BIOMOD LABS · RESEARCH PEPTIDE CO.

RESEARCH COMPOUND MONOGRAPH · SERIES 1 · NO. 018

MOTS-c

Mitochondrial Open Reading frame of the 12S rRNA Type-c — a 16-residue mitochondrial-derived peptide encoded by the MT-RNR1 region of the mitochondrial genome, discovered by Lee, Cohen and colleagues in 2015 and characterised as a nuclear-translocating regulator of metabolic gene expression under cellular stress.

CAS REGISTRY	CATALOG REFERENCE	CLASS	DATE OF ISSUE
1627580-64-6	BM-LYO-018	Synthetic peptide · 16 a.a. · mitochondrial-derived	May 2026

MOTS-c (Mitochondrial Open Reading frame of the 12S rRNA Type-c) is a 16-residue mitochondrial-derived peptide of sequence Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg, encoded by a short open reading frame within the MT-RNR1 mitochondrial gene (the 12S rRNA region of the mitochondrial genome). The molecule was identified in 2015 by Changhan Lee and Pinchas Cohen at the USC Davis School of Gerontology through systematic bioinformatic and biochemical analysis of small mitochondrial open reading frames, building on the 2003 discovery of the related mitochondrial-derived peptide humanin. MOTS-c is the second well-characterised member of the mitochondrial-derived peptide family. Under cellular metabolic stress, MOTS-c translocates from mitochondria to the nucleus, where it regulates nuclear gene expression in response to mitochondrial signalling — a defining feature of the molecule's pharmacology characterised in detail in the Kim and Lee 2018 Cell Metabolism paper. ***This monograph summarises published cellular pharmacology and preclinical findings for laboratory research reference only.***

01 Compound Profile

COMMON DESIGNATION	MOTS-c · Mitochondrial Open Reading frame of the 12S rRNA Type-c
PRIMARY SEQUENCE	Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg (MRWQEMGYIFYPRKLR)
GENETIC ORIGIN	Encoded by a short open reading frame within the MT-RNR1 mitochondrial gene (the 12S rRNA region of the human mitochondrial genome)[1]
CAS REGISTRY	1627580-64-6
MOLECULAR FORMULA	$C_{102}H_{153}N_{27}O_{22}S_2$
AVERAGE MOLECULAR MASS	2174.62 g · mol^{-1}
PRIMARY MOLECULAR TARGETS	AMPK pathway activation in skeletal muscle and other tissues; nuclear translocation under metabolic stress with regulation of NRF2-pathway and antioxidant-response-element gene expression[2]
PHYSICAL FORM	White lyophilised solid
SOLUBILITY (LAB RECONSTITUTION)	Water-soluble; the sequence contains two methionine residues (Met1, Met6) and three aromatic residues (Trp3, Tyr8, Tyr11) — handling considerations for both oxidation and photo-oxidation apply
STORAGE (RESEARCH HANDLING)	Lyophilised solid: −18 °C, desiccated, light-protected; reconstituted solution refrigerated 2–8 °C; long-term aliquots at −18 °C; the two methionines are oxidation-susceptible — air-exposure minimisation recommended
ANALYTICAL SPECIFICATION	≥ 95 % purity by HPLC (BIOMOD Labs internal release specification)

02 Origin and Chemistry

MOTS-c was identified in 2015 by Changhan Lee, working in the laboratory of Pinchas Cohen at the USC Davis School of Gerontology. The Lee 2015 *Cell Metabolism* discovery paper characterised the 16-residue peptide as a product of a short open reading frame within the MT-RNR1 mitochondrial gene — a region traditionally annotated as the 12S rRNA encoding region and not previously known to encode any protein product. The mitochondrial-derived peptide concept had been established earlier with the 2003 discovery of humanin (encoded by a different short open reading frame in the same MT-RNR1 region), and MOTS-c is the second well-characterised mitochondrial-derived peptide.[1]

Chemically, MOTS-c is rich in basic residues (3 Arg, 1 Lys) at the C-terminal half, with two methionines (positions 1 and 6) and three aromatic residues (Trp3, Tyr8, Tyr11) clustered in the N-terminal half. The two methionines are oxidation-susceptible; the tryptophan is photo-oxidation susceptible. Plasma MOTS-c levels in humans and rodents have been reported to decline with age, paralleling the age-associated decline in mitochondrial function and contributing to the molecule's characterisation as a candidate longevity peptide.[3]

03 Molecular Targets and Cellular Signalling

MOTS-c has two principal modes of cellular action characterised in published preclinical literature. First, in **cellular metabolic regulation**, MOTS-c activates the AMP-activated protein kinase (AMPK) pathway in skeletal muscle and other tissues, with downstream effects on glucose uptake, fatty acid oxidation, and mitochondrial biogenesis through PGC-1α. The Lee 2015 discovery paper documented MOTS-c effects on AMPK pathway activation and glucose handling in skeletal muscle cell-culture and mouse preparations. Second, in **nuclear gene regulation**, MOTS-c translocates from mitochondria to the nucleus under cellular metabolic stress, where it interacts with regulatory elements of nuclear genes — the Kim and Lee 2018 *Cell Metabolism* paper characterised this nuclear translocation and identified NRF2-pathway and antioxidant-response-element genes as downstream regulatory targets.[2] PRECLINICAL · MOUSE

04 Preclinical Findings

SYSTEM	ANIMAL MODEL / PREPARATION	REPORTED OBSERVATION	REF.
Discovery & characterisation	Bioinformatic identification, skeletal muscle cell culture	16-residue peptide encoded by MT-RNR1; AMPK pathway activation	1
Glucose metabolism	Mouse skeletal muscle preparations	Improved glucose handling; insulin sensitivity	1
Nuclear translocation	Cell-culture metabolic-stress preparations	Translocation from mitochondria to nucleus; regulation of nuclear gene expression	2
Aging biology	Aged mouse preparations	Plasma MOTS-c declines with age; administration improves physical fitness	3
Exercise mimetic	Mouse exercise & sedentary preparations	MOTS-c upregulated with exercise; administration partially recapitulates exercise effects	1
Skeletal muscle aging	Aging-skeletal-muscle preparations in humans	Muscle MOTS-c levels increase with age; correlation with fast-to-slow fiber transition	4

05 Research Synthesis & Limitations

METHODOLOGICAL NOTES

MOTS-c is a relatively recently discovered peptide (2015) with a growing but still developing preclinical literature concentrated in the Lee/Cohen laboratory and collaborators. The unusual genetic origin (mitochondrial-derived peptide encoded within a region previously annotated only as an rRNA gene) is mechanistically distinctive and has implications for the broader concept of "small open reading frame" peptides in mitochondrial and nuclear genomes. For researchers, the principal handling considerations are (a) the two methionines confer oxidation susceptibility, addressed by air-exposure minimisation; and (b) the Trp3 photo-oxidation susceptibility, addressed by light protection.

06 Laboratory Handling, Reconstitution, and Storage

Lyophilised MOTS-c is supplied under research-use specifications. Reconstitution in sterile water for injection or phosphate-buffered saline is standard practice. **The two methionines are oxidation-susceptible** and **the Trp3 is photo-oxidation susceptible** — light protection and air-exposure minimisation are both recommended. Lyophilised storage at −18 °C, desiccated, light-protected; reconstituted solutions held refrigerated 2–8 °C, light-protected; aliquoted long-term storage at −18 °C with strict minimisation of freeze–thaw. Working concentrations are determined by the investigator's experimental design.

07 References

1. Lee C, Zeng J, Drew BG, Sallam T, Martin-Montalvo A, Wan J, Kim SJ, Mehta H, Hevener AL, de Cabo R, Cohen P. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab.* 2015;21(3):443–454. pubmed.ncbi.nlm.nih.gov/25738459
2. Kim KH, Son JM, Benayoun BA, Lee C. The mitochondrial-encoded peptide MOTS-c translocates to the nucleus to regulate nuclear gene expression in response to metabolic stress. *Cell Metab.* 2018;28(3):516–524.e7. pubmed.ncbi.nlm.nih.gov/29983246
3. Reynolds JC, Lai RW, Woodhead JST, Joly JH, Mitchell CJ, Cameron-Smith D, Lu R, Cohen P, Graham NA, Benayoun BA, Merry TL, Lee C. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. *Nat Commun.* 2021;12(1):470. pubmed.ncbi.nlm.nih.gov/33473109
4. D'Souza RF, Woodhead JST, Hedges CP, Zeng N, Wan J, Kumagai H, Lee C, Cohen P, Cameron-Smith D, Mitchell CJ, Merry TL. Increased expression of the mitochondrial derived peptide, MOTS-c, in skeletal muscle of healthy aging men is associated with myofiber composition. *Aging (Albany NY).* 2020;12(6):5244–5258. pubmed.ncbi.nlm.nih.gov/32182211
5. Mohtashami Z, Singh MK, Salimiaghdam N, Ozgul M, Kenney MC. MOTS-c, the Most Recent Mitochondrial Derived Peptide in Human Aging and Age-Related Diseases. *Int J Mol Sci.* 2022;23(19):11991. PMID: 36233287. pubmed.ncbi.nlm.nih.gov/36233287