

RESEARCH MONOGRAPH · COMPOUND PROFILE

MOTS-c

A short open reading frame encoded within mitochondrial 12S rRNA, reported to modulate insulin sensitivity, exercise capacity, and metabolic homeostasis through AMPK-dependent mechanisms.

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ABSTRACT

MOTS-c (Mitochondrial Open reading frame of the Twelve S rRNA-c; sequence Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg; CAS 1627580-64-6; molecular formula C₁₀₀H₁₅₂N₂₈O₂₂S₂; molecular weight 2174.59) is a 16-amino-acid peptide encoded within an open reading frame in the mitochondrial 12S ribosomal RNA gene MT-RNR1, first characterized in 2015 by Changan Lee, Pinchas Cohen, and colleagues at the University of Southern California. It is the first short open reading frame (sORF) peptide identified in the mitochondrial genome, and its discovery has opened a substantial line of work on small mitochondrial-encoded peptides as endocrine and paracrine signals. Reported activities include enhanced insulin sensitivity in diet-induced and genetic obesity models, increased exercise capacity, improved glucose homeostasis through AMP-activated protein kinase (AMPK) activation, attenuated age-related insulin resistance, and effects on bone mineral density and immune function. Plasma MOTS-c levels decline with age in humans, which is the rationale for the geroprotective framing of the compound in research-grade vendor literature. The published preclinical literature is robust and has expanded steadily since 2015 with multiple independent laboratories contributing replication and extension studies. There is no FDA-approved IND for MOTS-c in any indication; preliminary Phase 1 work has been initiated by CohBar, Inc., the company that has licensed the platform from USC. The compound is not approved by any regulatory authority for human or veterinary use.

Compound identification

Nomenclature and synonyms

The compound is referred to as MOTS-c (mitochondrial-derived peptide encoded within 12S rRNA), MOTSc, or occasionally as the 16-mer mitochondrial peptide. The CAS number is 1627580-64-6. The PubChem CID is 134812942. The compound is part of a broader family of mitochondrial-derived peptides (MDPs) that includes humanin, the SHLP family (small humanin-like peptides), and others; MOTS-c is the most extensively characterized member of the family after humanin.

The naming convention "MOTS-c" derives from "Mitochondrial Open reading frame of the Twelve S rRNA-c," with the lowercase "c" reflecting that the peptide is encoded on the complementary strand of the 12S rRNA gene. The mitochondrial origin is biologically important: the peptide is encoded within the mitochondrial genome rather than the nuclear genome, and the cellular machinery for its translation involves mitochondrial ribosomes followed by export to the cytoplasm and to the extracellular space.

Structural chemistry

The amino acid sequence is L-methionine - L-arginine - L-tryptophan - L-glutamine - L-glutamic acid - L-methionine - L-glycine - L-tyrosine - L-isoleucine - L-phenylalanine - L-tyrosine - L-proline - L-arginine - L-lysine - L-leucine - L-arginine. The peptide is 16 residues, with two methionines, three arginines, two tyrosines, one tryptophan, and one phenylalanine, conferring substantial UV absorbance and complicating standard quantification approaches.

The molecular formula is C₁₀₀H₁₅₂N₂₈O₂₂S₂; the average molecular weight is 2174.59 g/mol; the monoisotopic mass is 2173.16 daltons. The peptide has no disulfide bridges in the standard form, no post-translational modifications, and no characterized stable secondary structure; it exists as a random coil in dilute aqueous solution. The high arginine and lysine content gives the peptide a substantial net positive charge at physiological pH.

Physicochemical properties

MOTS-c is supplied as a white lyophilized powder. The lot of record (Kodiac biolabs lot 20260123) conforms to this description. Solubility in water and bacteriostatic water is moderate to high; concentrations up to 5 mg/mL are routinely prepared. Dissolution is sometimes slower than for shorter peptides due to mild aggregation; gentle warming to 30 degrees Celsius assists if dissolution is incomplete after 90 seconds. The peptide is also soluble in 0.9 percent saline, PBS, and standard biological buffers. Solubility in DMSO is poor.

The peptide is stable in the lyophilized state at minus 20 degrees Celsius for at least 24 months under standard light protection. The two methionine residues are oxidation-sensitive and prolonged exposure to atmospheric oxygen at elevated temperature can produce methionine sulfoxide impurities; lyophilized storage at minus 20 degrees minimizes this risk. Reconstituted solutions are stable at 2 to 8 degrees Celsius for 30 days minimum, with extended stability up to 60 days under controlled refrigeration. Freeze-thaw cycles should be avoided.

Discovery and developmental history

Origin in the Lee and Cohen laboratories

MOTS-c was first characterized in a 2015 paper by Changhan Lee and colleagues working in the Pinchas Cohen laboratory at the University of Southern California Davis School of Gerontology. The discovery emerged from a systematic search for short open reading frames within the mitochondrial genome and from the recognition that the 12S rRNA gene contained an in-frame coding sequence that produced a stable peptide product. Mass spectrometric identification of the endogenous peptide in human plasma and tissues confirmed that MOTS-c is genuinely produced in vivo at physiologically relevant concentrations (low nanomolar in fasting plasma).

The original paper reported that MOTS-c administration enhances insulin sensitivity, increases glucose disposal during glucose tolerance tests, and attenuates the development of diet-induced insulin resistance in mice. Subsequent papers from the Cohen laboratory and from independent groups have extended the findings to exercise capacity, age-related metabolic decline, immune function, and bone mineral density.

Clinical translation

CohBar, Inc., a publicly traded biotechnology company, has licensed the mitochondrial-derived peptide platform from USC and has progressed several MDP candidates toward clinical development. CB4211, a MOTS-c-derived therapeutic candidate, has entered Phase 1 trials for nonalcoholic steatohepatitis (NASH). The clinical record at the time of this revision is limited to early Phase 1 safety data; full efficacy results have not been published. There is no FDA-approved indication for MOTS-c.

Mechanism of action

AMPK pathway activation

The most-cited mechanism is activation of AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis. MOTS-c administration produces phosphorylation and activation of AMPK in skeletal muscle, liver, and adipose tissue. The downstream consequences include increased glucose uptake (through GLUT4 translocation in muscle), increased fatty acid oxidation, increased mitochondrial biogenesis, and improved insulin sensitivity. The mechanism by which MOTS-c activates AMPK is not fully characterized; proposed pathways include direct binding to a yet-unidentified surface receptor, modulation of folate metabolism through inhibition of methionine adenosyltransferase, and changes in cellular AMP:ATP ratios secondary to upstream metabolic effects.

Methionine and folate cycle modulation

A more specific mechanistic claim from the Lee and Cohen group is that MOTS-c inhibits the folate-methionine cycle at the level of AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) accumulation, which then activates AMPK by mimicking the AMP signal. The proposed mechanism involves competitive inhibition of methionine adenosyltransferase by MOTS-c, leading to AICAR accumulation. This mechanism is consistent with the AMPK activation phenotype but the upstream binding interaction has not been crystallographically resolved.

Insulin sensitivity

The metabolic phenotype produced by MOTS-c administration in diet-induced obesity models includes restored insulin sensitivity, improved glucose tolerance, reduced hepatic steatosis, and a shift from fat storage toward fat oxidation in adipose tissue and skeletal muscle. The magnitude of the effect is substantial in published studies, with insulin sensitivity restored to near-control levels in mice maintained on high-fat diet.

Exercise capacity

Independent reports document that MOTS-c administration enhances exercise capacity in rodents, with both treadmill running endurance and grip strength improved relative to vehicle controls. The mechanism involves both the AMPK-mediated metabolic adaptations and direct effects on skeletal muscle stress-resistance gene expression. Plasma MOTS-c concentrations rise transiently after exercise in humans, consistent with a model in which the peptide is part of the endogenous response to exercise stress.

Age-related effects

Plasma MOTS-c concentrations decline with age in humans, in parallel with the age-related decline in insulin sensitivity and exercise capacity. Administration of exogenous MOTS-c partially restores the metabolic phenotype of older animals to that of younger controls. The aging-related framing of the peptide is supported by these data, though clinical translation to humans remains preliminary.

Limits of the mechanistic model

The mechanistic literature is robust and growing, with multiple independent laboratories contributing. The principal limitation is that the upstream binding interaction (the receptor or direct enzymatic target through which MOTS-c initiates the AMPK cascade) has not been definitively identified; multiple proposals are in circulation and the field has not converged. The downstream metabolic effects are well documented; the upstream initiating event is less clear.

Pharmacokinetics

Routes of administration

Subcutaneous, intraperitoneal, and intravenous administration are the standard routes in published preclinical work. Subcutaneous administration produces predictable absorption with peak plasma concentrations within 30 to 60 minutes. Oral bioavailability has not been extensively characterized but is expected to be poor based on the size and the absence of unnatural amino acids that would protect against gastric peptidases.

Plasma half-life and tissue distribution

Plasma half-life following subcutaneous administration is approximately 1 to 2 hours in rodents. Tissue distribution is broad; the peptide is detectable in skeletal muscle, liver, adipose tissue, kidney, and brain following systemic administration. Brain penetration is modest but non-negligible. The biological half-life relevant for AMPK activation extends substantially longer than the plasma half-life, on the order of 8 to 12 hours, reflecting the persistence of downstream signaling effects after the peptide has cleared.

Metabolism and excretion

MOTS-c is hydrolyzed by serum and tissue peptidases at the central tyrosine and proline positions and at the C-terminal lysine and arginine. Major metabolites are biologically inactive in the published assays. Renal excretion of intact peptide and shorter fragments is the primary clearance route. The compound is not a known inducer or inhibitor of major CYP isoforms.

Reported research dose ranges

The published preclinical literature reports rodent doses ranging from 0.1 to 15 milligrams per kilogram by various routes, with the bulk of pharmacology studies clustering around 0.5 to 5 milligrams per kilogram subcutaneously, daily or every other day for chronic studies. Allometric scaling places the equivalent human exposure in the range of 14 micrograms to 700 micrograms per kilogram per dose, or approximately 1 to 50 milligrams per dose for a 70 kg subject.

The dose range commonly cited in research-grade vendor literature (5 to 10 milligrams per research subject, two to three times per week, over 6 to 12 week cycles) is at the upper end of the allometrically scaled range. Dose-response data in the published literature support the lower end of the cited range as effective for metabolic endpoints; higher doses do not consistently produce larger effects and may risk peptide aggregation or methionine oxidation issues. Investigators should treat the published research-grade dose ranges as approximate guidance.

Sourcing and quality verification

Synthesis route

MOTS-c is produced by solid-phase peptide synthesis using Fmoc chemistry. The 16-residue length is well within routine SPPS capacity. The principal synthetic concerns are coupling efficiency at the central proline position (which is prone to chain aggregation on the resin), oxidation of the two methionine residues during prolonged synthesis, and racemization at the central tyrosine and tryptophan positions.

The lot of record (Kodiak biolabs lot 20260123) was synthesized by the supplier of record and shipped in lyophilized acetate salt form. The vendor analytical report records compliance with the ≥ 98.0 percent purity specification; the COA does not disclose the exact value, which is a limitation of the supplier's documentation that the planned Janoshik third-party verification will address.

Common adulterants and impurities

The research-grade MOTS-c supply chain has documented patterns of substandard product. Reported issues include:

1. Methionine sulfoxide formation at one or both of the methionines (M1 and M6), producing a peptide of mass +16 or +32 daltons relative to the parent. Mass spectrometry detects this readily; standard reversed-phase HPLC may show shifted retention times for the oxidized impurity.
2. Deletion sequences from incomplete coupling, primarily at the central proline. The 14- and 15-mer impurities are biologically inactive.
3. Racemization at the central tyrosine, tryptophan, or proline positions, producing a peptide of correct mass but altered receptor engagement. Chiral HPLC is required to detect this.
4. Excess acetate or trifluoroacetate counterions inflating apparent mass by 5 to 12 percent.
5. Endotoxin contamination from non-pyrogen-controlled synthesis.

Independent verification by HPLC and mass spectrometry on every batch is essential, with particular attention to the methionine oxidation status. The vendor COA is necessary but not sufficient. Kodiak biolabs is in the process of establishing third-party verification through Janoshik Analytical.

Analytical standards

Reverse-phase HPLC on a C18 column with gradient elution from aqueous TFA (0.1 percent) to acetonitrile, monitoring at 215 nm and 280 nm (the latter exploiting the substantial tyrosine and tryptophan absorbance), is the standard purity assay. Identity confirmation by LC-MS yields the $[M+H]^+$ peak at 2175.6 m/z and the $[M+2H]^{2+}$ peak at 1088.3 m/z. The acceptance criteria are: total purity above 98.0 percent at both wavelengths, identity confirmation within 0.5 ppm of theoretical mass, methionine sulfoxide impurity below 0.5 percent, and absence of major impurity peaks above 0.5 percent of the parent peak.

Reconstitution and handling

Solvent system

MOTS-c dissolves in water, bacteriostatic water, and 0.9 percent saline. The standard reconstitution protocol uses bacteriostatic water for any solution intended for storage beyond a single use. For acute experiments, sterile water for injection or PBS works. DMSO is not the appropriate vehicle.

Reconstitution protocol

A 10 mg vial reconstituted in 2 mL produces a 5 mg/mL solution. Dissolution may be slightly slower than for shorter peptides; allow 90 to 120 seconds rest after solvent addition, then gently swirl. The peptide should fully dissolve; if cloudiness persists, brief gentle warming to 30 degrees Celsius typically resolves it. Vigorous shaking introduces foaming and is not necessary.

Storage stability

Lyophilized MOTS-c in the unopened vial: stable at minus 20 degrees Celsius for at least 24 months. Reconstituted aqueous solutions: stable at 2 to 8 degrees Celsius for 30 days minimum. Aliquot working solutions to avoid freeze-thaw cycles. The methionines are oxidation-sensitive at elevated temperature; do not store reconstituted solutions at room temperature beyond 24 hours.

Stack interaction considerations

MOTS-c is occasionally combined with NAD⁺ in research-grade protocols on the rationale that both compounds intersect with mitochondrial energetics and AMPK activity. The mechanistic case for synergy is plausible (NAD⁺ supplementation supports sirtuin activity, which connects to AMPK signaling at multiple nodes) but not formally established in controlled comparison studies.

Combination with the GHS family (Ipamorelin, CJC-1295) is sometimes reported on the rationale that GH-axis stimulation supports mitochondrial biogenesis. The mechanistic case is plausible but not specifically documented for MOTS-c.

Stacking with insulin-sensitizing pharmacotherapy (metformin in particular) is mechanistically interesting because both compounds activate AMPK through different upstream routes. The combination has not been specifically studied in controlled comparison; the additive or synergistic effect cannot be predicted without experimental data in the model of interest.

Pharmacokinetic interactions with CYP-substrate compounds are not expected. MOTS-c has no documented receptor-level interactions with conventional small-molecule pharmacotherapy.

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