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Hypermetabolism and energetic constraints in mitochondrial disorders

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The prevailing notion that mitochondrial diseases arise from ATP deficiency is challenged by recent evidence that oxidative phosphorylation defects trigger maladaptive stress responses consuming excess energy. We argue that this chronic state of hypermetabolism imposes energetic constraints, thus causing mitochondrial disease pathophysiology, calling for careful translational studies from organelle to organism.

The prevailing model of mitochondrial disease pathogenesis is rooted in the central dogma of DNA–RNA–protein function, in which defective gene products impair oxidative phosphorylation (OxPhos) and ATP producing capacity in cells and tissues (Fig. 1a). In this model, ATP deficiency and the resulting loss-of-function are presumed to directly cause disease. Since the discovery of the first genetic mitochondrial disorders in the late 1980s, the 'gene–protein–ATP deficiency' model has productively guided progress in mitochondrial science. But nearly around 60 years after the first mitochondrial disease was identified by Luft, we still lack effective therapies for patients with mitochondrial diseases.

Energy flux and the cost of living in mitochondrial diseases

How much energy does it cost to live with a mitochondrial OxPhos defect? Surprisingly few studies have directly assessed energy flux or the energetic requirements in cells, animal models or people with OxPhos deficiency. Many people with OxPhos deficiency have similar tissue ATP levels to healthy controls (but recover their phosphorylation state more slowly after depletion)[1], challenging the notion that 'ATP deficiency' is the main driver of disease.

Taking an interdisciplinary perspective that integrates mitochondrial biology, human energetics and nutrition, and clinical mitochondrial medicine, we call into question the prevailing model. If ATP deficiency caused losses-of-function that led to pathophysiology, mitochondrial diseases would trigger energy conservation by downregulating numerous biological and physiological processes.

But OxPhos defects do not downregulate most biological processes. Rather, they activate and upregulate multiple compensatory responses at the cellular, tissue and organ levels. Because these stress responses necessarily consume energy, OxPhos defects should then elevate whole-body energetic demand — resulting in hypermetabolism, or an increase in the energetic cost of life. In turn, hypermetabolism can interfere with normal physiology by imposing energy trade-offs, diverting limited resources away from nominal process to others, thereby compromising health and well-being (Fig. 1b).

In this Comment, we summarize in vitro, animal and clinical evidence for this hypothesis, discuss research directions necessary to test it and highlight some therapeutic implications.

Evidence of hypermetabolism in people with OxPhos defects

The clinical manifestations of OxPhos deficiency include fatigue and a general slowing of gross functions such as digestion, physical activity and sometimes cognition. In addition to these apparent clinical signs, patients show elevated resting ventilation and heart rate[2] and a hyperkinetic cardiorespiratory response to physical activity[3]. At rest, patients with the most common mitochondrial DNA (mtDNA) pathogenic variant (m.3243A>G, which can cause mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)) show internal signs including significantly higher counts of total circulating white blood cells, platelets and immunoglobulins, elevated insulin and elevated abundance of signalling proteins (for example, GDF15) and metabolites (for example, lactate)[4]. These physiological and molecular adaptations impose energetic costs that must elevate whole-body energy expenditure (EE).

Some hormones, including thyroid hormones and catecholamines, contribute to accelerating cellular and organismal metabolic rates. Patients with OxPhos defects show higher circulating norepinephrine levels[2], which directly elevates resting metabolic rate. Accordingly, at the cellular level, OxPhoshos-deficient tissues exhibit several gains-of-function. The cellular hallmarks of mitochondrial disease include upregulated mitochondrial biogenesis leading to ragged-red fibres (excessive accumulation of mitochondria), increased capillarization around OxPhos-deficient cells and activation of the integrated stress response (ISR), resulting in increased secretion of cytokines and metabokines[2,4,5]. Each of these processes costs energy. Interestingly, the thermogenic thyroid hormones are downregulated in affected patients[4], representing a potential physiological attempt to curb systemic hypermetabolism.

Thus, although the behavioural picture of mitochondrial diseases is one of hypoactivity, the physiological and cellular manifestations reflect hyperactivity. In a recent meta-analysis (n = 17 studies; 690 patients)[2], people with OxPhos defects consumed on average 30% more oxygen than healthy controls per unit of body mass — reflecting a state of hypermetabolism. The body with OxPhos-deficient cells appears to require more, not less, energy. Given that no study was designed specifically to examine this question and that adequate standardization procedures were not used, the magnitude of these findings must be interpreted with caution.

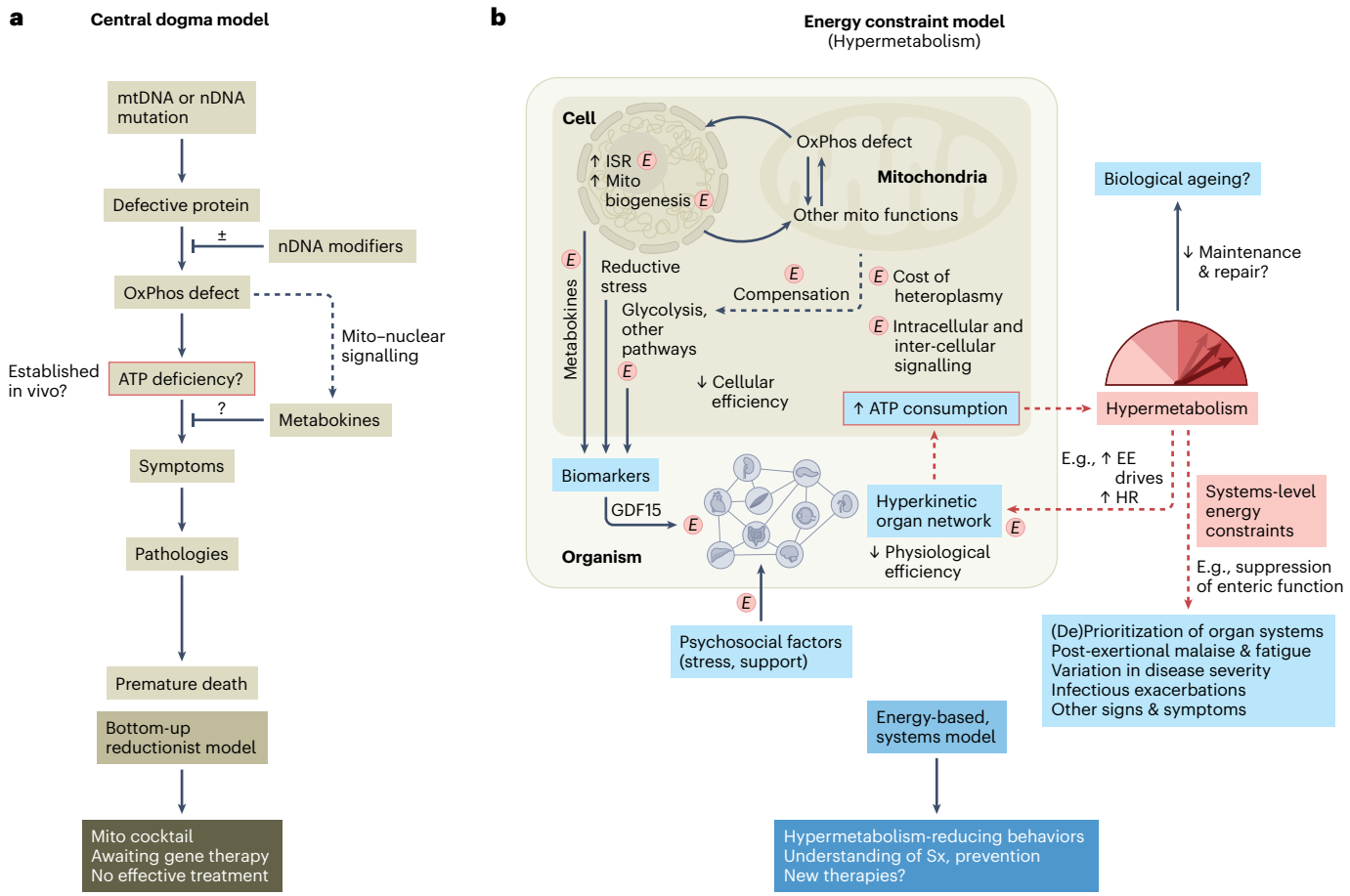

Fig. 1 | Proposed model of mitochondrial diseases pathophysiology centred on the (hyper)metabolic phenotype of clinical and pre-clinical models of mitochondrial OxPhos defects. a, The accepted model of mitochondrial diseases is based on the central dogma of biology (gene, RNA, protein). It assumes that symptoms (Sx) caused by mutations in the mitochondrial (mtDNA) or nuclear (nDNA) genomes are triggered by ATP deficiency in vivo, which has not consistently been observed. **b**, Proposed model based on principles of cellular bioenergetics and physiology. The model highlights three main components: first, the role of mito–nuclear crosstalk in the initiation of energetically costly cellular responses, including the ISR, which markedly increases ATP consumption or flux rate (by more than 90–100% in human fibroblasts with genetic or pharmacological OxPhos defects[2]); second, the systemic energetic cost of the hyperkinetic organ-level cardiorespiratory, endocrine and immune responses on cellular and whole-body energy expenditure — or hypermetabolism; and finally hypermetabolism as a driver of energy trade-offs and physiological constraints that inhibit growth, maintenance and repair processes, culminating in accelerated ageing and the onset of signs and symptoms. The proposed energy-based, systems-level model requires empirical testing and has implications for the treatment of mitochondrial diseases, as well as for other clinical disorders characterized by hypermetabolism. The red 'E' denotes upregulated energy-dependent processes that contribute to hypermetabolism. HR, heart rate.

How do animals respond energetically to OxPhos defects?

No preclinical study to date was specifically designed to investigate the energetic cost of living with an OxPhos defect. However, meta-analysing 29 available reports of EE measurements in animal models with mitochondrial defects provides converging evidence that tissue-specific or whole-body mutations produce a similar hypermetabolic effect in animal models as they do in humans[5]. Similar to in humans with OxPhos deficiency, animals with mitochondrial defects also are considerably less physically active. Strikingly, in 39% of surveyed experimental conditions, mutant animals showed elevated whole-body EE despite reduced activity. OxPhos defects restricted to even a single cell type can trigger whole-body hypermetabolism, accelerated ageing and premature death[6].

As in humans with OxPhos deficiency, OxPhos-deficient mice increase mitochondrial biogenesis and accumulate defective mitochondria. OxPhos defects activate the ISR in affected tissues, inducing GDF15 and FGF21 metabokine secretion[7]. Similar to people with severe mitochondrial diseases who are unexplainably lean, animals with OxPhos defects consistently exhibit resistance to high-fat diet-induced obesity and insulin resistance, which may arise from the unappreciated state of hypermetabolism that burns excess calories[5].

How do human cells energetically respond to OxPhos defects?

To understand how cells energetically respond to OxPhos defects, we performed longitudinal molecular and bioenergetic assays in primary

human fibroblasts with either genetic (*SURF1*, complex IV defect) or pharmacological (oligomycin, complex V defect) OxPhos deficiencies[2]. OxPhos-deficient cells reduced division rates by 32–48%, theoretically nearly halving the energetic costs of biomass production and conferring substantial energy savings.

But the molecular phenotype of OxPhos-deficient cells was one of marked hyperactivity and stress pathway upregulation. As in affected animal tissues, OxPhos defects activated the ISR, increased GDF15 secretion, induced release of extracellular cell-free mitochondrial DNA and elevated the production and secretion of cytokines by as much as ten-fold, necessarily incurring energetic costs[2]. Costly developmental programs and the ribosomal translation machinery were also upregulated. Despite their quiescent gross behaviour, OxPhos-deficient cells acquire numerous energetically costly biological gains-of-function[2].

To determine if the hyperactivity of specific cellular processes balanced the potential energy savings of reduced replication, we estimated ATP derived from respiration and extracellular acidification as proxies for OxPhos and glycolysis to calculate total ATP synthesis rates[2]. Compared to control cells with competent mitochondria, cellular EE in OxPhos-deficient cells was nearly doubled (increasing by 91% for complex IV deficiency and 108% for complex V deficiency). Considering reduced growth rates, OxPhos defects increased the energetic cost of each cell division by two to three times. Thus, OxPhos defects induce cell-autonomous hypermetabolism.

What drives hypermetabolism in people with OxPhos defects?

Based on these cellular results, an emerging question is whether whole-body hypermetabolism is driven by cell-autonomous hypermetabolism or by systemic physiological responses.

As mentioned above, a common feature among OxPhos-deficient cells and animals is ISR activation leading to GDF15 and FGF21 hypersecretion. The ISR is a well-conserved and important damage-repair response in mammals, however the health impact of chronic ISR activation is less understood. GDF15 and, in some cases, FGF21, may elevate whole-body EE. GDF15 deletion rescued hypermetabolism in mice with tissue-specific OxPhos perturbations[8], and FGF21 deletion normalized body weight and excessive oxygen consumption (VO_2) in Deletor mice[7], suggesting that these and potentially other systemic factors are necessary to elevate whole-body EE in mouse models of OxPhos defects. GDF15 and FGF21 are two of the best-known biomarkers of mitochondrial myopathy in humans. As in mice, could metabokine signalling contribute to elevated EE in people with OxPhos deficiency?

How does hypermetabolism cause disease manifestations?

Why do people with OxPhos deficiency — if they are not ATP starved — feel tired, develop multiple disease manifestations and live shorter lives? We see two non-mutually exclusive, testable hypotheses linking hypermetabolism to accelerated ageing and physiological decline.

Increased molecular entropy associated with elevated EE. Hypermetabolism increases chronic resting energy flux, which elevates intracellular Gibbs free energy dissipation rate, increasing entropy and thereby driving faster accumulation of molecular damage[9]. In turn, chronic molecular damage can overwhelm repair mechanisms, leading to tissue stress and functional decline across the lifespan. This model is consistent with the documented genomic instability and accelerated telomere shortening rates in OxPhos-deficient cells and tissues[2].

Energetic trade-offs: systemic energy allocation is altered in response to local overconsumption. Species-specific mammalian metabolic rates are predicted from optimizing oxygen and substrate delivery networks, implying that finite resources are managed as an economy, distributed in a 'competitive' manner among organ systems. Due to these constraints, OxPhos defects-driven activation of high-priority stress responses evolved to maintain short-term vital functions (for example, catecholamines, ISR) by sapping resources from longer-term, longevity-promoting processes that maintain molecular quality control and prevent gradual decline.

We propose that OxPhos defects reduce fitness and lifespan by reprioritizing and diverting EE away from longevity-promoting processes in a futile effort to perpetually heal what is broken.

These hypotheses provide two possible testable mechanisms by which hypermetabolism may directly trigger mitochondrial disease manifestations and shorten lifespan (Fig. 1). They may explain: why many patients do not tolerate alcohol, which triggers hypermetabolism; why infectious diseases that monopolize the energy budget are the number one cause of death in this population[10] and why patients nap and sleep longer than healthy individuals (sleep dampens stress arousal, freeing the energy budget[11]). Rigorous application of cellular and whole-body energy expenditure measurements[12,13] is needed to test these hypotheses.

Therapeutic outlook and conclusions

The central dogma model of ATP deficiency (Fig. 1a) drives palliative prescriptions, including 'mito cocktails' of vitamins and supplements that target the OxPhos system, and limits us to working towards yet-unrealized gene therapies aiming to correct upstream disease-causing genetic lesions. If hypermetabolism is a bona-fide feature of mitochondrial diseases, this opens new research questions and potential treatments for patients.

We suggest that leveraging known determinants of whole-body energetic efficiency and stress signalling may bear therapeutic benefits for adults with clinically manageable disease severity. We propose three avenues for research and treatment: 1) sleep, 2) psychological and behavioural interventions, and 3) molecular therapies to improve bioenergetic efficiency.

Sleep. Patients show high rates of sleep disorders and report frequent napping. EE is reduced by roughly 25% during sleep and the urge to rest and nap may be an attempt to obtain relief from hypermetabolism. Studying and implementing interventions to improve sleep quality and duration in patients could produce meaningful clinical benefits.

Psychological and behavioural interventions. Physical and psychological stressors trigger energy-consuming processes[11]. In contrast, contemplative practices including yoga reduce resting EE by 15% and deep meditation may decrease whole-body EE by >20%[14], providing proof-of-concept for non-pharmacological approaches to reducing or normalizing EE. Implementing behavioural and psychosocial interventions to prevent chronic and excessive physiological stress responses and improve resilience should be explored in adult patients.

Molecular therapies. The ISR and master energy regulating metabokines GDF15 and FGF21 may be sufficient to elevate whole-body EE and mediate hypermetabolism in OxPhos-deficient animals. If this is also the case in humans, new compounds targeting upstream ISR activation mechanisms including reductive stress[4,6], or metabokine

signalling on target cells, could potentially mitigate hypermetabolism, reduce symptoms and slow disease progression in people with hypermetabolism and mitochondrial diseases.

Conclusion

The current prevailing model of mitochondrial disorders does not explain the hyperactive molecular, cellular, physiological and whole-body energy expenditure phenotypes of OxPhos deficiency. Our collective goal is to understand and treat inherited and acquired (that is, secondary) mitochondrial disorders, as well as to promote health and healing[15]. Considering that OxPhos deficiency triggers costly stress responses and recalibrations culminating in hypermetabolism, a key to achieving this goal will be to define the origin, magnitude and consequences of hypermetabolism in OxPhos-deficient cells and organisms. This challenge calls scientists and physicians across disciplines to unite the precision of molecular biology with the holistic meaningfulness of human energetics and patient experiences.

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Author contributions

A.J.S. and M.P. conceived the model and prepared the manuscript. G.S., D.G., M.P.S.O., C.P.K., H.P. and M.H. made substantial conceptual and editorial contributions to the final article.

Competing interests

The authors declare no competing interests.