling, modulation of endoplasmic reticulum stress, and clearance of irreversibly congested cells are predicted to produce more durable benefits than energy supplementation, with structured exercise as the prototype of demand-driven recoupling. This perspective offers a path toward a precision pharmacology of frailty grounded in molecular stratification of patients.

1. Introduction

Frailty is a clinical syndrome of reduced physiological reserve and disproportionate vulnerability to stressors in older adults [1,2]. Its public health relevance is increasing rapidly. Indeed, the global population aged 65 years and older is projected to reach 1.6 billion by 2050, more than double its current size [3], and the gains in life expectancy achieved over the past century have not been matched by comparable gains in healthspan, generating a growing burden of late-life multimorbidity, disability and dependence [2,4]. Frailty is the principal clinical expression of this divergence, identifying older individuals in whom unhealthy aging has reached a threshold of measurable functional decline [1,2]. Current definitions, whether the physical frailty phenotype proposed by Fried and colleagues [5] or the deficit-accumulation index proposed by Rockwood and colleagues [6], predict mortality, incident disability and hospitalisation independently of chronological age and comorbidity burden, with prevalence estimates ranging from approximately 12% in community-dwelling adults aged 65 and older to over 40% in long-term care settings [7,8]. These clinical advances notwithstanding, the pathophysiological basis of frailty remains incompletely understood and is likely to involve heterogeneous alterations across molecular, cellular and tissue levels [2,9]. Recent multi-omics characterisations of frailty in older populations remain organised along tissue-specific axes, with sarcopenia, cognitive decline, heart failure, liver disease, etc. examined as discrete components [10–14]. This compartmentalised approach leaves unresolved the question of whether the multi-organ vulnerability in frailty reflects shared cellular process that operate convergently across tissues, or the

Abbreviations: **ADP**, adenosine diphosphate; **AMPK**, AMP-activated protein kinase; **ATP**, adenosine triphosphate; **BAT**, brown adipose tissue; **BCAA**, branched-chain amino acids; **cGAS**, cyclic GMP-AMP synthase; **ER**, endoplasmic reticulum; **FDG**, fluorodeoxyglucose; **FMN**, flavin mononucleotide; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1**, glucagon-like peptide 1; **GSH / GSSG**, glutathione, reduced and oxidised forms; **HFpEF**, heart failure with preserved ejection fraction; **MAM**, mitochondria-associated ER membrane; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **mtDNA**, mitochondrial DNA; **mTORC1**, mechanistic target of rapamycin complex 1; **NAD^+ / NADH**, nicotinamide adenine dinucleotide, oxidised and reduced forms; **NADPH**, nicotinamide adenine dinucleotide phosphate; **NLRP3**, NLR family pyrin domain containing 3; **NMN**, nicotinamide mononucleotide; **NR**, nicotinamide riboside; **PGC-1α**, peroxisome proliferator-activated receptor γ coactivator 1-alpha; **PPAR**, peroxisome proliferator-activated receptor; **RET**, reverse electron transport; **ROS**, reactive oxygen species; **STING**, stimulator of interferon genes; **TCA**, tricarboxylic acid cycle; **UCP1**, uncoupling protein 1; **ULK1**, Unc-51-like kinase 1; **WASF3**, WASP family member 3; **Δp**, proton-motive force; **Δψm**, mitochondrial membrane potential.

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parallel manifestation of partly independent processes. The dominant cellular model attributes frailty to mitochondrial bioenergetic insufficiency, supported by convergent evidence of reduced mitochondrial respiratory capacity, lower mtDNA content and altered substrate metabolism in frail individuals across multiple tissues [15–17] and has shaped the design of geroscience-oriented therapeutic trials over the past decade. Several reproducible features of the phenotype are nevertheless difficult to reconcile with a strict bioenergetic deficit interpretation. Particularly consequential for the present proposal is that cellular energetic demand itself declines progressively with age. Sedentariness, reduced muscle mass, anabolic resistance and the involution of brown adipose tissue together reduce cellular ATP turnover [18,19], shifting the balance between substrate input and demand toward chronic excess of input relative to consumption.

Building on these considerations and on a recent multi-omics characterisation of skeletal muscle in a two-hit aging model of sarcopenic obesity [20], we propose a complementary framework in which frailty originates in energetic congestion, a state in which a chronically reduced demand allows substrate to persist beyond utilisation, while substrate input itself remains broadly preserved, with the consequence that the regulatory coupling between substrate availability and cellular need is progressively lost. Mitochondrial dysfunction in this view is real but reframed in its directionality. The mitochondrion is not failing because fuel is scarce. It is failing because the fall in demand-driven ATP turnover is not matched by a comparable reduction in substrate delivery, so that oxidative flux is uncoupled from cellular need, while mitochondrial adaptability, the capacity of the organelle to coordinate output with fluctuating energetic demand, is progressively impaired (Fig. 1). The clinical phenotype of frailty, namely decreased reserve when challenged, maps naturally onto a cellular state that already operates at saturation, with no additional capacity to mobilise. The implications of this reframing might range from the systemic extension of frailty across organ systems to the development of mechanistically-targeted pharmacological strategies.

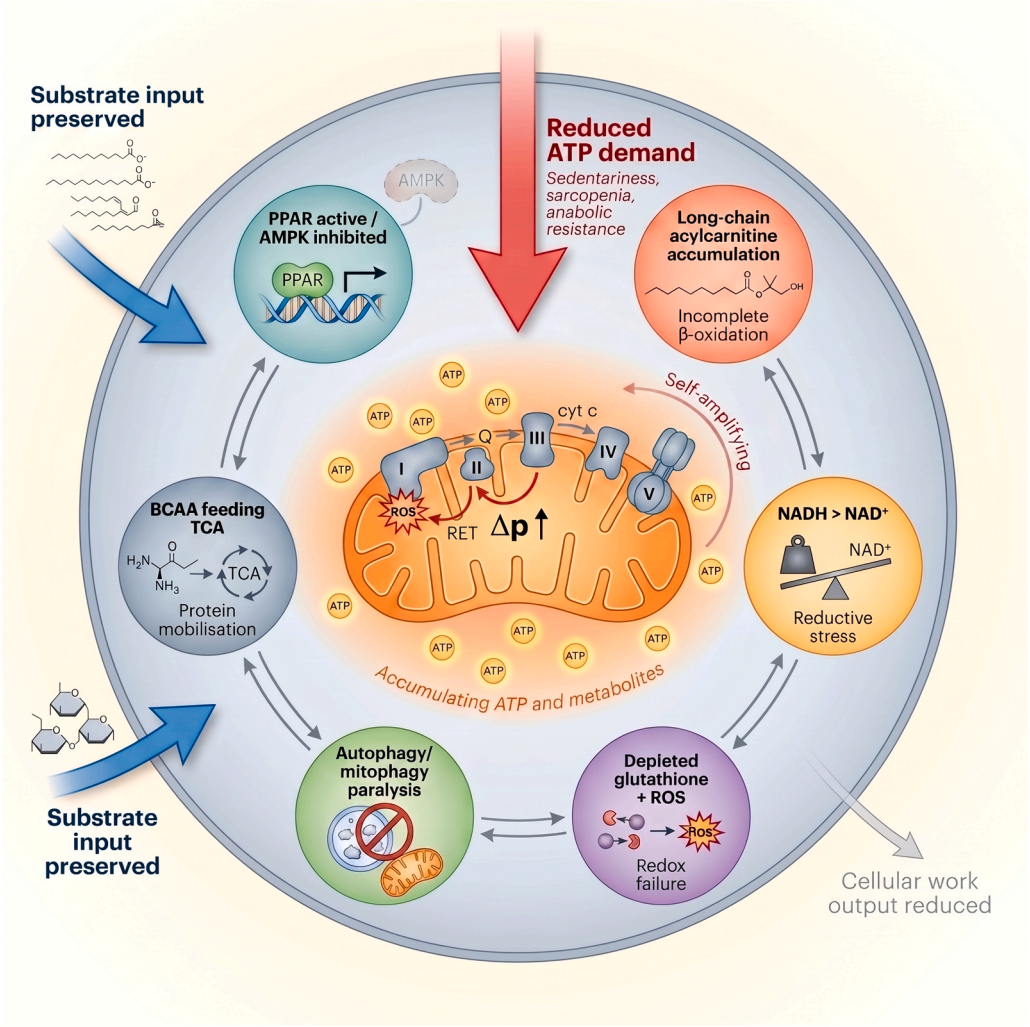


Fig. 1. Cellular energetic congestion in aging and frailty. Substrate input is preserved (long-chain fatty acid, top-left; glucose, bottom-left) while ATP demand collapses due to sedentariness, sarcopenia, and anabolic resistance (top, red arrow). The asymmetry drives accumulation of ATP and metabolic intermediates. Sustained substrate delivery into a chain with reduced ADP availability elevates the proton-motive force (Δp ↑) and reduces the ubiquinone pool, driving reverse electron transport (RET) from Q back to Complex I, with superoxide generation at the FMN site (ROS). The cycle is self-amplifying. Six interconnected cellular features follow: active PPAR with suppressed AMPK (teal), long-chain acylcarnitine accumulation from incomplete β-oxidation (coral), elevated NADH/NAD⁺ ratio and reductive stress (amber), glutathione depletion and redox failure (violet), autophagy/mitophagy paralysis (green), and BCAA-driven anaplerosis through protein mobilisation (blue-gray). The net consequence is reduced cellular work output (bottom-right). This saturated state, unable to mobilise further reserve, is the proposed cellular correlate of the loss of physiological reserve that clinically defines frailty. Abbreviations: AMPK, AMP-activated protein kinase; BCAA, branched-chain amino acids; cyt c, cytochrome c; Δp, proton-motive force; FMN, flavin mononucleotide; PPAR, peroxisome proliferator-activated receptor; Q, ubiquinone pool; RET, reverse electron transport; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; I–V, respiratory chain complexes.

1.1. Bioenergetic insufficiency as a partial account of frailty

The mitochondrial theory of aging, formulated by Harman [21] and developed through subsequent work on mtDNA mutations, respiratory complex stoichiometry and oxidative damage, has provided the conceptual scaffold for understanding frailty in molecular terms. The model predicts that tissues with the highest energetic demand, including skeletal muscle and brain and immune system, are the first to fail as ATP-generating capacity declines, producing the phenotypes most closely identified with frailty, namely sarcopenia, exercise intolerance, cognitive slowing, and low-grade inflammation [15,22]. Experimental support is extensive. In the Baltimore Longitudinal Study of Aging, lower in vivo mitochondrial oxidative capacity measured by ^{31}P-magnetic resonance spectroscopy was associated with elevated markers of systemic inflammation independently of age and sex [23]. Post-exercise phosphocreatine recovery times are prolonged in frail compared with non-frail older adults and correlate with reduced exercise tolerance [24]. Peripheral blood mononuclear cells from frail older adults display decreased respiration and lower mtDNA content [17,25], and metabolomic profiling has identified consistent perturbations of carnitine shuttle metabolites in frailty across multiple cohorts [26,27]. The case for a mitochondrial root of frailty has therefore become firmly embedded in current geriatric pathophysiology [15].

Multiple observations, however, are not readily accommodated within a strict bioenergetic deficit model. The behaviour of cellular energy sensors provides the most informative inconsistency. AMP-activated protein kinase (AMPK), whose activation by elevated AMP/ATP and ADP/ATP ratios is the canonical biochemical response to falling energy charge, is consistently downregulated in aged tissues. Reductions in AMPK γ2 and γ3 subunit content and blunted contraction-induced activation are documented in aged skeletal muscle [28,29], and conditional ablation of AMPKα1/α2 in skeletal muscle in mice phenocopies major features of sarcopenia [30]. Reduced AMPK activity is similarly documented in aged adipose tissue [31] and in hepatocytes [31]. This pattern aligns with the deregulated nutrient-sensing hallmark of aging [14], whose defining feature is the dissociation between the metabolic state of the cell and the transcriptional and post-translational programs that should respond to it. A cell in genuine energetic deficit should engage AMPK. By contrast, aged and frail tissues do not.

A second consideration, rarely explicit in the bioenergetic deficit model, is the parallel decline in cellular ATP demand with aging. Daily total energy expenditure declines progressively after age 60, only partly attributable to lean mass loss [18], and resting energy expenditure decreases in older adults independently of body composition [32]. Habitual physical activity declines steeply in late life [33], and contractile activity is the dominant determinant of muscle ATP turnover [34]. Sarcopenia amplifies this effect through a direct mechanism. As contractile mass and function decrease, basal and post-exertional ATP turnover in muscle falls correspondingly [35], and the cellular demand for oxidative phosphorylation drops below the rate at which substrate is supplied through the still-active machinery of fatty acid uptake and oxidation. Anabolic resistance further reduces the ATP cost of protein synthesis [36]. Brown adipose tissue, a major site of dissipative oxidative metabolism, involutes substantially in older adults, reducing the systemic capacity to consume substrate through uncoupling [37]. The aggregate consequence is that, in many aged individuals, cellular substrate supply remains broadly sustained while cellular substrate demand falls progressively. This asymmetry between substrate input and demand-driven dispatch is the conceptual gap that the bioenergetic deficit model has left open.

The therapeutic record is consistent with this reading. Resistance and aerobic exercise act primarily by raising cellular ATP demand and re-engaging AMPK and PGC−1α signalling [38,39]. Caloric restriction and intermittent fasting, which reduce substrate supply, extend healthspan across multiple species and improve functional outcomes in older adults [14,40]. Metformin, which mimics low cellular energy charge, is being evaluated as a means of slowing frailty progression in older adults [41], most directly in the ongoing Targeting Aging with Metformin (TAME) trial [42], while epidemiological evidence in metformin users points in the same direction. By contrast, trials of mitochondrial cofactors and antioxidant supplements have produced modest and inconsistent benefits [43,44], and a recent meta-analysis of the NAD^+ precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) in older adults concluded that these interventions do not consistently improve muscle mass or function despite effective elevation of tissue NAD^+ [45,46]. The absence of consistent benefit is compatible with the present reading, although the heterogeneity of these trials in duration, dose and endpoints limits what can be inferred from it. The overall direction of this evidence is more readily reconciled with a regulatory failure in coupling ATP production to demand than with insufficient ATP generation.

1.2. A complementary paradigm: frailty as energetic congestion

We propose that the cellular state underlying frailty is one of *energetic congestion*, a chronic mismatch between three quantities that, in the healthy young cell, are tightly coupled, namely substrate input, energetic demand, and the metabolic capacity to dispatch the resulting flux through oxidative phosphorylation toward useful work or controlled dissipation. The cell retains its metabolic machinery but loses the regulatory coupling that would direct it toward demand-driven turnover. Substrate continues to enter and ATP and reducing equivalents are produced, but in the absence of sufficient downstream demand or dissipative capacity the system reaches a low-throughput steady state in which energetic intermediates accumulate relative to their consumption. The metabolic consequences, namely substrate overflow, redox imbalance, suppressed energy sensing, paralysis of self-correction, and mobilisation of structural proteins for anaplerosis, are, in this perspective, the cellular correlates of the clinical phenotype of frailty.

This cellular state echoes the well-established concept of metabolic flexibility, the capacity of a tissue to adjust substrate selection between glucose and fatty acids in response to nutritional state and energetic demand. Loss of metabolic flexibility characterises metabolic diseases and aging [47]. The two phenomena describe different axes of metabolic regulation, namely a qualitative choice between substrates in the case of metabolic flexibility and a quantitative imbalance between substrate input, demand and dispatch capacity in the case of energetic congestion, and may coexist in the same cell, particularly under conditions of chronic substrate excess and reduced demand, where impaired substrate switching and overall flux mismatch can reinforce each other. The incomplete fatty acid oxidation and acylcarnitine accumulation that mark the loss of metabolic flexibility in skeletal muscle [48] are, in this view, also among the metabolic correlates of energetic congestion.

The present perspective does not introduce novel experimental claims. Each mechanistic component is independently documented in the recent literature on aging metabolism, mitochondrial physiology, lipotoxicity and nutrient sensing, including in studies of skeletal muscle and circulating biomarkers in frail older adults [16,17,26,27,49]. The contribution of the present perspective lies in their integration into a coherent causal architecture, motivated and exemplified by the convergent molecular signature of skeletal muscle in our recent multi-omics analysis of sarcopenic obesity [20]. Although the study is tissue-specific, the model is intended to be general. Energetic congestion is expected to operate in any post-mitotic, energy-consuming cell in which chronic substrate availability coexists with declining demand. The molecular components of this state are organised below into six interconnected nodes (Table 1).

1.2.1. Substrate-driven transcriptional activation decoupled from energetic demand

PPAR isoforms are directly activated by long-chain fatty acids as endogenous ligands, independently of AMPK signalling [50,51],

Table 1
The six mechanistic nodes of energetic congestion.

Node	Molecular phenomenon	Significance for the congested state	Supporting references
Substrate-driven transcriptional activation decoupled from energetic demand	PPAR isoforms are activated by fatty acid ligands independently of AMPK, while AMPK signalling is attenuated. Fatty acid uptake and oxidation gene programs (Cd36, Fabp3, Lpl, Acadl) remain transcriptionally active.	Transcriptional control of fatty acid oxidation is governed by substrate supply and dissociated from energetic demand, generating a feed-forward activation that persists independently of cellular need. In sarcopenic obesity, an absolute systemic excess of substrate is superimposed on the reduced demand, aggravating the mismatch.	[20,50–52]
Bottlenecked oxidative throughput	Incomplete β-oxidation yields accumulation of long-chain acylcarnitines (C14–C20) with concurrent depletion of free L-carnitine.	Substrate entry exceeds the rate of oxidative disposal, placing the rate limitation downstream, namely in NAD^+ availability, electron-acceptor capacity and forward respiratory flux.	[20,26,27,48,49]
Reductive stress and reverse electron transport	At low ATP demand the proton-motive force remains elevated and NADH reoxidation lags its generation, raising the matrix NADH/NAD^+ ratio. NADH allosterically inhibits TCA dehydrogenases, and reverse electron transport at Complex I generates superoxide.	The elevated NADH/NAD^+ ratio establishes reductive stress and constrains TCA throughput. The associated superoxide production is consistent with electron oversupply to a chain operating under reduced demand.	[59,60,62,64,65]
Bidirectional failure of redox homeostasis	Superoxide production from reverse electron transport rises while the pentose phosphate pathway, the principal source of NADPH for glutathione regeneration, is downregulated. The GSH/GSSG pool is correspondingly depleted.	Redox control is compromised simultaneously at the level of generation and of regeneration. Because the limitation lies at the metabolic source, it is a stable feature of the congested state.	[20,44,66,67]
Paralysis of cellular self-correction pathways	Chronic AMPK suppression impairs autophagy and mitophagy. ER stress generates a sustained unfolded protein response that inhibits mTORC1 and induces WASF3, disrupting supercomplex assembly.	Suppression of AMPK disables the autophagic and mitophagic pathways that would otherwise clear dysfunctional organelles and remodel the metabolic network. The consequent loss of self-correction renders the state progressive and self-amplifying once established.	[30,69,70,73]
Anaplerotic protein mobilisation	Under TCA cycle restriction, branched-chain amino acid catabolism is transcriptionally upregulated as a source of anaplerotic carbon.	Anaplerotic maintenance of the restricted cycle draws on net protein hydrolysis, diverting structural protein to sustain residual flux. In skeletal muscle, this links the congested state to worsening sarcopenia and complements accounts based on anabolic resistance and inflammation.	[20,74,76,77]

Across all nodes, the proximate abnormality is a mismatch between substrate supply and demand-driven dispatch, rather than an absolute excess of substrate. The imbalance reflects a fall in energetic demand (e.g. sarcopenia, sedentariness, anabolic resistance, brown adipose tissue involution) against maintained substrate supply (e.g. lipolytic spillover, expanding visceral adiposity, sustained fatty acid delivery).

whereas AMPK reflects cytosolic energy charge through its α/β/γ heterotrimer architecture [42,52]. When these two regulatory arms are dissociated, with PPAR engaged by lipid ligand availability while AMPK signalling is attenuated, fatty acid oxidation gene programs are sustained by substrate supply rather than by energetic demand. In aging, redistribution of body composition delivers fatty acids to skeletal muscle even in the absence of systemic lipid excess, as declining muscle-driven substrate disposal and brown adipose tissue involution coincide with a progressive shift toward visceral adiposity and intramuscular fat deposition [19,37,53,54]. Chronic cellular lipid oversupply, as in sarcopenic obesity, exacerbates this configuration and accelerates the same trajectory of body-composition change that aging produces on its own, with expanding visceral adiposity, dysfunctional white adipose tissue and lipolytic spillover, and worsening myosteatosis, sustaining fatty acid delivery to tissues whose oxidative demand has correspondingly declined. Under such conditions, upregulated fatty acid transporters increase intracellular fatty acid concentrations and generate further PPAR ligands [51], establishing a feed-forward loop in which transcriptional activation persists regardless of actual cellular need [52]. This configuration is recognisable in muscle in sarcopenic obesity during aging, where transcriptional programs of fatty acid uptake and oxidation (Cd36, Fabp3, Lpl, Acadl) and downstream PPARα/δ target genes are robustly upregulated while regulatory subunits of AMPK (Prkag3, Prkab2) are concurrently suppressed [20]. The decoupling between substrate availability and demand-driven transcriptional control extends beyond skeletal muscle, including to hepatocytes, where it contributes to steatosis [55], and to aged adipose depots [53] (Fig. 2).

1.2.2. Bottlenecked oxidative throughput

Incomplete β-oxidation under substrate overload generates accumulation of long-chain acylcarnitines with concurrent depletion of free L-carnitine as a recognised metabolic signature, indicating that the rate-limiting step of fatty acid catabolism lies not at the level of enzyme abundance but in downstream factors, namely NAD^+ availability,

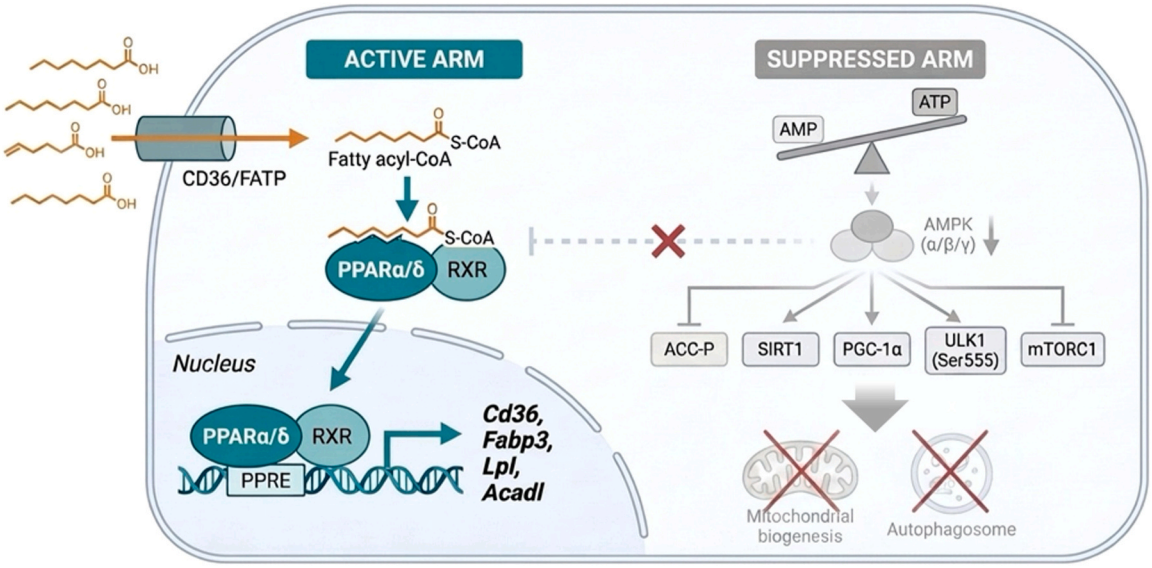


Fig. 2. Decoupling of PPAR and AMPK signalling in energetic congestion. Long-chain free fatty acids enter the cell through CD36/FATP and are converted to long-chain fatty acyl-CoA. In the active arm (teal), fatty acyl ligands bind PPARα/δ, which heterodimerises with RXR, translocates to the nucleus and binds the peroxisome proliferator response element (PPRE), sustaining transcription of fatty acid uptake and β-oxidation genes (Cd36, Fabp3, Lpl, Acadl). This activation is ligand-driven and independent of AMPK, so transcriptional control of fatty acid oxidation follows substrate supply rather than energetic demand. In the suppressed arm (grey), the maintained energy charge, shown as a low AMP/ATP ratio, together with the reduced abundance of AMPK subunits in aged tissue, leaves AMPK downregulated and inactive (downward arrow). The inhibitory restraint that AMPK would normally exert on lipid oxidation is therefore lost (red X). The downstream targets of AMPK, namely ACC, SIRT1, PGC−1α, ULK1 and mTORC1, are correspondingly disengaged: activating connectors are shown with arrowheads and inhibitory connectors with flat bars, all greyed to indicate that these actions do not occur. The consequence is a loss of the cellular self-correction pathways, with mitochondrial biogenesis not engaged and autophagy and mitophagy disabled (crossed icons). The net configuration is one in which substrate-driven transcriptional activation persists while demand-driven regulatory control is absent, so that fatty acid oxidation programs are sustained by substrate availability rather than by energetic demand. Abbreviations: ACC, acetyl-CoA carboxylase; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; CD36, cluster of differentiation 36; CoA, coenzyme A; FATP, fatty acid transport protein; mTORC1, mechanistic target of rapamycin complex 1; PGC−1α, peroxisome proliferator-activated receptor γ coactivator 1-alpha; PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator response element; RXR, retinoid X receptor; SIRT1, sirtuin 1; ULK1, Unc−51-like kinase 1.

electron acceptor capacity and the rate of forward flux through the respiratory chain [48,56]. Skeletal muscle in sarcopenic obesity reproduces this pattern despite transcriptional activation of fatty acid oxidation, with accumulation of long-chain acylcarnitines (C14–C20) and depletion of free L-carnitine [20]. Plasma acylcarnitine alterations have been documented as a circulating signature of human frailty and sarcopenia in large epidemiological cohorts, with the specific pattern depending on the species considered [26,27,49]. Long-chain acylcarnitines, generated as intermediates of incomplete β-oxidation, tend to be elevated in frailty when measured in plasma [26,27], whereas free L-carnitine and short-chain acylcarnitines including acetylcarnitine tend to be reduced in conditions of established sarcopenia [20,57,58], reflecting carnitine sequestration in tissue and reduced export of complete oxidation products. The convergence of muscle-tissue and circulating signatures supports the interpretation that incomplete substrate oxidation is a structural feature of the cellular state underlying frailty.

1.2.3. Reductive stress and reverse electron transport

A central consequence of bottlenecked oxidative throughput, particularly relevant in the setting of reduced energetic demand, is the progressive reduction of the mitochondrial pyridine nucleotide pool. When ATP demand is low, ADP availability falls, ATP synthase flux decreases, the proton-motive force remains elevated, and forward electron transfer slows [59]. NADH cannot be reoxidised at a rate matching its generation, and the matrix NADH/NAD^+ ratio rises progressively. The resulting elevation defines mitochondrial reductive stress, recently formalised as an active regulator of metabolic reprogramming in metabolic disease, obesity and aging [60,61]. Structural and kinetic studies have demonstrated that mitochondrial NAD^+-dependent isocitrate dehydrogenase is allosterically inhibited by NADH at both the catalytic and the regulatory ADP/citrate site [62,63], and α-ketoglutarate dehydrogenase exhibits comparable sensitivity [64]. The biochemical principle is that, when substrate input persists in the face of insufficient demand, the TCA cycle becomes a regulated bottleneck rather than an unconstrained hub.

The most direct consequence of the saturated respiratory chain is at Complex I itself. When the ubiquinone pool is highly reduced and the proton-motive force is elevated, electrons flow backward through Complex I in a process termed reverse electron transport (RET), generating superoxide at the NADH dehydrogenase module and further consuming matrix NAD^+ [59,65]. RET was first established as a major source of mitochondrial ROS in ischemia-reperfusion injury [59] and has since been shown to be active during normal aging, with genetic or pharmacological inhibition of RET extending lifespan in *Drosophila* through NAD^+-dependent sirtuin- and FoxO-mediated pathways [65]. Mitochondrial ROS therefore in aged tissues are not the byproduct of failing respiration but the predictable consequence of electron oversupply to a chain operating under chronically reduced demand.

1.2.4. Bidirectional failure of redox homeostasis

Oxidative stress with glutathione depletion is a long-recognised feature of aging muscle, classically interpreted as a driver of sarcopenia [22]. The model refines this interpretation by recognising two non-redundant components. On one side, RET at Complex I increases superoxide generation when the respiratory chain is saturated and the proton-motive force is high [59,65]. On the other side, the pentose phosphate pathway, the principal source of cytosolic NADPH and therefore of the reducing equivalents required by glutathione reductase to regenerate GSH from GSSG [66,67], is downregulated. Sarcopenic obese muscle illustrates both components, with GSH/GSSG depletion

and concurrent upregulation of antioxidant response genes, together with significant suppression of pentose phosphate pathway transcripts [20]. Increased oxidative challenge coupled with reduced regenerative capacity provides a mechanistic explanation for the modest performance of antioxidant supplementation in clinical trials of sarcopenia and physical frailty [44,68]. Exogenous antioxidants cannot restore a redox pool whose regenerative supply has been compromised at the metabolic source.

1.2.5. Paralysis of cellular self-correction pathways

A critical implication concerns the cellular pathways that normally correct mitochondrial dysfunction. AMPK is the principal upstream activator of macroautophagy and mitophagy, phosphorylating ULK1 at Ser555, activating Beclin−1, and inhibiting mTORC1 to release the ULK1 complex from translational repression [69,70]. Genetic ablation of AMPK in skeletal muscle results in defective ULK1 phosphorylation, accumulation of p62 and Parkin, mitochondrial dysfunction and an age-mimicking muscle phenotype [30]. The chronic suppression of AMPK signalling that characterises the congested state therefore has a second-order consequence. The cellular pathways normally responsible for clearing dysfunctional organelles and reorganising the metabolic network are themselves disabled. The system loses its capacity to self-correct. Endoplasmic reticulum stress, documented in aged and obese skeletal muscle [71,72], generates a sustained unfolded protein response that further inhibits mTORC1 and induces WASF3, which translocates to mitochondria and disrupts respiratory supercomplex assembly [73]. The loss of autophagy and the persistence of ER stress are causally linked through the AMPK signalling deficit, and together they might explain why the cellular state, once established, is progressive and self-amplifying.

1.2.6. Anaplerotic protein mobilisation

Under conditions of tricarboxylic acid cycle restriction, anaplerotic substrate input is required to sustain residual cycling. Branched-chain amino acid catabolism contributes succinyl-CoA via propionyl-CoA and provides α-ketoglutarate via transamination. Also, it is a major route of anaplerosis in skeletal muscle [74,75]. The transcriptional upregulation of branched-chain amino acid degradation observed in skeletal muscle of aging sarcopenic obese mice [20] is consistent with this mechanism. Anaplerotic mobilisation of amino acids in chronically congested tissue requires net hydrolysis of muscle protein, with consequent atrophy [74,76]. This interpretation complements rather than replaces existing accounts of age-related muscle wasting based on anabolic resistance and chronic inflammation [36,77].

Taken together, these six interconnected nodes define a coherent cellular state. Each component is supported by independent experimental literature. Their integration provides a coherent account in which the multiple mitochondrial and metabolic alterations documented in frail tissues are reorganised as predictable downstream consequences of a single upstream abnormality, namely the chronic mismatch between energetic input, energetic demand, and dispatch capacity (Fig. 1).

1.3. Reduced cellular demand and self-amplifying congestion

The cellular state described tends to amplify rather than resolve. In the sedentary or sarcopenic older individual, mitochondrial ATP demand falls chronically while substrate supply continues, establishing sustained State 4 conditions in which the proton-motive force (Δp) remains elevated and ADP availability is low [34,78,79]. Three biochemical consequences follow. First, NADH cannot be reoxidised at a rate matching its production, and the matrix NADH/NAD^+ ratio rises. Second, the ubiquinone pool becomes increasingly reduced. Third, forward electron transfer at Complex I becomes thermodynamically unfavourable and electrons flow in reverse (reverse electron transport, RET), generating superoxide at the flavin mononucleotide site [59,80–82]. The resulting reactive oxygen species damage mitochondrial DNA, peroxidise cardiolipin and oxidise respiratory complex subunits [81,83,84], reducing respiratory capacity and making the conditions favourable to RET more stable. The cycle is therefore self-amplifying: reduced demand elevates Δp, RET-derived superoxide damages the respiratory chain, and the resulting decline in capacity further compromises forward electron flow even when activity is restored. Studies of muscle disuse in older adults confirm that mitochondrial dysfunction develops within days of immobilisation, before measurable atrophy, and that bioenergetic recovery remains incomplete even when mass is restored [85–87]. The principle extends to any post-mitotic cell whose ATP demand declines while substrate supply continues.

1.4. Energetic congestion across organ systems

The generalisation of energetic congestion across organ systems is supported by three converging axes of cellular dysregulation that operate, with tissue-specific variation, in each affected compartment: the progressive dissociation of nutrient and energy sensors (AMPK, mTORC1, sirtuins) from actual metabolic state, creating the regulatory conditions for chronic substrate-demand mismatch [14,29,31,88–90]; the deterioration of mitochondria-associated ER membrane (MAM) contacts, which impairs calcium-mediated activation of matrix dehydrogenases and inter-organelle lipid transfer [91,92]; and retrograde inflammatory signalling, in which mtDNA released from dysfunctional mitochondria activates the cGAS-STING pathway and NLRP3 inflammasome, translating the cellular phenotype into systemic inflammaging [93–97]. These three axes operate in interlocking fashion and are declined below through the organ systems that contribute to the multisystem phenotype of frailty.

1.4.1. Skeletal muscle

The centrality of skeletal muscle in the clinical construct of frailty is not coincidental. Sarcopenia is among the defining components of the Fried phenotype [5] and contributes to multiple of its criteria, including weakness, slow gait speed, low physical activity and weight loss. The cellular configuration in which a chronically reduced demand allows substrate to persist beyond utilisation finds in skeletal muscle a particularly direct expression, because the same contractile activity that maintains cellular ATP turnover also governs the criteria by which frailty is clinically assessed. The configuration is not confined to states of overt substrate excess. Ectopic lipid within skeletal muscle increases with age and physical inactivity and relates only weakly to body mass index [98], and the redistribution of adipose tissue in aging can preserve or increase intramuscular fat even as subcutaneous depots decline [54]. The lean, sarcopenic phenotype is therefore consistent with, rather than contrary to, a local mismatch between preserved substrate availability and reduced contractile demand. Sarcopenic obesity, from which the present model was derived, is in this view not a defining condition but the case in which this mismatch is amplified by an absolute systemic excess of substrate. The temporal sequence by which the configuration unfolds, with functional decline preceding measurable loss of muscle mass [86,99], defines a pre-clinical window in which the syndrome could in principle be modified pharmacologically before structural damage becomes irreversible. Beyond its diagnostic centrality, skeletal muscle is the principal substrate-consuming organ in the body, accounting for approximately 40% of body mass and for the majority of postprandial glucose disposal under insulin stimulation [100,101]. Contracting muscle also releases a repertoire of myokines, including IL-6, irisin, BDNF, FGF21 and myostatin, whose secretion is contraction-dependent and whose targets include adipocytes, hepatocytes, leucocytes and neurons [100]. The progressive decline in contractile activity in aging populations therefore reduces both the local capacity to dispatch substrate and the endocrine signal that sustains the metabolic homeostasis of distant tissues. Mitochondria-associated ER membrane contacts in striated muscle decline by approximately half

across the lifespan, with parallel alterations in calcium-handling and autophagic-regulator proteins [92], providing a structural basis for the progressive impairment of demand-coupled mitochondrial activation.

1.4.2. Adipose tissue

Adipose tissue undergoes substantial functional remodelling with aging. Brown adipose tissue (BAT), the principal site of regulated dissipation of metabolic substrate through uncoupling protein 1 (UCP1) mediated thermogenesis, involutes progressively in older adults [37,102], and the capacity of beige adipocytes to undergo cold-induced or β-adrenergic recruitment is correspondingly reduced [103]. White adipose tissue expands, becomes hypoxic and develops a low-grade inflammatory infiltrate, with reduced lipolytic responsiveness and impaired adipogenesis[53,104]. The systemic consequence is twofold. The aged adipose system loses its principal route for dissipation of substrate through uncoupling, removing a critical safety valve for excess metabolic flux, and at the same time becomes a chronic source of free fatty acids and pro-inflammatory adipokines that fuel substrate-driven, AMPK-independent gene programs in other tissues [53,105]. Adipose dysfunction in this view is not only a local expression of congestion but a systemic enabler of congestion elsewhere. The current therapeutic interest in pharmacological re-induction of BAT activity [106] may be reframed accordingly as an attempt to restore the systemic dissipative capacity that has been progressively eroded.

1.4.3. Liver

The liver provides perhaps the most fully developed example of energetic congestion at the tissue level, although the relevant literature has converged on this configuration under different terminology. Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease, affects approximately 30% of adults globally, with prevalence approaching 70% in older populations and in individuals with obesity or type 2 diabetes [107,108]. In MASLD, sustained substrate availability activates PPARα-driven fatty acid oxidation programs that cannot keep pace with substrate inflow, leading to triglyceride accumulation and accumulation of lipotoxic intermediates [55,107]. AMPK signalling is suppressed [31], mTORC1 is chronically engaged despite developing anabolic resistance [109], and autophagy and mitophagy are impaired [110]. Mitochondrial respiratory capacity declines with disease progression, with evidence of reductive stress and elevated ROS production [61,111]. Goodman and colleagues have shown that hepatic NADH reductive stress underlies common variation in metabolic traits in humans [61], providing direct quantitative support for this model in the hepatic setting. The recent regulatory approval of resmetirom, a thyroid hormone receptor β agonist that enhances hepatic substrate disposal, for the treatment of metabolic dysfunction-associated steatohepatitis [112], supports the therapeutic logic of relieving congestion at the tissue level. Retrograde inflammatory signalling is also operative in this setting: hepatocyte mitochondrial stress promotes mtDNA release and cGAS-STING activation, contributing to the transition from simple steatosis to steatohepatitis [95,96].

1.4.4. Heart

The cardiac manifestation of energy congestion is most readily recognised in heart failure with preserved ejection fraction (HFpEF), a syndrome that predominantly affects older adults with obesity, diabetes and hypertension and that is strongly associated with clinical frailty [113,114]. Aged and diseased cardiomyocytes exhibit a shift in substrate preference toward free fatty acid utilisation with reduced flexibility for glucose oxidation, intracellular triglyceride accumulation and lipotoxicity, mitochondrial dysfunction with reduced respiratory efficiency, and impaired calcium handling related to MAM dysfunction [115–117]. Schiattarella and colleagues showed that HFpEF in mice is driven by a unifying mechanism of cardiomyocyte stress involving inducible nitric oxide synthase and dysregulated unfolded protein response [116]. The systemic features of HFpEF, namely exercise intolerance, skeletal muscle wasting, and inflammation, parallel those of frailty and may reflect the integration of cardiac and peripheral metabolic dysfunction. HFpEF may thus be interpreted as the cardiac expression of a systemic state in which substrate supply exceeds tissue-level dispatch capacity, with the additional vulnerability that the heart, unlike skeletal muscle, cannot reduce its workload to match its diminished metabolic capacity.

1.4.5. Central nervous system

Cognitive frailty might appear, at first glance, distant from the foregoing discussion, because the brain does not exhibit the sedentariness-driven decline in demand that characterises skeletal muscle. The aged brain, however, undergoes a number of changes that suggest a comparable state of declining neuronal demand and impaired demand-coupled metabolic utilisation. Cerebral glucose metabolism measured by ^{18}F-FDG positron emission tomography declines with age in a region-specific manner, with the most pronounced reductions in frontal and temporal cortices and an accelerated pattern in pre-clinical and clinical Alzheimer disease [118,119]. The reduction reflects, at least in part, decreased neuronal activity and synaptic transmission rather than reduced perfusion alone [120]. Brain insulin resistance, documented in aging and in Alzheimer disease, suggests a configuration in which substrate availability persists in the face of impaired demand-coupled utilisation [121,122]. Aged neurons accumulate lipid droplets, exhibit mitochondrial dysfunction with reduced respiratory capacity and elevated ROS, and show evidence of impaired mitophagy [123,124]. Microglia in aged brains activate cGAS-STING signalling in response to released mtDNA, generating a sustained type I interferon response that contributes to neuroinflammation and cognitive decline, and whose pharmacological inhibition rescues age-related cognitive impairment in mice [95]. It is tempting to speculate that cognitive frailty represents the cerebral manifestation of a state in which neuronal demand has declined relative to substrate availability, mitochondrial dispatch is impaired, and the resulting retrograde signalling drives chronic neuroinflammation. Direct experimental tests of this mapping are an important direction for future work.

1.5. Therapeutic implications

The described cellular reframing has implications for the implementation of pharmacological strategies for frailty. The primary goal would be to restore demand-coupled metabolic flux. The two complementary strategies of activating energy sensors and constraining substrate supply share this objective, and their convergence is mechanistically informative. AMPK activation, whether direct or indirect, re-engages the regulatory coupling between cellular metabolic state and downstream programs of substrate utilisation, autophagy and mitochondrial biogenesis [52,125]. Metformin remains the most clinically validated AMPK activator and is currently being evaluated for its capacity to slow frailty progression in a randomised placebo-controlled trial in older adults with glucose intolerance [41]. Next-generation direct AMPK activators (PF−06409577, MK−8722) are advancing through preclinical development and may offer more selective re-engagement of muscle and adipose tissue AMPK signalling [125]. Substrate-supply restriction, achieved through caloric restriction, intermittent fasting or, more recently, pharmacological reduction of substrate intake with GLP−1 receptor agonists and dual GLP−1/GIP agonists, also activates AMPK and engages autophagy [14,40,126]. The systemic relevance of substrate restriction extends beyond frailty and obesity into MASLD and HFpEF [127,128]. The risk of lean-mass loss with substrate-restriction must be balanced against its benefit in older adults and warrants explicit evaluation.

NAD^+ precursors are repositioned as redox modulators rather than primary fuel donors. The benefit of NAD^+ repletion is to restore the NAD^+/NADH ratio compromised by reductive stress and to support

sirtuin activity [60,129]. The clinical track record of NR and NMN, with reliable elevation of tissue NAD^+ but inconsistent functional benefit in older adults [45,46], is consistent with a strategy that addresses one component of the cellular abnormality without addressing its upstream cause. NAD^+ precursors are expected to be most effective when combined with interventions that restore energetic demand.

Mild mitochondrial uncoupling acquires a stronger rationale in this reading. By dissipating a portion of the proton-motive force, mild protonophores increase forward electron transfer through the respiratory chain, reduce the reduction state of the ubiquinone pool and thereby diminish the conditions favourable to RET [130]. The next-generation uncoupler BAM15 has demonstrated reductions in adiposity, improvements in insulin sensitivity and reduced oxidative damage in preclinical models of diet-induced obesity, without the cardiovascular toxicity that limited 2,4-dinitrophenol[130,131]. Mild uncoupling is therefore among the most direct pharmacological strategies to address the proximate biochemical abnormality, and its translational development for sarcopenia, MASLD and HFpEF deserves explicit consideration, with appropriate attention to the risk of net catabolic effects.

Modulation of ER stress and supercomplex assembly introduces a discrete molecular target through the identification of WASF3 [73]. Pharmacological alleviation of ER stress with chemical chaperones (tauroursodeoxycholic acid, 4-phenylbutyrate) has shown preclinical efficacy in metabolic disease [132]. Senolytics target cells in a state of irreversible congestion, and pharmacological clearance with dasatinib plus quercetin has shown preliminary clinical signals in older adults at risk of Alzheimer disease and in patients with idiopathic pulmonary fibrosis [133,134]. Rather than restoring metabolic coupling in living cells, the senolytic approach removes cells that have entered a non-recoverable state and would otherwise continue to propagate inflammatory signalling.

Structured exercise remains the most efficacious of all current interventions, and the cellular reframing developed above provides a mechanistic explanation. Resistance and aerobic exercise raise cellular ATP demand, restore demand-driven ADP supply to the respiratory chain, reduce the proton-motive force, lower the ubiquinone reduction state, suppress RET, and re-engage AMPK and PGC−1α signalling [38,39,101]. Exercise is, in mechanistic terms, the prototype of an intervention that directly relieves congestion. The therapeutic challenge is that the patients most in need of exercise are those least able to perform it, and the development of pharmacological exercise mimetics that reproduce the demand-side effects of contractile activity is among the most important translational goals in this area [135]. Biomarker-guided selection of patients for AMPK activation, NAD^+ repletion or mild uncoupling, using plasma acylcarnitine elevations and reduced acetylcarnitine as circulating signatures of the substrate-overflow component [26,49], offers a path toward mechanism-based stratification in frailty therapeutics.

1.6. Open questions and future directions

Several questions of mechanism and clinical translation remain open.

First, direct in vivo measurement is needed. At the biochemical level, energetic congestion would be expected to differ from bioenergetic deficit through specific features, namely elevated NADH/NAD^+ ratio, elevated proton-motive force at rest, evidence of RET, and substrate accumulation upstream of mitochondrial entry. Hyperpolarised ^{13}C-magnetic resonance spectroscopy for in vivo flux measurement [136], optical genetically-encoded redox sensors in transgenic models [137], and ^{31}P-MRS measurement of muscle ATP turnover at rest and during exercise [24] offer the means to test these expectations directly. Studies that distinguish reduced bioenergetic capacity from reduced bioenergetic demand are particularly needed, since current measurements largely conflate the two.

Second, tissue specificity deserves direct comparative investigation. Congestion-like states would manifest differently in tissues with different demand profiles, and the heart and the brain illustrate this. Neither undergoes the disuse-driven fall in demand seen in skeletal muscle, yet both fit the same framework, as in each the proximate abnormality is a decoupling of substrate entry from oxidative disposal rather than a shortfall in supply. In the myocardium, oxidative capacity declines, yet the workload, set by circulatory demand, cannot be adjusted to this diminished capacity. In the brain, declining synaptic activity reduces demand-coupled oxidative flux while substrate availability is not correspondingly reduced. What is tissue-specific is the route by which entry and disposal become uncoupled, not the resulting configuration, and comparative multi-omics characterisation of these signatures across tissues in aging and frailty is a high-priority direction. Third, sex differences remain an open question of clinical importance. The case study that motivated this work was performed in female mice [20], and whether the mechanistic features generalise to males, and whether sex hormones modulate susceptibility, are open questions [138]. Fourth, reversibility has direct therapeutic implications. Whether the cellular state, once established, is fully reversible or whether it converges with cellular senescence at a clinical threshold beyond which recoupling becomes ineffective bears on the choice between recoupling and senolytic strategies. Fifth, the model is intended to describe frailty in which reduced energetic demand is the proximate driver; cachectic states dominated by systemic inflammation, in which resting energy expenditure is frequently elevated rather than reduced [139], fall outside its core domain and may represent a mechanistically distinct route to the same phenotype. Sixth, the link with epigenetic aging is testable. DNA methylation clocks would be expected to capture accelerated biological aging in affected tissues [140], providing an integrated metabolic-epigenetic readout that could complement the in vivo measurements above. Finally, trial design must accommodate the molecular heterogeneity of frailty. If the cellular reframing is correct, trials of pharmacological interventions should be stratified by molecular signature rather than by clinical phenotype alone, an adaptive design familiar from oncology that may be required to demonstrate the efficacy of mechanistically targeted interventions in heterogeneous older populations.

Two specific predictions stand out as the most direct opportunities for empirical testing. The first is that interventions which raise cellular energetic demand should produce convergent benefits across multiple congestion-related conditions, while interventions that supplement substrate or augment ATP production in isolation should not, even when their biochemical engagement is documented. The recent record of NAD^+ precursors, exercise mimetics and metformin is broadly consistent with this expectation. The second is that biochemical signatures specific to a congested cellular state, namely NADH reductive stress, elevated $\Delta\psi m$ at rest, and evidence of RET, should be present in affected tissues across the spectrum of age-associated conditions and should respond coherently to recoupling interventions. The systematic measurement of these signatures in clinical samples represents the most direct test of the proposal and is brought within prospective reach by the in vivo measurement approaches outlined above.

2. Conclusions

Frailty is a clinical syndrome whose molecular basis has remained incompletely defined, and the dominant cellular model of primary mitochondrial bioenergetic insufficiency does not accommodate several reproducible features of the phenotype, namely the suppression rather than activation of energy sensors in aged tissues, the observed efficacy of demand-side over supply-side interventions, and the progressive decline in cellular energetic demand that parallels the decline in functional capacity. We have proposed a complementary framework in which the proximate cellular abnormality of frailty is energetic congestion, a chronic mismatch between substrate input, energetic demand and the capacity to dispatch the resulting flux through demand-driven

metabolism. The model, assembled from a broad and convergent body of independent literature on aging metabolism, organelle communication, redox biology and innate immunity, reorganises the multiple molecular features of frail tissues as predictable downstream consequences of a shared upstream dysregulation. The mitochondrial dysfunction documented in frail tissues is real and consequential, but its nature is reframed. The mitochondrion is not failing to produce energy. It is operating under saturating substrate input with progressively impaired regulatory coupling and reduced adaptability. Strategies that re-engage demand-driven metabolic flux are predicted to produce more durable benefits than strategies focused on energy supplementation alone, with structured exercise as the prototype of demand-driven recoupling. The reach of this perspective, suggested by the convergence of cellular features across skeletal muscle, adipose tissue, liver, heart and brain, requires validation through the identification of distinguishing predictions and through systematic measurement in clinical samples. Pharmacological development guided by this model, combined with molecular stratification of patients, may offer a path toward a precision pharmacology of frailty, and of age-associated disease more generally, that current undifferentiated approaches have been unable to deliver.

CRediT authorship contribution statement

Rebecca De Lorenzo: Writing – original draft, Conceptualization. **Rovere Querini Patrizia:** Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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