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Review Article

Targeting Mitochondrial Bioenergetic Failure in Metabolic Syndrome: Translational Roles of Mitochondrial and Multi-Organ Peptides

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Abstract

Metabolic syndrome (MetS) is a multisystem disorder defined by insulin resistance, ectopic lipid deposition, chronic low-grade inflammation, and vascular dysfunction, and is increasingly recognized as a distributed failure of mitochondrial bioenergetics and quality control. Convergent defects in oxidative phosphorylation, mitochondrial biogenesis, redox balance, and mitophagy propagate metabolic inflexibility across hepatocytes, myocytes, pancreatic β-cells, renal tubular epithelium, intestinal barrier tissues, and vascular endothelium. Mitochondrial-derived peptides (MDPs), including MOTS-c, Humanin, and small Humanin-like peptides, have emerged as endogenous regulators of mitonuclear communication capable of activating AMPK-SIRT1-PGC-1α signaling, enhancing mitochondrial biogenesis, attenuating oxidative stress, and stabilizing stress-response pathways. In parallel, multi-organ peptide constructs such as LPPSIMKE (liver, pancreas, placenta, stomach, intestinal mucosa, kidney, eye) have been proposed as systems-oriented modulators of organ-specific mitochondrial dysfunction. Conceptually, LPPSIMKE aligns with the pathophysiologic architecture of MetS by targeting multiple nodes within the hepatopancreatic-gut-renal-vascular axis, where mitochondrial inefficiency drives lipid dysregulation, impaired insulin secretion, inflammatory amplification, tubular energy failure, and endothelial oxidative injury. Proteomic characterization of organ-derived peptide ultrafiltrates supports the presence of bioactive peptide networks enriched in metabolic and stress-response pathways, although mechanistic and clinical validation remains limited. Integrating established MDP biology with organ-contextual peptide signaling suggests a coordinated remodeling model encompassing AMPK activation, PGC-1α-dependent transcriptional reinforcement, NRF2-mediated antioxidant defense, and restoration of mitophagic quality control via the PINK1-Parkin axis. Such convergence offers a biologically plausible strategy for restoring metabolic flexibility and attenuating cardiometabolic risk. However, rigorous translational studies incorporating pharmacokinetics, mitochondrial functional endpoints, and randomized clinical outcomes are required to define therapeutic efficacy and safety. Mitochondrial peptide-based interventions, particularly multi-organ constructs such as LPPSIMKE, therefore represent a hypothesis-driven but mechanistically coherent approach to targeting the mitochondrial substrate of MetS.

Introduction

Metabolic syndrome (MetS) is a pathophysiologic network state defined clinically by the clustering of (i) central adiposity, (ii) hyperglycemia/insulin resistance, (iii) atherogenic dyslipidemia (elevated triglycerides and/or reduced HDL cholesterol), and (iv) elevated blood pressure, with consensus criteria formalized by major international bodies [1-3] Mechanistically, MetS is not a single disease entity but a multi-organ failure of metabolic flexibility, the capacity to switch appropriately between carbohydrate and lipid oxidation in response to nutrient availability and hormonal cues, resulting in chronic nutrient surplus, ectopic lipid deposition, and maladaptive stress signaling across metabolically active tissues [4,5]. At the systems level, MetS emerges from the intersection of (a) adipose tissue expandability limits6, (b) lipotoxic spillover [6], (c) immune-metabolic activation [7], and (d) neurohormonal and vascular dysregulation [4,7,8]. As adipocytes reach their storage threshold, excess free fatty acids and lipid intermediates (e.g., diacylglycerols and ceramides) accumulate in liver, skeletal muscle, pancreas, and kidney, promoting insulin resistance via stress kinase activation (JNK, IKKβ) and altered insulin receptor substrate (IRS) phosphorylation, while simultaneously driving hepatocellular steatosis and dyslipoproteinemia [9-11]. In parallel, adipose tissue hypoxia and remodeling promote macrophage infiltration and proinflammatory cytokine production (e.g., TNF-α, IL-6), establishing chronic low-grade inflammation that amplifies insulin resistance and endothelial dysfunction [12]. MetS therefore represents a distributed disorder of inter-organ communication, where endocrine, paracrine, neural, and immune signals couple metabolic overload in one tissue to dysfunction in others.

A central mechanistic premise increasingly supported by human and preclinical studies is that mitochondrial impairment is a unifying lesion in MetS [13,14]. Under chronic nutrient excess, mitochondrial substrate influx outpaces oxidative capacity, increasing electron pressure on the respiratory chain and promoting electron leak at Complex I and III with consequent reactive oxygen species (ROS) generation [15,16]. Mitochondrial ROS are not only damaging oxidants; they also function as second messengers that activate stress-responsive pathways (e.g., JNK/NF-κB), impair insulin signaling, and potentiate inflammatory programs [17]. Concomitantly, impaired mitochondrial quality control, via reduced biogenesis, dysregulated fusion-fission dynamics, and defective mitophagy, permits the persistence of low-functioning organelles, locking tissues into a state of metabolic inflexibility and stress signaling [18]. In this framework, MetS can be conceptualized as a multi-system mitochondriopathy in which organ-specific phenotypes (NAFLD, β-cell failure, vascular dysfunction, nephropathy, and retinal metabolic stress) arise from a shared upstream architecture of mitochondrial bioenergetic inefficiency and maladaptive mitochondrial-immune signaling [19,20]. Key mitochondrial abnormalities repeatedly implicated in MetS include: (i) reduced oxidative phosphorylation (OXPHOS) capacity, (ii) increased mitochondrial ROS and redox imbalance, (iii) blunted mitochondrial biogenesis (PGC-1α/NRF/TFAM axis), (iv) altered mitochondrial dynamics (excess fission vs fusion), and (v) impaired mitophagy (PINK1-Parkin and related pathways) [21]. Beyond ATP generation, mitochondria orchestrate innate immune tone, apoptotic thresholds, and adaptive stress programs such as the mitochondrial unfolded protein response (UPRmt), thereby integrating nutrient sensing with inflammatory and survival signaling [22,23]. Consequently, therapeutic strategies that restore mitochondrial efficiency and quality control have the potential to exert distributed, cross-organ benefits rather than isolated single-tissue effects.

Mitochondrial-derived peptides (MDPs), short bioactive peptides encoded by mitochondrial DNA, have emerged as endogenous regulators of this mitochondrial-metabolic interface [24]. MOTS-c [25,26], Humanin [27], and small Humanin-like peptides (SHLPs) [28] have been shown to modulate AMPK signaling, insulin sensitivity, cytoprotection, and oxidative stress responses, positioning them as candidate mediators of mitohormesis and nuclear-mitochondrial communication. In parallel, short organ-derived peptide bioregulators (here considered as multi-organ combinations including liver, pancreas, placenta, stomach, intestinal mucosa, kidney, and eye, [LPPSMKE]) have been proposed to exert tissue-preferential effects on mitochondrial proteostasis, redox handling, and metabolic programming, although high-quality mechanistic and human data remain limited. This review integrates established mitochondrial mechanisms in metabolic disease with emerging peptide-based regulatory systems and proposes a testable systems biology model in which MDPs and organ-specific peptides converge on AMPK-SIRT1-PGC-1α signaling, antioxidant defense (e.g., Nrf2), mitochondrial dynamics, and mitophagy to reverse metabolic inflexibility across the organ network that defines MetS.

Mitochondrial Dysfunction in MetS

Impaired Oxidative Phosphorylation and Redox Signaling

Human and preclinical studies indicate that insulin-resistant states are associated with reduced mitochondrial respiratory efficiency in skeletal muscle and liver, including impaired activity and/or coupling at electron transport chain (ETC) nodes frequently centered on Complex I and Complex III [29]. When substrate delivery (glucose- and fatty acid-derived reducing equivalents) exceeds ETC throughput, the respiratory chain becomes highly reduced, increasing the probability of electron leak and one-electron reduction of oxygen to superoxide, with downstream formation of other ROS. This redox shift is not only injurious but also signal-transducing, activating stress-responsive kinase networks that directly antagonize insulin signaling. Mechanistically, increased mitochondrial ROS contribute directly to the development of insulin resistance by engaging stress-activated kinase networks that interfere with canonical insulin signaling. Excess electron leak from an over-reduced electron transport chain during nutrient surplus elevates superox-

ide and downstream oxidant species, which activate c-Jun N-terminal kinase (JNK) and related serine/threonine stress kinases. Activation of these kinases promotes inhibitory serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby impairing its ability to undergo insulin-stimulated tyrosine phosphorylation and to recruit phosphatidylinositol 3-kinase (PI3K) [30]. This disruption attenuates downstream Akt activation, leading to reduced GLUT4 translocation in skeletal muscle and diminished glycogen synthesis, hallmarks of peripheral insulin resistance. Experimental evidence demonstrates that mitochondrial ROS elevation can acutely induce insulin resistance independent of gross defects in oxidative phosphorylation, underscoring the signaling, not merely cytotoxic role of redox imbalance in metabolic dysfunction [31]. In parallel, mitochondrial ROS amplify redox-sensitive transcriptional programs, including activation of NF-κB and other inflammatory pathways, further reinforcing insulin resistance through cytokine-mediated feedback and additional serine phosphorylation events on IRS proteins [32]. Collectively, this electron transport chain-ROS-stress kinase axis establishes a mechanistic bridge between bioenergetic overload and impaired insulin action, particularly under conditions of chronic nutrient excess characteristic of MetS.

3.2. Defective Mitochondrial Biogenesis and Transcriptional Control of Oxidative Capacity

Mitochondrial content and oxidative capacity are dynamically governed by the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), which integrates nutrient availability, hormonal signaling, and contractile stimuli into coordinated nuclear programs that determine mitochondrial gene expression and respiratory capacity [33]. In skeletal muscle from individuals with type 2 diabetes, reduced expression and/or activity of PGC-1α has been reported alongside coordinated downregulation of oxidative phosphorylation gene networks, a molecular signature consistent with diminished mitochondrial oxidative capacity and impaired metabolic flexibility [34]. PGC-1α executes mitochondrial biogenesis by coactivating nuclear transcription factors that drive expression of nuclear-encoded mitochondrial proteins and the machinery required for respiratory chain assembly and substrate oxidation, prominently including nuclear respiratory factors 1 and 2 (NRF1 and NRF2).[2] In parallel, PGC-1α induces mitochondrial transcription factor A (TFAM), a key regulator of mitochondrial DNA (mtDNA) transcription, replication, and nucleoid stability, thereby linking nuclear transcriptional control to maintenance and expansion of the mitochondrial genome.[2] Through the integrated PGC-1α-NRF-TFAM axis, cells increase mtDNA copy number, upregulate electron transport chain components, and expand functional mitochondrial networks, collectively enhancing respiratory reserve and improving the capacity to oxidize lipid and glucose substrates in a demand-matched manner [35]. In MetS, attenuation of this adaptive program constrains mitochondrial biogenic responsiveness and limits respiratory reserve, increasing reliance on stressed, inefficient mitochondria during nutrient excess and thereby heightening susceptibility to redox imbalance and downstream insulin resistance.

Impaired Mitophagy and Mitochondrial Quality Control Failure

Mitochondrial quality control depends on selective removal of dysfunctional organelles via mitophagy, a process strongly linked to the PINK1-Parkin pathway. Loss of membrane potential or other damage signals stabilize PINK1 on the outer mitochondrial membrane, triggering Parkin recruitment, ubiquitination of outer membrane proteins, and autophagic clearance of the damaged mitochondrion. In MetS and insulin-resistant states, reduced mitophagic capacity contributes to persistence and accumulation of inefficient, ROS-generating mitochondria, reinforcing metabolic inflexibility and stress signaling [36]. Functionally, impaired mitophagy in MetS promotes the persistence of structurally and bioenergetically compromised mitochondria, thereby expanding the intracellular pool of organelles characterized by reduced membrane potential, inefficient electron transport chain coupling, and increased electron leak. The resulting elevation in mitochondrial ROS not only exacerbates oxidative damage to lipids, proteins, and mtDNA but also sustains redox-sensitive stress kinase activation and inflammasome signaling, reinforcing insulin resistance and low-grade inflammation. In parallel, defective clearance of damaged mitochondria constrains the dynamic remodeling of the mitochondrial network that is normally required to match oxidative capacity to fluctuations in nutrient availability and energetic demand. Under physiological conditions, coordinated cycles of fission, fusion, biogenesis, and selective autophagic turnover enable rapid adaptation to shifts between lipid and glucose oxidation; in MetS, attenuation of PINK1-Parkin-mediated mitophagy disrupts this quality-control equilibrium, limiting removal of dysfunctional organelles and preventing efficient renewal of the mitochondrial reticulum. When coupled with reduced mitochondrial biogenesis, this failure of turnover yields a progressive decline in overall mitochondrial fitness. Such cumulative deterioration provides a mechanistic substrate for the chronicity, tissue interdependence, and multisystem manifestations that typify MetS.

Mitochondrial Network Remodeling as a Therapeutic Strategy in MetS

MDPs operationalize an increasingly validated concept in mitochondrial biology: that short open reading frames within mtDNA encode bioactive micropeptides capable of coordinating cellular stress sensing with adaptive metabolic remodeling across tissues [37]. MOTS-c, encoded within the mitochondrial 12S rRNA locus, was first shown to act as a systemically active metabolic signal that improves insulin sensitivity and protects against both diet-induced obesity and age-associated insulin resistance in murine models, thereby implicating skeletal muscle substrate handling and whole-body fuel partitioning as key effector domains [38]. Mechanistically, MOTS-c engages canonical energy-sensing circuitry by promoting

AMPK activation, with downstream phosphorylation of acetyl-CoA carboxylase (ACC) to reduce malonyl-CoA-dependent lipogenesis and to favor mitochondrial fatty-acid entry and oxidation [39]. In parallel, AMPK-linked transcriptional coactivation (including PGC-1α-dependent programs) provides a mechanistic bridge from acute energy stress to longer-horizon increases in oxidative capacity [40] and mitochondrial biogenesis [41]. A critical advance supporting therapeutic plausibility is that MOTS-c can translocate to the nucleus under metabolic stress, where it modulates broad adaptive gene networks enriched for stress-response elements and interfaces with redox-defense regulators, including NRF2, thereby integrating energetic control, antioxidant capacity, and proteostasis within a single retrograde signaling axis [42]. Although interventional human trials of MOTS-c for metabolic disease have not yet produced peer-reviewed efficacy data, clinical observational evidence supports translational relevance. Circulating MOTS-c concentrations are altered in human metabolic states, with decreased levels reported in obese children and adolescents and associations with insulin resistance metrics [43]. Moreover, a recent systematic review/meta-analysis of human studies reporting that circulating MOTS-c is reduced in diabetes while exhibiting directionally different behavior in obesity, consistent with context-dependent regulation and potential compensatory dynamics across stages of metabolic decompensation [39,43].

Humanin, the prototypic MDP arising from the mitochondrial 16S rRNA region, complements MOTS-c by prioritizing mitochondrial integrity and stress survival, mechanisms directly germane to β-cell attrition, endothelial dysfunction, renal tubular vulnerability, and retinal oxidative injury in MetS. Humanin was initially identified as a broadly cytoprotective rescue factor, establishing its role as an endogenous survival signal under toxic stress conditions [44]. Subsequent mechanistic work demonstrated that Humanin directly interferes with Bax activation, suppressing the intrinsic mitochondrial apoptotic cascade upstream of cytochrome c release and caspase activation [45]. In addition, Humanin participates in extracellular and intracellular signaling networks that intersect with insulin/IGF biology; specifically, Humanin binds IGFBP-3 and modulates IGFBP-3 interactions with importin-β1, providing a defined molecular mechanism by which a mitochondrial peptide can influence nuclear trafficking events linked to apoptosis and stress susceptibility [46]. In disease-relevant models, Humanin mitigates ER stress-induced apoptosis and improves mitochondrial redox buffering capacity (including restoration of mitochondrial glutathione in retinal pigment epithelial cells), supporting a coherent mechanistic role in ER-mitochondrial proteostasis and oxidative injury limitation.[8] Extending this family, SHLPs encoded within the same mitochondrial rRNA region demonstrate differential bioactivity; SHLP2 has been shown to improve insulin sensitivity in vivo using hyperinsulinemic-euglycemic clamp physiology in rodents, strengthening the argument that mitochondria-encoded micropeptides can drive quantitatively measurable improvements in insulin action through centrally integrated and peripherally expressed pathways [47].

These MDP mechanisms align directly with the organ-specific mitochondrial failure modes that define MetS as a multisystem disorder rather than a single-tissue phenotype. In NAFLD, sustained nutrient excess induces mitochondrial adaptations that can become maladaptive thereby rationalizing therapies that improve mitochondrial efficiency and redox handling while restoring transcriptional governance of lipid flux [48]. In pancreatic β-cells, ATP generation through oxidative phosphorylation is the proximate trigger for insulin secretion, and mitochondrial dysfunction propagates impaired glucose-stimulated insulin secretion alongside ROS-mediated cell loss, which mechanistically prioritizes peptide strategies that stabilize mitochondrial integrity and attenuate apoptotic susceptibility [49]. At the gut-immune-metabolic interface, metabolic endotoxemia (diet-associated increases in circulating lipopolysaccharide) activates innate immune pathways and promotes low-grade inflammation with insulin resistance, suggesting that improving epithelial bioenergetics and barrier resilience may reduce systemic immunometabolic load [50]. In the kidney, proximal tubular cells are highly dependent on mitochondrial fatty acid oxidation, and defective FAO promotes ATP depletion, lipid accumulation, and profibrotic remodeling, positioning mitochondrial metabolic reprogramming as a plausible disease-modifying approach in metabolically linked chronic kidney disease [13]. Vascular endothelium and retina similarly converge on mitochondrial redox biology. NRF2 is a master transcriptional regulator of antioxidant defenses (including SOD2, catalase, and HO-1), and impaired NRF2 signaling contributes to oxidative endothelial injury [51]. Within this mechanistic landscape, the utility of a multi-organ peptide construct such as LPPSIMKE can be rationalized as an attempt to match therapeutic architecture to disease architecture, i.e., to intervene at multiple organ nodes that collectively generate and sustain metabolic dysfunction. As MetS emerges from coupled failures across systems, a multi-tissue peptide approach is hypothesized to provide tissue-contextual cues capable of converging on conserved mitochondrial control nodes (AMPK-centered substrate switching, PGC-1α-linked mitochondrial capacity, NRF2-dependent redox defense, and quality-control pathways such as mitophagy) while simultaneously addressing organ-specific energetic bottlenecks that cannot be fully normalized by single-pathway agonism. A mechanistic foundation for "organ-specific peptide/protein ultrafiltrate" constructs has been established by proteomic characterization of rabbit-derived organ ultrafiltrates, demonstrating that such preparations contain complex protein/peptide signatures and pathway enrichments relevant to metabolism, oxidative stress, inflammatory response, and lipid-handling biology [52].

Clinical Implications

Positioning MDPs and multi-organ peptide constructs within the pathophysiologic architecture of MetS yields a set of clinically measurable endpoints that are mechanistically anchored rather than purely phenotypic. If these agents meaningfully recalibrate

AMPK-centered substrate partitioning, reinforce PGC-1α-dependent mitochondrial capacity, and attenuate redox-driven inflammatory signaling, improvements would be expected across both metabolic and vascular domains. At the level of systemic insulin sensitivity, reductions in HOMA-IR and, more rigorously, improvements in hyperinsulinemic-euglycemic clamp-derived glucose disposal rates would represent direct functional correlates of restored mitochondrial substrate handling. Hepatic mitochondrial remodeling should translate into measurable reductions in intrahepatic triglyceride content assessed by MRI-proton density fat fraction (MRI-PDFF), a validated quantitative biomarker of NAFLD severity and therapeutic response. Improvements in mitochondrial oxidative efficiency at the skeletal muscle level could be reflected by increases in peak oxygen consumption (VO_2 max), an integrated physiologic marker of mitochondrial respiratory capacity and cardiometabolic fitness. Given the tight coupling between mitochondrial ROS production and low-grade inflammation, reductions in circulating high-sensitivity C-reactive protein (hsCRP) and other inflammatory biomarkers would be anticipated if redox tone and inflammasome activation are attenuated. Finally, because endothelial dysfunction in MetS is closely linked to mitochondrial oxidative stress and impaired nitric oxide bioavailability, improvements in flow-mediated dilation (FMD) or other validated measures of endothelial function would provide a clinically relevant vascular readout of mitochondrial-targeted intervention. Collectively, these endpoints move beyond glycemic control alone and align outcome assessment with the multisystem mitochondrial model underlying the therapeutic hypothesis. Despite compelling mechanistic plausibility and robust preclinical data for MOTS-c, Humanin, and related peptides, randomized human trials remain limited. To date, most human evidence consists of observational associations between circulating MDP levels and metabolic phenotypes, along with small exploratory studies rather than adequately powered, placebo-controlled interventional trials. Consequently, definitive conclusions regarding efficacy in MetS, NAFLD, or cardiometabolic risk reduction cannot yet be drawn. The translational gap underscores the necessity for rigorously designed phase I-II trials incorporating prespecified mechanistic and clinical endpoints.

Several limitations constrain current interpretation of peptide-based mitochondrial therapeutics. First, human pharmacokinetic and pharmacodynamic data are sparse, including limited information regarding absorption, distribution, half-life, tissue penetration, receptor engagement, and dose-response relationships. Without these parameters, extrapolation from preclinical dosing paradigms to clinically meaningful exposures remains speculative. Second, the relative scarcity of randomized, placebo-controlled trials precludes robust assessment of efficacy, durability of response, and safety across diverse metabolic phenotypes. Third, many published studies rely on systemic metabolic markers without incorporating direct mitochondrial functional readouts, limiting mechanistic inference.

Future trials would benefit from the integration of quantitative mitochondrial endpoints alongside clinical measures. These may include high-resolution respirometry or Seahorse-based oxygen consumption rate analysis in peripheral blood mononuclear cells or skeletal muscle biopsies; mtDNA copy number and heteroplasmy assessment; transcriptomic profiling of PGC-1α-regulated gene networks; circulating mitokine quantification; and redox-sensitive biomarkers. Incorporation of these endpoints would enable confirmation that observed metabolic improvements correspond to valid mitochondrial remodeling rather than indirect systemic effects. For multi-organ constructs such as LPPSIMKE, proteomic characterization, batch consistency validation, and identification of active peptide fractions are essential to establish reproducibility and regulatory clarity.

Conclusions

MetS is increasingly recognized as a distributed disorder of mitochondrial bioenergetics, redox imbalance, and impaired organ-specific quality control rather than solely a defect in insulin receptor signaling. Mitochondrial-derived peptides, particularly MOTS-c and Humanin, engage conserved metabolic control nodes that directly intersect with the molecular lesions characteristic of insulin resistance, NAFLD, endothelial dysfunction, and β-cell stress. Multi-organ peptide constructs such as LPPSIMKE are conceptually aligned with the multisystem nature of MetS, aiming to provide coordinated mitochondrial modulation across hepatic, pancreatic, intestinal, renal, and vascular tissues. However, therapeutic viability requires comprehensive translational validation. Future investigations must couple rigorously controlled clinical trials with integrated mitochondrial phenotyping to determine whether peptide-mediated modulation of mitochondrial networks can reproducibly restore metabolic flexibility, reduce inflammatory amplification, and improve cardiometabolic outcomes in humans.

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