

From Mitokine to Therapeutic: Mitochondrial-Derived Peptides (MOTS-c, Humanin, SHLPs, and Synthetic Analogs) as Exercise Mimetics and Adjuncts in Metabolic Disease and Aging

Riju Mathew^{1*}, Jithesh T K², Sheena Joe³

¹Associate Professor, Department of Biochemistry, Believers Church Medical College Hospital, Thiruvalla, Kerala, India – 689103;

rijumathew@bcmch.edu.in; <https://orcid.org/0000-0003-3266-6715>

²Professor, Department of Biochemistry at MES Medical College, Perinthalmanna, Malappuram, Kerala.

³Supervisor, Department of Microbiology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India – 689103

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Address for Correspondence

Dr. Riju Mathew

Department of Biochemistry

Believers Church Medical College Hospital, Thiruvalla, Kerala, India

rijumathew@bcmch.edu.in

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ABSTRACT

Background: Progressive mitochondrial dysfunction, insulin resistance, and sarcopenia are central pathological hallmarks of metabolic decline and biological aging. Although physical activity remains the most effective non-pharmacological intervention to restore metabolic homeostasis, substantial clinical populations—including frail older adults, bedridden patients, and individuals with severe neuromuscular or cardiovascular impairment—cannot sustain sufficient exercise. Mitochondrial-derived peptides (MDPs), including MOTS-c, Humanin, and Small Humanin-Like Peptides (SHLPs), constitute an endocrine-like mitokine network encoded within short open reading frames of mtDNA that govern systemic bioenergetics and recapitulate key physiological adaptations of physical exertion.

Objective: To systematically review and critically appraise preclinical and clinical evidence regarding the structural biogenesis, intracellular and endocrine signaling mechanisms, and therapeutic efficacy of MOTS-c, Humanin, SHLP2/3, and synthetic analogs (notably HNG and CB4211) as standalone exercise mimetics or adjunct therapies in metabolic disease, sarcopenia, and age-related functional decline.

Methods: A PRISMA 2020-compliant search was conducted across MEDLINE (PubMed), Embase, and Web of Science Core Collection from database inception through July 2026. Original investigations, clinical trials, and mechanistic translational studies evaluating exogenous MDP administration or endogenous MDP modulation were extracted and appraised for signaling targets (AMPK, AKT, PGC-1 α , gp130, FPRL1, STAT3) and translational validity.

Results: MOTS-c inhibits the folate–methionine cycle, elevates ZMP, and activates AMPK at Thr172, thereby promoting insulin-independent GLUT4 translocation, PGC-1 α -driven mitochondrial biogenesis, and nuclear translocation with NRF2 to engage antioxidant response elements. Humanin and its analog HNG signal through a heterotrimeric

gp130/WSX-1/IL-27R α complex and FPRL1 while sequestering BAX to suppress caspase-3/9 cleavage, mitigating skeletal muscle atrophy and endothelial dysfunction. In clinical translation, the MOTS-c analog CB4211 (NCT04123558) achieved significant ALT (−21%) and AST (−28%) reductions in Phase 1b clinical testing in MASH and obesity.

Conclusions: MDPs display robust exercise-mimetic signatures across multiple organ systems. MDPs are best conceptualized as exercise rescue agents and synergistic metabolic adjuncts for patients unable to perform sufficient physical activity.

Keywords: Mitochondrial-derived peptides; MOTS-c; Humanin; SHLP2; Exercise mimetics; AMPK signaling; Sarcopenia; Metabolic disease; Aging; CB4211

1. INTRODUCTION

Physical exercise elicits a complex, multi-tissue systemic adaptation driven by mechanical tension, intermittent oxidative fluxes, substrate depletion, and hormonal reprogramming [1, 2]. At the epicentre of this adaptation lies the mitochondrion. Long regarded as the eukaryotic bioenergetic organelle responsible for adenosine triphosphate (ATP) synthesis via oxidative phosphorylation (OXPHOS), the mitochondrion is now recognized as a dynamic signaling hub capable of retrograde communication with the nuclear genome and of secreting endocrine-like factors termed mitokines [3, 4]. The discovery that mammalian mitochondrial DNA (mtDNA) encodes, in addition to the canonical 13 OXPHOS subunits, 22 tRNAs, and 2 rRNAs, a repertoire of bioactive peptides translated from short open reading frames (sORFs) has overturned the long-held assumption that the mitochondrial genome is a strictly structural element [3-5]. These mitochondrial-derived peptides (MDPs)—notably Humanin, MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c), and the Small Humanin-Like Peptide (SHLP) family—act as systemic regulators of bioenergetics, redox balance, and cytoprotection [3-9].

The clinical motivation for studying MDPs is straightforward. Metabolic diseases—type 2 diabetes mellitus (T2D), metabolic dysfunction-associated steatohepatitis (MASH), sarcopenic obesity, and cardiovascular insulin resistance—are characterized by failure of mitochondrial quality control, tissue-specific insulin resistance, chronic low-grade sterile inflammation, and structural muscle wasting [10-14]. Endurance and resistance training remain the most effective interventions to counteract these pathologies; however, strict adherence is frequently precluded in populations with advanced age, severe osteoarthritic degradation, cardiorespiratory insufficiency, critical-care cachexia, or neurological motor impairment [13, 15]. Pharmacological agents that mirror the polygenic and metabolic adaptations of exercise—so-called exercise mimetics—therefore represent a major therapeutic frontier [16, 17].

Among candidate exercise-mimetic scaffolds, MDPs occupy a privileged position because their endogenous biology is intimately coupled to the very organelle that

exercise most powerfully modulates. MOTS-c, for example, is released from mitochondria in response to metabolic stress and reproduces several signature adaptations of contraction, including AMP-activated protein kinase (AMPK) activation, insulin-independent glucose transporter 4 (GLUT4) translocation, and peroxisome proliferator-activated receptor γ coactivator 1- α (PGC-1 α) induction [6, 7, 18, 19]. Humanin and its synthetic analog HNG, in turn, engage the gp130/WSX-1 cytokine receptor and formyl peptide receptor-like 1 (FPRL1), suppress BAX-mediated apoptosis, and protect skeletal muscle, endothelium, and myocardium [20-23]. The SHLP family, encoded within the 16S rRNA locus alongside Humanin, includes members (notably SHLP2) with centrally and peripherally mediated insulin-sensitizing properties [24, 25].

Translational momentum has accelerated with the clinical development of CB4211, an engineered MOTS-c analog that, in a randomized, double-blind, placebo-controlled Phase 1b trial (ClinicalTrials.gov NCT04123558), produced significant reductions in serum aminotransferases and fasting glucose in subjects with MASH and obesity, providing the first-in-human proof-of-concept that the MOTS-c pharmacophore is druggable [26]. Nevertheless, the broader MDP field remains in a transitional state: preclinical evidence is abundant, but Phase 2/3 randomized controlled trials with hard clinical endpoints are absent; pharmacokinetic liabilities of native peptides remain unresolved; and long-term oncological safety has not been formally characterized.

This review synthesizes the structural biology, intracellular and endocrine signaling networks, preclinical evidence, and translational pipeline of MOTS-c, Humanin, SHLPs, and their synthetic derivatives, clarifying their feasibility as standalone exercise mimetics or adjunct therapies [15, 17].

2. METHODS

2.1 Search Strategy and Information Sources

This systematic review was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [27]. A search was performed across MEDLINE (via

PubMed), Embase, and Web of Science Core Collection from database inception through 31 July 2026 using the search terms: ("mitochondrial-derived peptides" OR "MOTS-c" OR "Humanin" OR "HNG" OR "SHLP" OR "SHLP2" OR "CB4211") AND ("exercise mimetic"

OR "physical activity" OR "AMPK" OR "PGC-1alpha" OR "insulin resistance" OR "type 2 diabetes" OR "sarcopenia" OR "aging" OR "MASH" OR "NAFLD"). The complete study selection process is illustrated in Figure 1.

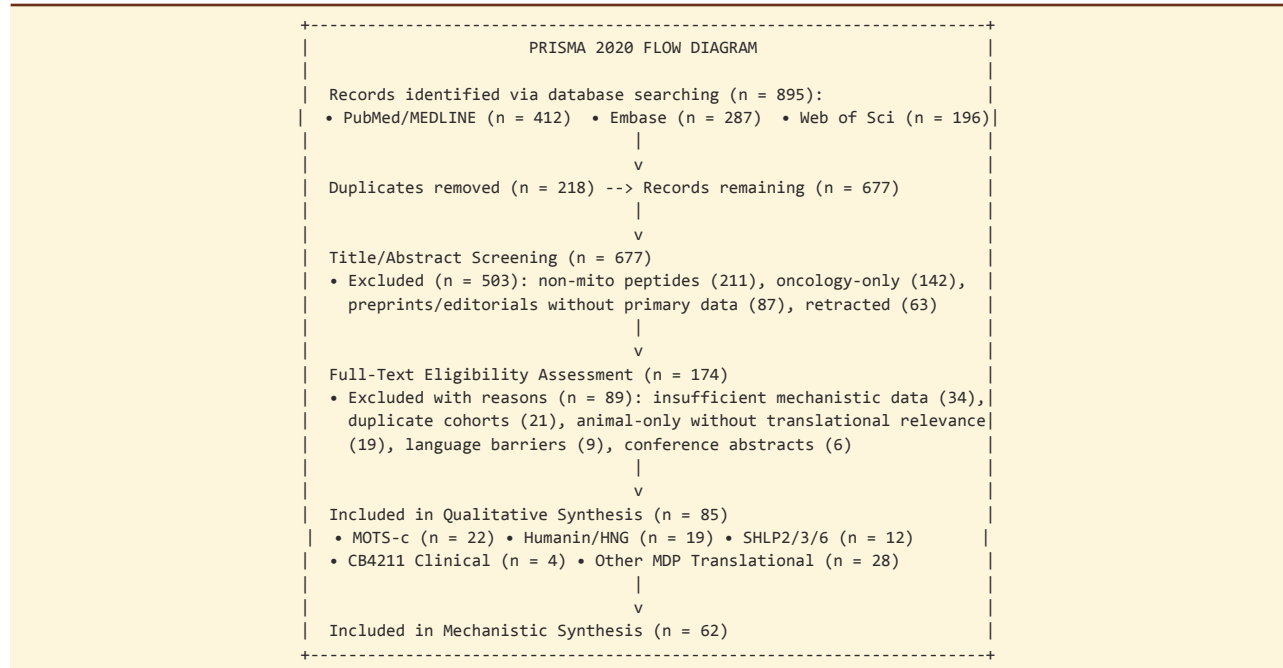


Figure 1. PRISMA 2020 flow diagram detailing literature identification, screening, eligibility, and inclusion for MDPs as exercise mimetics.

2.2 Eligibility Criteria

Peer-reviewed original investigations, clinical trials, and translational studies evaluating exogenous MDP administration or endogenous MDP modulation in mammalian cell, rodent, non-human primate, or human models reporting explicit downstream signaling nodes (e.g., AMPK, PGC-1 α , gp130, STAT3, AKT, FPRL1) or clinical metabolic parameters were included. Non-peer-reviewed articles, editorials, and retracted studies were excluded.

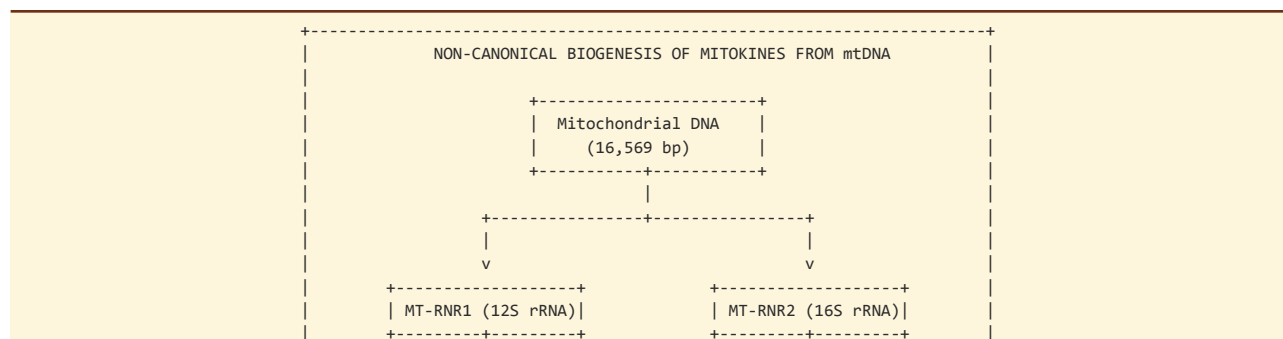
2.3 Data Extraction and Risk-of-Bias Appraisal

Two reviewers independently extracted study parameters (peptide identity, model, dosage/route, signaling readouts, clinical endpoints). Preclinical study

bias was appraised using the SYRCLE tool, and the single clinical trial (NCT04123558) was evaluated using the Cochrane Risk of Bias 2.0 tool [26].

3. STRUCTURAL BIOLOGY AND NON-CANONICAL BIOGENESIS OF MDPs

MDPs are translated directly from sORFs embedded within the mitochondrial genes encoding structural ribosomal RNAs (rRNAs) [3-7, 28, 29]. Unlike conventional nuclear-encoded secretomes, these peptides originate from the mitochondrial matrix and require retro-translocation pathways to engage cytosolic and systemic targets (Figure 2).



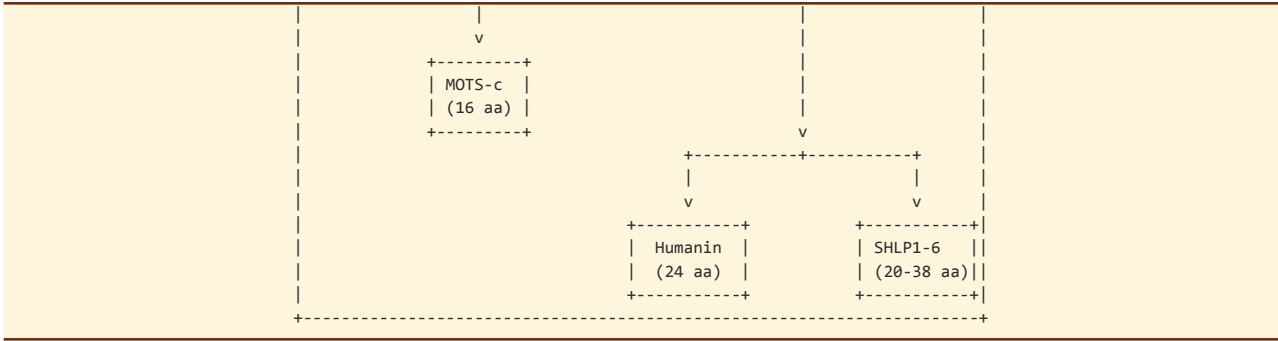


Figure 2. Non-canonical biogenesis of mitochondrial-derived peptides (MOTS-c, Humanin, SHLPs) from short open reading frames within the 12S (MT-RNR1) and 16S (MT-RNR2) rRNA loci.

3.1 MOTS-c (Mitochondrial Open Reading Frame of the 12S rRNA Type-c)

Discovered in 2015 by Lee and colleagues, MOTS-c is a 16-amino-acid peptide (sequence MRWQEMGYIFYPRKLR; ~2174.7 Da) encoded within the MT-RNR1 locus [6]. Three mechanistic features distinguish MOTS-c:

- **Folate-Cycle Blockade:** Its primary intracellular target is the folate–methionine one-carbon cycle: MOTS-c inhibits 5-methyltetrahydrofolate production, disrupting de novo purine synthesis and leading to accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) [6, 7].
- **AMPK Activation:** AICAR is converted by adenosine kinase to ZMP (an AMP mimetic), which binds the cystathionine β-synthase (CBS) domains of the AMPK γ-subunit, promoting allosteric activation and Thr172 phosphorylation on the catalytic α-subunit by LKB1 without requiring total ATP depletion [6, 19].
- **Nuclear Translocation:** Under metabolic stress or physical exertion, MOTS-c translocates to the nucleus in an AMPK-dependent manner, physically binding chromatin and engaging NRF2 (nuclear factor erythroid 2-related factor 2) to activate antioxidant response element (ARE)-dependent transcription [6, 7, 9, 30].

3.2 Humanin and Its Synthetic Derivative HNG

Humanin was identified in 2001 by Hashimoto et al. as a survival peptide abolishing neuronal cell death [5]. It is a 24-amino-acid peptide (sequence MAPRGFSCLLLTSEIDLVPVKRRA; ~2687.3 Da) encoded within the MT-RNR2 locus [3-5]. Humanin signals through two distinct cell-surface receptor complexes:

- A heterotrimeric receptor comprising gp130, WSX-1 (IL-27Rα), and IL-2Rβ, activating downstream STAT3 and ERK1/2 signaling [3, 4, 22].
- The G-protein-coupled formyl peptide receptor-like 1 (FRL1/FPR2), mediating chemotactic and anti-inflammatory cascades [3, 21].

Intracellularly, Humanin directly binds and sequesters pro-apoptotic BAX, preventing its translocation to the outer mitochondrial membrane and halting cytochrome c release and caspase-3/9 cleavage [20, 23]. The synthetic derivative HNG ([Gly14]-Humanin) exhibits a ~1,000-fold increase in cytoprotective potency over native Humanin due to increased peptide flexibility and enhanced receptor binding affinity [3-5, 33-35].

3.3 Small Humanin-Like Peptides (SHLP1-6)

The MT-RNR2 locus also encodes SHLP1 through SHLP6 (20–38 amino acids) [24]. SHLP2 (26 amino acids; sequence MGLEPINFRILTLWSFLCFLYTYSI) acts as a peripheral and central insulin sensitizer [24, 25]. Exogenous SHLP2 administration increases cell viability, suppresses reactive oxygen species (ROS) generation, prevents mitochondrial membrane depolarization (loss), and stabilizes respiratory chain Complexes I–V [24]. Circulating SHLP2 and Humanin levels decline with chronological age in rodents and humans [4, 7, 24, 36-38]. Continuous peripheral SHLP2 infusion improves glucose clearance, preserves functional islet -cell mass, and extends lifespan in mice [24]. By contrast, SHLP6 acts as an endogenous pro-apoptotic factor [24].

4. EXERCISE-MIMETIC SIGNALING CASCADES

Physical exercise coordinates mechanical strain, glycogen depletion, and vascular shear stress [1, 2, 15]. Table 1 details the signaling pathways and physiological adaptations engaged by MDPs, and Figure 3 illustrates the MOTS-c signaling pathway.

Table 1. Molecular architecture, signaling networks, and exercise-mimetic convergences of key mitochondrial-derived peptides and synthetic analogs.

Peptide / Analog	Biogenetic Source	Primary Target / Receptor	Downstream Signaling Cascades	Exercise-Mimetic Phenotype
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MOTS-c	MT-RNR1 (12S rRNA)	Folate cycle; AICAR; Nuclear AREs	AMPK α (Thr172); PGC-1 α ; NRF2; AS160 phosphorylation	Insulin-independent GLUT4 translocation; fatty acid β -oxidation; endurance
CB4211	Synthetic MOTS-c analog	Folate/AMPK axis; Insulin sensitivity	AMPK phosphorylation; Hepatic lipogenesis	ALT/AST reduction ($\sim 21\%/\sim 28\%$); hepatic steatosis $\downarrow$; insulin sensitivity $\uparrow$
Humanin (HN)	MT-RNR2 (16S rRNA)	gp130/WSX-1/IL-27R α ; FPRL1; BAX	JAK2/STAT3; PI3K/Akt; BAX sequestration; Caspase-3/9	Lean mass preservation; eNOS activation; anti-apoptotic protection
HNG	Synthetic [Gly14]-Humanin	High-affinity gp130 complex; FPRL1	Potentiated STAT3/Akt/eNOS; TNF- α /IL-6 suppression	Neuroprotection; systemic insulin sensitisation; anti-atrophic effects
SHLP2	MT-RNR2 (16S rRNA)	Hypothalamic & Peripheral targets	Hypothalamic leptin/insulin signaling; OXPHOS Complexes I–V stability	Enhanced glucose disposal; basal metabolic rate maintenance; anti-aging

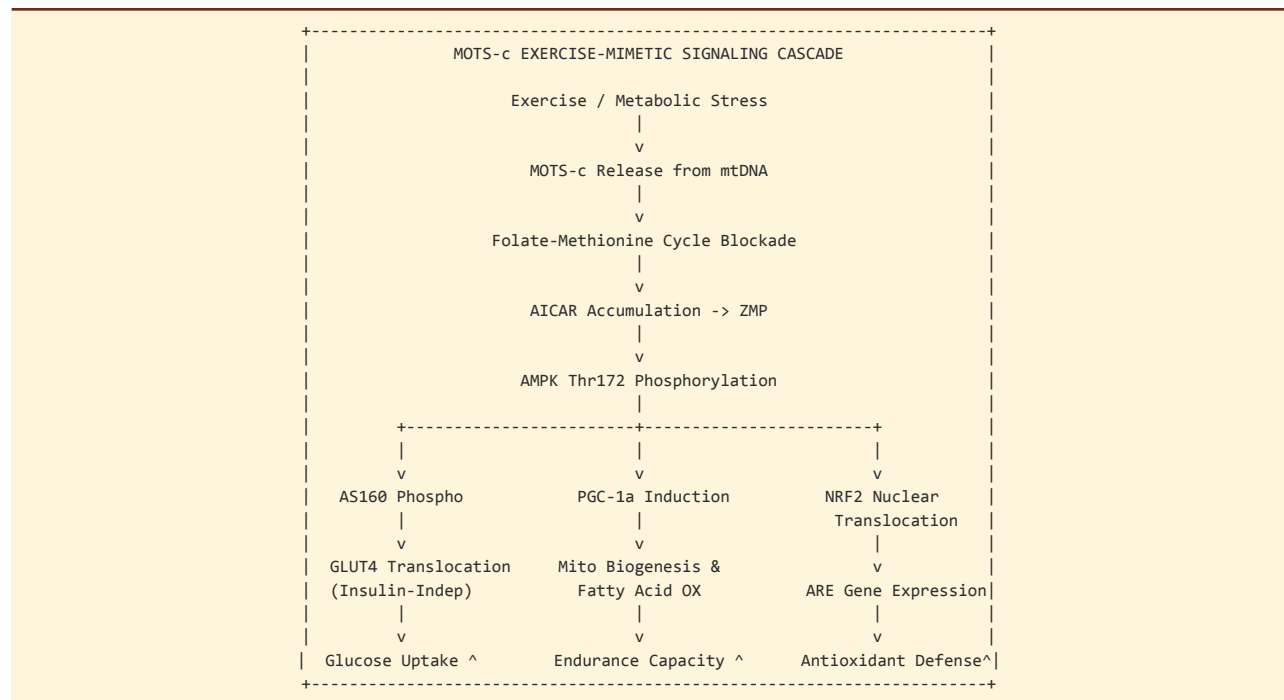


Figure 3. The MOTS-c signaling cascade: Folate cycle inhibition leads to ZMP-mediated AMPK activation at Thr172, driving GLUT4 translocation, PGC-1 α biogenesis, and NRF2 antioxidant responses.

4.1 The AMPK–PGC-1 α –GLUT4 Axis: Insulin-Independent Glucose Uptake

A hallmark adaptation of exercise is contraction-stimulated, insulin-independent glucose uptake into skeletal muscle [2, 15, 17]. Contraction elevates the intracellular AMP:ATP ratio, activating AMPK, which directly phosphorylates TBC1D4 (AS160). Phosphorylated AS160 permits GLUT4 exocytosis to the sarcolemma, bypassing insulin receptor substrate 1 (IRS-1)/PI3K activation [2, 6, 19].

MOTS-c replicates this cascade. Exogenous MOTS-c induces AMPK α Thr172 phosphorylation via ZMP accumulation [6, 7, 19]. Activated AMPK

phosphorylates AS160, promoting GLUT4 translocation even in insulin-resistant skeletal muscle [6, 7]. Concurrently, AMPK activates PGC-1 α , promoting mitochondrial cristae restructuring, upregulation of carnitine palmitoyltransferase 1 (CPT-1) and medium-chain acyl-CoA dehydrogenase (MCAD), and increased oxidative capacity [2, 6, 39, 40]. This demonstrates that the AMPK–PGC-1 α –AS160 axis can be engaged pharmacologically without mechanical loading, establishing MOTS-c as a functional exercise mimetic [2, 6, 12, 17].

4.2 Preservation of Muscle Mass and Attenuation of Sarcopenia

Sarcopenia is driven by an imbalance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB), mediated by ubiquitin–proteasome system (UPS) activity, autophagy dysregulation, and apoptosis [11, 13, 43, 44]. FoxO transcription factors (FoxO1, FoxO3a) transactivate E3 ubiquitin ligases—MuRF1/TRIM63 and Atrogin-1/FBXO32 [43, 44].

Humanin and HNG oppose sarcopenic signaling through complementary mechanisms:

- **Receptor Signaling:** Engagement of the gp130/WSX-1 complex activates JAK2, STAT3, and Akt [3, 4, 22]. Akt directly phosphorylates and inhibits FoxO1/FoxO3a, suppressing MuRF1 and Atrogin-1 transcription [43, 44].
- **BAX Sequestration:** Humanin binds intracellular BAX, inhibiting cytochrome c release and caspase-3/9 activation, preserving fast-twitch (Type II) muscle fibers [20, 23].

Exogenous HNG administration in aged rodents restores insulin sensitivity, suppresses pro-inflammatory cytokines (TNF-, IL-6), and preserves grip strength and treadmill performance [4, 13, 35].

5. PRECLINICAL AND CLINICAL EVIDENCE

5.1 Metabolic Syndrome, Obesity, and MASH

In high-fat diet (HFD) rodent models, MOTS-c administration (0.5–5 mg/kg/day) reduces weight gain, adiposity, and hepatic steatosis; normalizes HOMA-IR; activates brown adipose tissue (BAT) UCP1 expression; and promotes subcutaneous white adipose tissue (WAT) browning [6, 7, 45–47].

CB4211, an engineered MOTS-c analog, completed a Phase 1a/1b clinical trial (NCT04123558) in subjects with MASH and obesity [26]. Subcutaneous daily dosing of CB4211 (25 mg for 4 weeks) achieved significant reductions relative to placebo in serum alanine aminotransferase (ALT, −21%,) and aspartate aminotransferase (AST, −28%,), alongside reduced fasting glucose [26]. Primary safety and tolerability endpoints were met with no serious adverse events, providing first-in-human clinical evidence for the MOTS-c pharmacophore [12, 26].

5.2 Sarcopenia, Dynapenia, and Aging

In 22-month-old mice, systemic MOTS-c treatment improved treadmill running distance, time to exhaustion, and grip strength, restoring skeletal muscle AMPK α Thr172 phosphorylation and PGC-1 α target gene expression (citrate synthase, COX IV, NRF1) to levels observed in young controls [7, 30]. Endogenous Humanin and SHLP2 levels decline with age in rodents and humans [4, 7, 24, 37, 38]. Continuous peripheral SHLP2 infusion in aged mice improves glucose tolerance, maintains -cell mass, preserves bone mineral density, and extends median lifespan [24].

5.3 Cardiovascular and Endothelial Homeostasis

Humanin and HNG promote eNOS Ser1177 phosphorylation via AMPK/Akt, restoring nitric oxide () bioavailability and suppressing endothelial senescence [4, 49]. In myocardial ischemia–reperfusion (I/R) injury models, prophylactic Humanin or HNG treatment reduces infarct size, depresses TNF- and IL-1 β , and preserves left-ventricular ejection fraction (LVEF) [3, 23, 35].

6. DRUGGABILITY, PHARMACOKINETICS, AND SYNTHETIC ANALOGS

Native MOTS-c and Humanin possess short circulating half-lives () due to rapid endopeptidase cleavage (neutral endopeptidase, DPP-4) and renal clearance [3, 4, 6, 7]. Four chemical engineering strategies have been developed to enhance stability:

- **Amino Acid Substitution:** The S14G mutation in HNG increases cytoprotective potency ~1,000-fold by enhancing receptor binding affinity [3, 4].
- **Backbone Cyclization & D-Amino Acids:** Terminal modifications restrict proteolytic cleavage, extending plasma half-life to 6–12 hours [52, 53].
- **Lipidation & Albumin Conjugation:** Appending C16/C18 fatty acyl chains enables reversible albumin binding, reducing renal clearance and extending half-life to [52–54].
- **Small-Molecule Pharmacophores:** Non-peptidic scaffolds targeting the C-terminal core of MOTS-c offer potential for oral bioavailability [6, 7, 17].

CB4211 demonstrates optimized subcutaneous bioavailability and plasma stability, validating the clinical viability of engineered mitokines [26].

7. TRANSLATIONAL ROADBLOCKS AND LIMITATIONS

Four principal barriers hinder clinical implementation:

- **Species Sequence Divergence:** Mitochondrial sORF sequence variations between rodents and humans complicate preclinical extrapolation [6, 7, 36].
- **The "Exercise Polypharmacology" Paradox:** MDPs engage single signaling nodes and cannot duplicate the systemic biomechanical loading, cardiorespiratory volume changes, or neural adaptations of exercise. MDPs should be categorized as exercise rescue agents or adjuncts rather than exercise replacements [13, 15, 17].
- **Oncological Safety:** Because Humanin and MOTS-c promote cell survival and inhibit BAX-mediated apoptosis, long-term safety surveillance is required to ensure pro-survival mitokine signaling does not support tumor growth [6, 20, 50, 51].
- **Lack of Phase 2/3 Trials:** Outside of the CB4211 Phase 1b study, randomized controlled trials evaluating hard clinical outcomes (, MRI muscle cross-sectional area, MRI-PDFF liver fat,) are absent [12, 13, 26, 54].

8. FUTURE RESEARCH DIRECTIONS

A three-pronged translational roadmap is outlined in Figure 4:

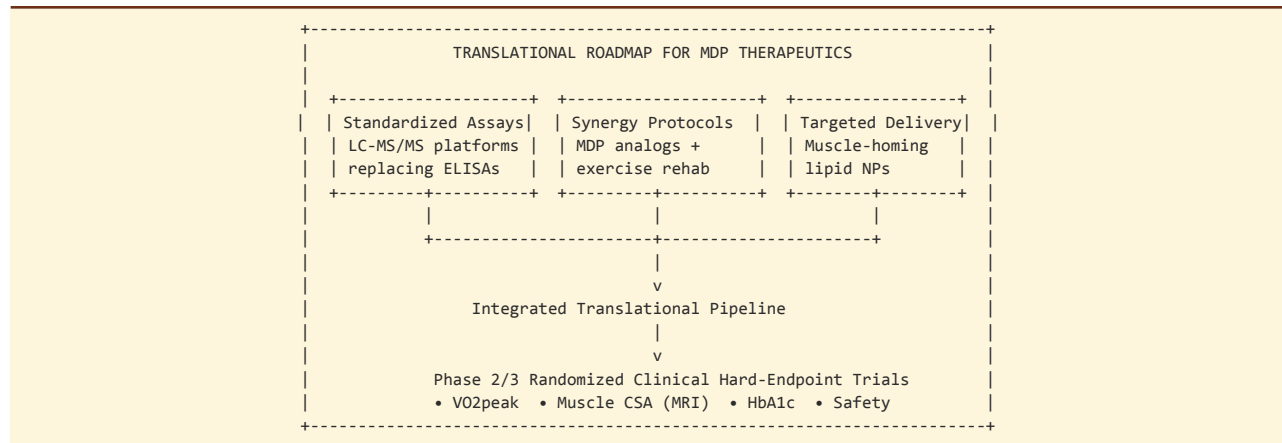


Figure 4. Translational roadmap detailing standardized LC-MS/MS assays, combination synergy protocols, and organ-targeted delivery platforms feeding into Phase 2/3 clinical trials.

- **Standardized Assays:** Validated mass spectrometry platforms (LC-MS/MS) must replace variable commercial ELISAs for accurate endogenous peptide quantification [4, 7, 36].
- **Synergy Protocols:** Clinical trials should evaluate combination therapies pairing MDP analogs with low-intensity supervised physical rehabilitation [13, 15, 17].
- **Targeted Delivery Platforms:** Muscle-homing peptide bioconjugates and lipid nanoparticle depot formulations should be developed to minimize off-target exposure and extend dosing intervals [52-54].

9. CONCLUSIONS

Mitochondrial-derived peptides (MOTS-c, Humanin, SHLP2) constitute a bioenergetic mitokine network linking mitochondrial stress adaptation to systemic metabolic control. By activating AMPK–PGC-1 α and STAT3–Akt signaling, MDPs stimulate insulin-independent glucose disposal, enhance fatty acid oxidation, preserve muscle protein integrity, and maintain endothelial function. The Phase 1b trial of CB4211 provides proof-of-concept that MDP-derived therapeutics are clinically active. While MDPs cannot replace physical exercise, they offer promise as exercise rescue agents and metabolic adjuncts for clinical populations unable to sustain sufficient physical exertion.

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