

MOTS-c

A mitochondrial-derived metabolic signalling peptide

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Medical review

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ABSTRACT

MOTS-c links mitochondrial coding to cellular nutrient sensing and can translocate to the nucleus under metabolic stress.

This monograph distinguishes endogenous MOTS-c physiology from administration of an exogenous MOTS-c preparation. It maps mitochondrial coding, metabolic-stress signalling, nuclear translocation, animal physiology and the absence of an adequate human therapeutic exposure programme.

This monograph begins with the molecule and follows the causal chain through biochemistry, cellular mechanism, exposure and integrated physiology. Population studies enter only at the terminal stress-test: useful for the proposition actually tested, incapable of defining the molecule or replacing the causal model.

ESTABLISHED	UNRESOLVED
• Mitochondrial coding origin • AMPK and metabolic-stress biology • Human endogenous associations	• Human exogenous PK • Immunogenicity • Controlled therapeutic efficacy

EVIDENCE HIERARCHY

Mechanistic evidence is not a lower-grade substitute for population medicine. Physical constraints, biochemical measurements, historical and non-English records, exposure studies and clinical outcomes answer different questions. Controlled clinical trials test the complete implemented proposition; they cannot manufacture a missing identity, mechanism or exposure bridge.

I	Molecular identity and chemistry
II	Biochemistry and target architecture
III	Cells and ex-vivo tissues
IV	Animal and in-vivo pharmacology
V	Integrated physiology and translation
VI	Human PK and observational signal
VII	Controlled clinical trials

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ACTION LEDGER

Describe the action before judging its value.

Benefit is a downstream clinical judgement. The scientific object is the action itself: what moves, under which exposure, in which biological state, and where the inference stops.

01 Attributed biochemical action	MOTS-c links mitochondrial coding to cellular nutrient sensing and can translocate to the nucleus under metabolic stress.
02 Exposure and reachability	Exogenous administration improves selected metabolic and performance outcomes in animal models. Human pharmacokinetics, immunogenicity and target-engagement after administration remain insufficiently characterised.
03 Physiological direction is contextual	MOTS-c biology connects mitochondrial stress sensing with cytosolic purine metabolism, AMPK and nuclear adaptation. The sign of that response depends on energy state, tissue, age and proliferative demand: an energy-conservation programme may improve metabolic resilience yet constrain growth or repair in another compartment. Endogenous concentration and injected exposure are separate physiological questions.
04 Individual adjudication boundary	Human exogenous exposure, immunogenicity and a validated administered-peptide target-engagement signature. An exercise-associated endogenous signal does not prove that injection reproduces exercise adaptation or benefits cellular regeneration.

METHODS AND COVERAGE

A reproducible boundary, not an implied exhaustive review.

This curated mechanistic monograph uses primary indexed records and reference-chaining. It does not claim systematic-review completeness. Absence of a retrieved result is not evidence that an effect is absent.

SEARCH SURFACE	PubMed/MEDLINE primary records, Russian-language indexed abstracts, and reference-chaining for entity-defining, historical and translational studies. Language, geography, regulatory status and journal fashion are not evidence grades.
QUERY FRAME	MOTS-c · mitochondrial-derived peptide · 12S rRNA · AMPK · folate cycle · purine synthesis · mitonuclear signalling
EVIDENCE CUTOFF	23 August 2026
ENTITY EXCLUSION	Endogenous MOTS-c concentration, genotype and synthetic exogenous administration are different scientific objects. Association studies cannot supply administered-product PK.
TRACEABILITY	12 extended claim units plus 2 historical records and 3 mechanistic-calculus records; 7 cited records in the complete corpus.
INTERPRETIVE RULE	Identity → physical constraint → measured reaction or binding → reachable exposure → system response → outcome. Statistical significance does not manufacture mechanism; mechanistic plausibility does not manufacture a patient outcome.

EVIDENCE ATLAS

Every claim keeps its experimental address.

12 claim units are mapped to evidentiary layer, experimental frame and source records. The layer describes the question answered; it is not a popularity score.

LAYER	EXPERIMENTAL FRAME	FINDING AND BOUNDARY	SOURCES
IMolecular identity	Mitochondrial coding and identity · claim 1	MOTS-c is a 16-amino-acid peptide encoded by a short open reading frame within mitochondrial 12S rRNA. Its discovery expanded the mitochondrial genome from a passive template for respiratory proteins to a source of signalling peptides capable of coordinating cellular and organismal metabolism.	[1]
IMolecular identity	Mitochondrial coding and identity · claim 2	Endogenous peptide measured in plasma or tissue and an administered synthetic preparation are not the same experiment. Correlation with disease, age or exercise can establish physiological association without establishing the pharmacokinetics or efficacy of exogenous MOTS-c.	[2][3][5]
II/VMechanism and physiological translation	Folate-cycle stress, purines and AMPK · claim 1	The original mechanistic work connected MOTS-c with inhibition of the folate cycle and de novo purine synthesis, accumulation of the AICAR intermediate and activation of AMPK. In mice, treatment improved insulin sensitivity and resisted diet-induced obesity under the studied conditions.	[1]
IVIntegrated in-vivo model	Folate-cycle stress, purines and AMPK · claim 2	AMPK activation is a central energy-stress response, not a universal endpoint of benefit. The direction of a downstream effect depends on cell type, nutrient state, duration and competing growth or repair requirements. Target engagement must therefore be connected to function rather than treated as its substitute.	[1][4][7]
II/VMechanism and physiological translation	Mitochondrial communication · claim 1	Under metabolic stress, MOTS-c translocated to the nucleus in an AMPK-dependent manner and interacted with stress-responsive transcriptional programmes including antioxidant-response-element regulation. This provides a direct molecular route through which a mitochondrial-encoded peptide can change nuclear gene expression.	[4]
IVIntegrated in-vivo model	Mitochondrial communication · claim 2	Nuclear translocation broadens the causal model beyond a circulating metabolic hormone. It also increases the need for context-specific analysis because a transcriptional response can support adaptation in one state while impairing proliferation or repair in another.	[4][7]

LAYER	EXPERIMENTAL FRAME	FINDING AND BOUNDARY	SOURCES
VIHuman exposure or signal	Exercise and muscle biology · claim 1	Animal work found improved physical performance across ages and increased late-life physical capacity in mice. Human components of the same programme reported changes in endogenous muscle and circulating MOTS-c with exercise, supporting a role in exercise physiology but not therapeutic equivalence.	[6]
VIHuman exposure or signal	Exercise and muscle biology · claim 2	A separate human exercise experiment found modality-dependent changes in circulating mitochondrial-derived peptides. Small sample size, assay behaviour and acute timing constrain interpretation. An exercise-responsive endogenous signal does not establish that injection reproduces training adaptation.	[5]
VIHuman exposure or signal	Human observations and the therapeutic gap · claim 1	Human studies have measured circulating MOTS-c in PCOS, insulin-resistance and exercise contexts. Lipid infusion increased circulating values and insulin attenuated that response in a small metabolic experiment. These data illuminate regulation of the endogenous peptide.	[2]
VIHuman exposure or signal	Human observations and the therapeutic gap · claim 2	At the evidence cutoff, adequate human PK, immunogenicity, dose-exposure modelling and controlled efficacy data for native exogenous MOTS-c were not established. This is the principal translation gap and cannot be filled by animal performance or human association studies.	[1][2][5][6]
VIHuman exposure or signal	Mechanistic counterevidence · claim 1	Recent work in human mesenchymal stromal cells reported AMPK activation alongside reduced proliferation, increased senescence-associated genes and impaired reparative function in the studied models. This is valuable counterevidence: metabolic target engagement did not guarantee cellular repair.	[7]
IVIntegrated in-vivo model	Mechanistic counterevidence · claim 2	The finding does not globally invalidate MOTS-c. It demonstrates that cell state and desired outcome matter. A programme aimed at metabolic flexibility cannot assume identical effects in tissue regeneration, cancer biology or senescent-cell systems.	[7]

SECTION 01

Molecular dossier: the entity before the outcome

ENTITY — 16-residue mitochondrial-derived peptide encoded within 12S rRNA

BIOCHEMICAL CLASS — Mitonuclear metabolic signalling peptide

PRIMARY SYSTEM — Folate/purine stress · AICAR · AMPK · nuclear stress-response programmes

IDENTITY BOUNDARY — Endogenous MOTS-c concentration, genotype and synthetic exogenous administration are different scientific objects. Association studies cannot supply administered-product PK.

SECTION 02

Historical and international corpus

MOTS-c was identified in 2015. It is genuinely recent, although it belongs to the older fields of mitochondrial genetics, purine metabolism and AMPK signalling.

Its youth should not diminish the chemical coherence of the AICAR-AMPK-nuclear-response chain, and its mechanistic elegance should not invent exogenous human pharmacology.

SECTION 03

2015: A new mitochondrial coding proposition

Identification of a 16-residue peptide encoded within mitochondrial 12S rRNA changed the scientific object: mitochondrial sequence could contribute a regulatory peptide rather than only canonical respiratory proteins and RNAs.[1]

SECTION 04

2018 onward: Mitonuclear signalling and human association diverge

Nuclear translocation, stress-responsive transcription, exercise-associated circulation and genotype studies expanded the mechanism. None measures the PK of a synthetic injected preparation.[2][3][4][5][6]

SECTION 05

Mechanistic calculus — CONSTRAINED: Endogenous and administered MOTS-c are different variables

Endogenous production, circulating measurement, mitochondrial genotype and exogenous dose have different source terms. They cannot be substituted in a causal model.[1][2][3]

SECTION 06

Mechanistic calculus — MEASURED: Purine stress provides a coherent biochemical bridge

Perturbation of folate and de-novo-purine metabolism, AICAR accumulation and AMPK activation connect peptide exposure to an energy-stress response through measurable intermediates.[1][4]

SECTION 07

Mechanistic calculus — MEASURED: Mechanistic sign depends on the tissue objective

A recent stromal-cell system showed metabolic signalling alongside impaired reparative behaviour. This directly falsifies the idea that AMPK engagement or a mitochondrial origin is inherently regenerative.[7]

SECTION 08

Causal architecture: Mitochondrial coding is the first distinction

MOTS-c originates from a short open reading frame within mitochondrial 12S rRNA. This identity situates the peptide within mitonuclear communication, not merely among circulating metabolic hormones.[1]

SECTION 09

Causal architecture: Purine stress connects to AMPK

Experimental work links MOTS-c to folate-cycle and de-novo-purine perturbation, accumulation of the AICAR intermediate and AMPK activation. This creates a chemically coherent path from peptide exposure to cellular energy-stress signalling.[1][4]

SECTION 10

Causal architecture: Nuclear translocation changes the causal scale

Under metabolic stress, MOTS-c can enter the nucleus and interact with stress-responsive transcriptional programmes. A transcriptional effect can coordinate adaptation, yet its direction depends on cell state, proliferative demand and duration.[4][7]

SECTION 11

Causal architecture: Metabolic signalling is not synonymous with repair

Recent stromal-cell work couples AMPK movement with reduced proliferation and impaired reparative behaviour in the studied setting. This counterexample demonstrates that a valid mechanism can produce an undesirable outcome for a different biological objective.[7]

SECTION 12

Molecular identity and entity resolution

MOTS-c is a 16-amino-acid peptide encoded within mitochondrial 12S rRNA. Endogenous MOTS-c and an administered preparation are related scientific questions, not interchangeable evidence.

SECTION 13

Biochemical mechanism and target architecture

Experimental work connects MOTS-c with folate-cycle stress, de novo purine synthesis, AMPK activation, glucose utilisation and mitochondrial-to-nuclear signalling.

SECTION 14

In-vivo pharmacology and exposure

Exogenous administration improves selected metabolic and performance outcomes in animal models. Human pharmacokinetics, immunogenicity and target-engagement after administration remain insufficiently characterised.

SECTION 15

Integrated physiology and individual terrain

MOTS-c biology connects mitochondrial stress sensing with cytosolic purine metabolism, AMPK and nuclear adaptation. The sign of that response depends on energy state, tissue, age and proliferative demand: an energy-conservation programme may improve metabolic resilience yet constrain growth or repair in another compartment. Endogenous concentration and injected exposure are separate physiological questions.

SECTION 16

Terminal human stress-test

Human studies associate circulating MOTS-c with metabolic status, PCOS, insulin resistance, muscle biology and exercise. These observations illuminate endogenous physiology but do not establish therapeutic efficacy.

SECTION 17

Counterevidence and causal boundaries

At the evidence cutoff, no adequate randomised human efficacy trial of native exogenous MOTS-c was identified. Association and exercise response cannot substitute for administered-product exposure.

SECTION 18

Scientific conclusion

MOTS-c has a strong mechanistic research programme and incomplete clinical translation. A credible human programme should resolve PK, immunogenicity and target engagement before broad energy or performance outcomes.

SECTION 19

Mitochondrial coding and identity

MOTS-c is a 16-amino-acid peptide encoded by a short open reading frame within mitochondrial 12S rRNA. Its discovery expanded the mitochondrial genome from a passive template for respiratory proteins to a source of signalling peptides capable of coordinating cellular and organismal metabolism.[1]

Endogenous peptide measured in plasma or tissue and an administered synthetic preparation are not the same experiment. Correlation with disease, age or exercise can establish physiological association without establishing the pharmacokinetics or efficacy of exogenous MOTS-c.[2][3][5]

SECTION 20

Folate-cycle stress, purines and AMPK

The original mechanistic work connected MOTS-c with inhibition of the folate cycle and de novo purine synthesis, accumulation of the AICAR intermediate and activation of AMPK. In mice, treatment improved insulin sensitivity and resisted diet-induced obesity under the studied conditions.[1]

AMPK activation is a central energy-stress response, not a universal endpoint of benefit. The direction of a downstream effect depends on cell type, nutrient state, duration and competing growth or repair requirements. Target engagement must therefore be connected to function rather than treated as its substitute.[1][4][7]

SECTION 21

Mitonuclear communication

Under metabolic stress, MOTS-c translocated to the nucleus in an AMPK-dependent manner and interacted with stress-responsive transcriptional programmes including antioxidant-response-element regulation. This provides a direct molecular route through which a mitochondrial-encoded peptide can change nuclear gene expression.[4]

Nuclear translocation broadens the causal model beyond a circulating metabolic hormone. It also increases the need for context-specific analysis because a transcriptional response can support adaptation in one state while impairing proliferation or repair in another.[4][7]

SECTION 22

Exercise and muscle biology

Animal work found improved physical performance across ages and increased late-life physical capacity in mice. Human components of the same programme reported changes in endogenous muscle and circulating MOTS-c with exercise, supporting a role in exercise physiology but not therapeutic equivalence.[6]

A separate human exercise experiment found modality-dependent changes in circulating mitochondrial-derived peptides. Small sample size, assay behaviour and acute timing constrain interpretation. An exercise-responsive endogenous signal does not establish that injection reproduces training adaptation.[5]

SECTION 23

Human observations and the therapeutic gap

Human studies have measured circulating MOTS-c in PCOS, insulin-resistance and exercise contexts. Lipid infusion increased circulating values and insulin attenuated that response in a small metabolic experiment. These data illuminate regulation of the endogenous peptide.[2]

At the evidence cutoff, adequate human PK, immunogenicity, dose-exposure modelling and controlled efficacy data for native exogenous MOTS-c were not established. This is the principal translation gap and cannot be filled by animal performance or human association studies.[1][2][5][6]

SECTION 24

Mechanistic counterevidence

Recent work in human mesenchymal stromal cells reported AMPK activation alongside reduced proliferation, increased senescence-associated genes and impaired reparative function in the studied models. This is valuable counterevidence: metabolic target engagement did not guarantee cellular repair.[7]

The finding does not globally invalidate MOTS-c. It demonstrates that cell state and desired outcome matter. A programme aimed at metabolic flexibility cannot assume identical effects in tissue regeneration, cancer biology or senescent-cell systems.[7]

SECTION 25

Falsification map

Failure of authenticated peptide to reproduce purine/AMPK signatures would weaken the core mechanism.

Absence of human exposure or target engagement after administration would block therapeutic translation.

Impaired repair or increased senescence markers would falsify a generic regeneration claim even if metabolic signalling occurs.

RESEARCH AGENDA

What would materially change the conclusion?

01 First-in-human exogenous PK and immunogenicity

02 Validated assays distinguishing endogenous from administered peptide

03 Human target-engagement biomarkers

04 Context-specific effects on senescence and repair

05 Controlled metabolic and functional outcomes

06 Sequence-variant effects across mitochondrial haplogroups

CITED PRIMARY EVIDENCE CORPUS

7 source records

This corpus documents the claims made in this monograph; it is not presented as an exhaustive systematic-review search.

Lee et al. Cell Metab. 2015;21:443-454. · PMID 25738459

Kumagai et al. Am J Physiol Endocrinol Metab. 2021. · PMID 33554779

Ramanjaneya et al. Clin Endocrinol. 2019;91:278-287. · PMID 31066084

Kim et al. MOTS-c translocates to the nucleus to regulate nuclear gene expression under metabolic stress. Cell Metab. 2018. · PMID 29983246

D'Souza et al. Acute endurance exercise stimulates circulating mitochondrial-derived peptides in humans. *J Appl Physiol.* 2021. · PMID 34351816

MOTS-c activates metabolic signalling but blunts reparative function in human mesenchymal stromal cells. *Stem Cell Res Ther.* 2026. · PMID 42324588

Reynolds et al. MOTS-c is an exercise-induced regulator of age-dependent physical decline. *Nat Commun.* 2021. · PMID 33473109

AUTHORSHIP AND ACCOUNTABILITY

Valentine Wibowo performed the conceptualisation, evidence synthesis, scientific interpretation and drafting. dr. I Wayan Cahyadi Surya Distira Putra, MPH completed medical review and approved the publication. Internal medical review is not represented as independent journal peer review.

No new patient data or human research were undertaken. The author and reviewer declare no personal financial competing interests. Clinic Terrain and Klinik Pratama Cepat Sehat provide clinical services; that institutional relationship is disclosed.