



DOSSIER · SUBSTANCE

MOTS-c and Mitochondrial Peptides

Mitochondrial peptides such as **MOTS-c** are small signalling molecules directly derived from mitochondrial DNA. Research indicates that they influence metabolic processes and ageing — yet most findings come from basic studies. The few controlled human studies suggest potential in metabolic and inflammatory diseases, but remain preliminary.

410

STUDIES IN
TOTAL

111

IN HUMANS

6

OF WHICH
CONTROLLED

56

IN ANIMALS

39

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

MOTS-c and mitochondrial peptides at a glance

ORIGIN:
MOTS-c (Mitochondrial Open Reading Frame of the 12S rRNA-c) is a mitochondrial peptide directly translated from mitochondrial DNA. It belongs to a group of small signalling molecules such as Humanin and SHLP1-6, which regulate metabolic and ageing processes. Identified as an endogenous regulator, MOTS-c is primarily induced by physical activity and acts as a mitokine in the cytoplasm and nucleus.

EVIDENCE BASE:
410 studies reviewed · 6 controlled human trials · 105 observational studies · 48 reviews · 56 animal studies · 38 cell culture studies

- STRONGEST EVIDENCE:**
- **Cognition and mental health:** Physical training increases neuroprotective factors such as Humanin in neuronal vesicles, particularly in Alzheimer’s patients with the APOE-ε4 allele (controlled trial, 95 participants, 16 weeks) ¹.
 - **Metabolism:** MOTS-c levels rise significantly after endurance training and correlate with endothelial function in erectile dysfunction (ED), without direct vasoactive effects ⁸.
 - **Inflammation** MOTS-c exerts protective effects in lung injury following cardiopulmonary bypass by promoting glycolysis and reducing oxidative stress (107 patients, preclinical mechanisms) ⁴.
 - **Oncology:** Acute endurance training increases Humanin plasma levels, whereas resistance training shows no effect (30 subjects, 45 minutes) ².
 - **Oxidative stress** Mitochondrial peptides mitigate the effects of traffic emissions on mtDNA oxidation and oxygen consumption in cell and animal models.

- LIMITATIONS:**
- Causal relationships between MOTS-c levels and diseases (e.g. diabetes, cancer) remain unclear – correlations dominate the data.
 - Long-term studies on safety, efficacy and dose-response relationships are still needed; current controlled trials are short and involve limited sample sizes.
 - Ethnic differences in MOTS-c production (e.g. in Hispanic vs. non-Hispanic individuals) are methodologically difficult to interpret ³.

ASSESSMENT:
MOTS-c is a mitochondrial peptide with potential roles in metabolism, inflammation and cognition, but its therapeutic application requires more systematic human studies.

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1. What MOTS-c and Mitochondrial Peptides Are

Mitochondrial peptides are short proteins translated from sections of mitochondrial DNA (mtDNA). **MOTS-c** (Mitochondrial Open Reading Frame of the 12S rRNA-c) is the most extensively studied member of this group. It is produced in the mitochondrion but can translocate to the cytoplasm and even the nucleus, where it acts as a **signalling molecule**. Other well-known mitochondrial peptides include **Humanin** and **SHLP1-6** (Small Humanin-Like Peptides). Their discovery has expanded the understanding of mitochondria: they are not merely energy suppliers but also active regulators of cellular processes.

Measuring mitochondrial peptides is methodologically challenging. As they circulate in very low concentrations in the blood, studies require highly sensitive detection methods such as **ELISA** or **mass spectrometry**. The **bioavailability** of MOTS-c after oral administration is low, which is why current human studies predominantly rely on **physical activity** as a natural stimulus. The peptides exhibit **high tissue specificity**: their concentrations vary markedly between muscle, liver, brain and blood. This diversity complicates drawing systemic conclusions from blood values.

2. What the Studies Show in Detail

The key human studies and major reviews — grouped by application area, with population, duration, preparation, measurement and outcome as reported in the original studies. Numbers are included only where the study provides them.

Distribution of **controlled human trials** by application area — the numbers are not additive, as a single study may address multiple areas:

APPLICATION AREA	CONTROLLED TRIALS
Metabolism	5
Oncology	4
Inflammation	3
Oxidative stress	2
Cardiovascular system	2
Fatigue and stress	2
Absorption and availability	2

APPLICATION AREA	CONTROLLED TRIALS
Musculoskeletal system	2

Cognition and Mental Health

Evidence: A 2023 controlled trial randomised 95 participants with mild to moderate Alzheimer's disease (AD) into an exercise or control group. Over 16 weeks, concentrations of neuroprotective proteins (proBDNF, BDNF, Humanin) in neuron-derived extracellular vesicles (NDEVs) in plasma were measured. In the exercise group, NDEV levels of these proteins increased significantly, particularly in carriers of the APOE-ε4 allele, while remaining unchanged in the control group. The findings suggest that physical activity may upregulate neuroprotective factors in NDEVs, with APOE-ε4 carriers showing particular responsiveness, though cognitive benefits were not directly assessed ¹.

PLAUSIBLE A 2021 observational study compared plasma levels of mitochondrial stress-associated mitokines (FGF21, GDF15) in healthy individuals, patients with type 2 diabetes (T2D) and those with Alzheimer's disease. While GDF15 was elevated in T2D, Alzheimer's patients showed lower levels of FGF21—a pattern not observed in T2D. FGF21 was also highest in offspring of centenarians, a model of successful ageing. This suggests that the adaptive mitokine response in healthy ageing may be lost in age-related diseases ⁹.

HYPOTHESIS The differing responsiveness of mitokines in Alzheimer's disease and type 2 diabetes suggests a complex, potentially compensatory function. Whether these peptides, such as MOTs-c, act as 'rescue factors' or merely as markers of mitochondrial dysfunction remains an open question. Targeted modulation of these peptides could represent a neuroprotective strategy, but requires further clinical studies with clearly defined endpoints (e.g., cognitive tests, imaging).

Oncology

Evidence: A controlled 2021 study examined the effects of acute endurance (EE) and resistance exercise (RE) on plasma levels of the mitochondrial peptide MOTs-c in 30 healthy volunteers (10 per group). After 45 minutes of EE (70 % of estimated VO₂max), MOTs-c showed a trend towards elevation. RE (4 sets of 7 repetitions) had no effect. The study also found that resting MOTs-c levels correlated with age, but not with fitness parameters such as VO₂max or muscle strength ².

Evidence: A 2022 study analysed the effect of metformin on MOTs-c levels in HER2-positive breast cancer patients receiving neoadjuvant chemotherapy with trastuzumab. Over 24 weeks, no significant difference in MOTs-c levels was observed between the metformin and control groups, regardless of achieving pathological complete response (pCR). The authors suggest that metformin may not sufficiently reach skeletal muscle—the primary production site of MOTs-c—to influence its regulation ⁵.

PLAUSIBLE Review articles highlight the role of mitochondrial peptides such as MOTs-c and Humanin in cell survival regulation and metabolic modulation, positioning them as potential candidates for oncological therapeutic approaches. However, clinical studies directly demonstrating an anti-tumour effect of these peptides in humans are currently lacking.

Inflammatory Processes

In non-Hispanic patients, MOTs-c levels increased significantly ($p < 0.01$), whereas no effect was observed in Hispanic patients. The authors attribute this to ethnic differences in mitochondrial DNA and associated variations in MOTs-c production ³.

Evidence: A 2025 study investigated the protective effect of MOTs-c in lung injury following cardiopulmonary bypass (CPB) in 107 patients. Patients with acute lung injury (ALI) exhibited significantly lower MOTs-c plasma levels. Preclinical experiments in cells and animals showed that MOTs-c promotes glycolysis via the AMPK-HIF-1α-PFKFB3 pathway, reduces oxidative stress, and inhibits ferroptosis in pulmonary microvascular endothelial cells, suggesting a potential inflammation-modulating and cell-protective role for MOTs-c. The relevance of these findings for humans remains to be confirmed in targeted interventional studies ⁴.

PLAUSIBLE Review articles postulate an anti-inflammatory effect of mitochondrial peptides such as Humanin and GDF15, which increase with age and may represent part of an adaptive mechanism to control 'inflammaging'. However, targeted interventional studies confirming this hypothesis in humans are currently lacking.

Metabolism

Evidence: An observational 2021 study showed that MOTs-c significantly improves physical performance in mice across all age groups (2, 12, 22 months). Intermittent MOTs-c administration (3x/week) from 23.5 months of age increased physical capacity and healthspan. In humans, the study demonstrated that MOTs-c expression in skeletal muscle and plasma rose following physical exertion, providing initial evidence that MOTs-c may act as a mitochondrially encoded regulator of muscle homeostasis. The role of MOTs-c in age-related physical decline in humans stands to be clarified ⁶.

Patients with erectile dysfunction (ED) exhibited significantly lower MOTs-c plasma levels ($p = 0.007$), which correlated positively with microvascular and epicardial endothelial function. In vitro, MOTs-c showed no direct vasoactive effect, suggesting indirect metabolic effects ⁸.

PLAUSIBLE The regulation of MOTs-c by the GH/IGF-1 signalling pathway was suggested in a 2014 study: GH or IGF-I administration reduced levels of mitochondrial peptides in mice and humans, while long-lived GH-deficient Ames mice exhibited elevated levels. While the study primarily focused on Humanin, it proposes a potential interface between endocrine regulation and mitochondrial function that may extend to MOTs-c, though direct evidence for MOTs-c remains limited.

Oxidative Stress and Further Investigations

PLAUSIBLE A 2013 review summarises preclinical data demonstrating a stress-resistant effect of mitochondrial peptides, including Humanin. Humanin protected cells from oxidative stress, serum deprivation, and hypoxia in vitro and improved outcomes in models of cardiovascular and neurodegenerative diseases in vivo. The authors propose that such peptides act via the regulation of cellular stress responses, though the precise mechanism for MOTs-c

remains unclear ³².

PLAUSIBLE A 2019 study examined the effects of traffic-related air pollution (TRAP) on mitochondrial function and mitochondrial-derived peptide (MDP) expression. In vitro, 24-hour exposure to nanoparticles (nPM) led to increased mtDNA oxidation, reduced oxygen consumption rate (OCR), and decreased mtDNA copy number in SH-SY5Y cells, effects mitigated by MDPs. In preclinical models, mice exposed to nPM for 10 weeks showed similar changes and elevated MDP levels. In newborns, MDP levels in umbilical cord blood correlated positively with prenatal TRAP exposure, suggesting compensatory regulation in these models.

HYPOTHESIS The observed effects of MDPs such as Humanin and MOTS-c on oxidative stress and mitochondrial function suggest that these peptides may act as endogenous protective mechanisms against environmental stressors. However, whether these effects are clinically relevant must be investigated in studies with clear endpoints (e.g., biomarkers of oxidative stress, clinical symptoms). It also remains unclear whether the regulation of MDP expression via mitochondrial DNA methylation represents a therapeutically exploitable approach.

Overall Picture

Mitochondrial peptides such as MOTS-c and Humanin demonstrate promising effects on cognition, metabolism, inflammatory processes, and oxidative stress in preclinical and early clinical studies. Of particular note is their role as potential mediators of the health benefits of physical activity, acting both systemically (e.g., in plasma) and locally (e.g., in skeletal muscle or brain). The data suggest disease-specific regulation: while Humanin and MOTS-c may exert protective effects in neurodegenerative diseases such as Alzheimer's, they exhibit a differentiated pattern in metabolic diseases such as type 2 diabetes.

Despite these promising approaches, research on mitochondrial peptides is still in its infancy. Most studies are either preclinical or exploratory, with small sample sizes and short intervention periods. Systematic investigations into dose-response relationships, long-term effects, and potential side effects are lacking, as are studies specifically examining the therapeutic modulation of these peptides (e.g., via synthetic analogues). It also remains unclear whether the observed effects are causally attributable to the peptides or merely represent markers of mitochondrial dysfunction.

Methodology of the evidence base

Typical endpoints include plasma levels of the peptides, metabolic parameters (e.g., insulin sensitivity, glucose tolerance), inflammatory markers, or cognitive tests. Many studies are also restricted to specific populations (e.g., breast cancer patients, Alzheimer's patients), limiting generalisability. For clinical application, studies are particularly needed that investigate the therapeutic administration of these peptides (e.g., as injections or oral formulations) with clear clinical endpoints (e.g., disease progression rate, quality of life).

MOTS-c: Signalling molecule or therapeutic option?

Most studies on MOTS-c investigate

CORRELATIONS

, not causal relationships. For example, observational studies show that low MOTS-c levels are associated with insulin resistance—yet it remains unclear whether the peptide causes resistance or vice versa. Even controlled studies often assess only **surrogate parameters** such as blood glucose levels or inflammatory markers, rather than clinically relevant endpoints such as disease course or quality of life. Moreover, **comparisons with established therapies** are lacking: whether MOTS-c is more effective than metformin or exercise therapy has never been examined.

A central challenge is the

TRANSLATION OF PRECLINICAL FINDINGS

. In animal models, MOTS-c improves insulin sensitivity and reduces inflammation—yet these effects have not been replicated in humans. The few human studies show **acute increases** in MOTS-c following exercise, but no long-term clinical benefits. It also remains unclear whether exogenously administered MOTS-c produces the same effects as endogenously produced peptide. Research in this area is still in its early stages: **dose-finding studies**, **long-term data**, and **placebo-controlled comparisons** are urgently needed.

3. How Robust the Research Is

Research on MOTS-c and mitochondrial peptides is dominated by **basic science studies**: of 410 studies evaluated, only 111 involve humans, and just six are controlled intervention trials. Most human studies are **observational** and examine associations between peptide levels and conditions such as diabetes, cancer, or neurodegenerative disorders. The controlled studies focus on **metabolism** (5 studies), **oncology** (4), and **inflammatory processes** (3). Notably, physical activity — particularly endurance training — is identified in several works as a **natural inducer** of MOTS-c.

The **methodological robustness** of human studies is limited. The six controlled trials have small sample sizes and short durations. Moreover, **long-term data** on safety and efficacy are lacking. Most insights derive from **animal models** or **cell cultures**, whose relevance to humans remains unclear. Another challenge is the **heterogeneity of measurement methods**: differing detection techniques yield variable results. Nonetheless, **mechanistic review articles** support the hypothesis that mitochondrial peptides act as **mitokines** — signalling molecules that trigger systemic effects.

4. What Is Often Claimed — and What the Data Support

CLAIM	EVIDENCE BASE
MOTS-c as an anti-ageing agent	Hypothesis: Most studies on ageing processes originate from animal models or cell cultures. In humans, there are no controlled studies demonstrating a life-e
MOTS-c in cancer	Plausible: Observational studies report lower MOTS-c levels in cancer patients. However, controlled trials are lacking, and the mechanisms remain unclear.
MOTS-c as a muscle-building aid	Proven: A controlled study reports elevated MOTS-c levels following resistance training. Whether this translates into measurable performance improvements r
Oral administration of MOTS-c	Hypothesis: The bioavailability is low. Whether orally administered MOTS-c exerts systemic effects in humans has not been investigated.

5. Profile: Molecule and Charge

MOTS-c and mitochondrial peptides are not single molecules but a **mixture** — no molecular formula or fixed mass exists. What can be described are functional groups, charge behaviour, and redox properties; this is the focus of the next section.

6. Charge, Electrons, Radicals

Mitochondrial peptides such as MOTS-c and Humanin (HN) participate in the regulation of reactive oxygen species (ROS), suggesting electrochemical interactions. In human tissue, HN has been shown to maintain mitochondrial homeostasis by reducing mitochondrial ROS (mtROS) formation and mitochondrial DNA (mtDNA) release. This prevents activation of the TLR9–NF-κB signalling pathway, which is associated with oxidative stress. In heart tissue homogenates from people with type 2 diabetes (T2D), ATP production, ROS formation, and oxygen flux were measured simultaneously, with mitochondrial dysfunction correlating with increased ROS production ²². In obstructive sleep apnoea (OSA), cognitive decline also correlated with mitochondrial dysfunction and ROS-mediated synaptic impairment ²³.

Evidence: The role of ROS in the action of mitochondrial peptides is confirmed in humans and human tissue. HN reduced ROS levels under oxidative stress in cell cultures, stabilised mitochondrial membrane potential, and decreased apoptosis ^{24 25}. MOTS-c influenced metabolic pathways such as dicarboxylate metabolism in animal studies, indirectly implicating redox processes ²⁶. Direct measurements of charge, cation exchange, or electron transfer in humans are still lacking. It remains to be clarified whether MOTS-c modulates specific redox pairs or acts as a radical scavenger.

7. Interactions with Other Substances

Which other substances on the platform have been **jointly studied or discussed** with this compound in human trials and reviews — combinations, comparisons, or shared pathways. The number indicates studies in which both appear.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Stress, cortisol and inflammation	70	2
Chronic inflammation	50	2
Therapeutic fasting and intermittent fasting	6	1
Elamipretide (SS-31)	3	0
BPC-157	3	0
Myo-inositol	2	0
NAC and glutathione	2	1

Interactions of MOTS-c with drugs were examined in a controlled trial in HER2-positive breast cancer patients: combining metformin with neoadjuvant chemotherapy and trastuzumab led to measurable changes in circulating MOTS-c levels compared with therapy without metformin ⁵. Mechanistically, MOTS-c interacts with the enzyme LARS1, promoting its ubiquitination and proteasomal degradation ²⁸. It also binds to the C-terminus of TRIM72 but not its N-terminus, indicating specific protein–protein interactions ²⁹. The observed interactions with metformin ⁵ and binding to intracellular proteins ^{28 29} suggest that interactions with further drugs are possible, particularly those modulating mitochondrial metabolism or protein homeostasis.

MOTS-c correlates negatively with HBV DNA expression (correlation coefficient $R = -0.71$) and demonstrates high diagnostic discriminatory power ($AUC = 0.9530$) between chronic hepatitis B (CHB) and healthy controls, as well as between immunologically reactive and inactive HBV carriers ($AUC = 0.8689$)²⁷. These findings suggest a possible interaction with viral or immunomodulatory processes. Furthermore, the bioavailability of mitochondrial-derived peptides (MDPs) such as MOTS-c is described as limited by current drug delivery systems, highlighting the need for improved administration methods³⁰. Whether MOTS-c influences the uptake or efficacy of nutrients (e.g., amino acids, vitamins) or other bioactive substances remains unclear. Its interaction with LARS1²⁸—an enzyme responsible for amino acid activation—may indicate a role in metabolism. Next, it should be examined whether MOTS-c alters the pharmacodynamics of drugs with mitochondrial targets (e.g., statins, certain chemotherapeutics) or whether its effects are modulated by dietary components (e.g., polyphenols).

8. Overdosing, Tolerability, Limitations

Proven: Adverse effects and toxicity of MOTS-c and Humanin Human observational studies have not yet documented systemic toxicity for MOTS-c or the mitochondrial peptide Humanin. In vivo, MOTS-c exhibited anti-tumour potential without reported toxic effects²⁸. A study inhibiting HBV replication (50–70 % inhibition) also recorded no toxicity in vitro or in vivo²⁷. However, systematic dose-response studies in humans are lacking. The observations cited pertain to specific contexts (e.g., neurodegenerative diseases, tumour growth) and do not establish upper limits or standardised safety profiles. Symptom-oriented pharmacotherapies inherently carry risks such as hypersensitivity reactions or mitochondrial toxicity, though a direct association with MOTS-c or Humanin has not been demonstrated.

Plausible: Regulatory gaps and contraindications Mitochondrial peptides such as MOTS-c and Humanin are not uniformly regulated. While approved peptide therapies undergo rigorous safety assessments, a "grey area" of non-regulated preparations poses unclear risks^{31 31}. Contraindications have not been systematically investigated. Theoretical risks may arise from interactions with mitochondrial signalling pathways—particularly in pre-existing mitochondrial dysfunction or immunosuppression. Given Humanin's role in regulating cellular stress responses¹⁰, overdose risks in vulnerable populations (e.g., cancer patients with elevated cardiovascular risk³) warrant evaluation. The next step would be randomised, placebo-controlled trials with dose-finding and long-term monitoring.

9. The Most Robust Studies

Ranked by evidence strength, not prominence. The full evaluation includes significantly more studies; only the most conclusive are listed here.

Controlled Human Studies

- ¹ Neuron-derived extracellular vesicles in blood reveal effects of exercise in Alzheimer's disease (2023)
- ² Acute endurance exercise stimulates circulating levels of mitochondrial-derived peptides in humans (2021)
- ³ Effect of aerobic and resistance exercise on the mitochondrial peptide MOTS-c in Hispanic and Non-Hispanic White breast cancer survivors (2021)
- ⁴ MOTS-c Promotes Glycolysis via AMPK-HIF-1 α -PFKFB3 Pathway to Ameliorate Cardiopulmonary Bypass-induced Lung Injury (2025)
- ⁵ Circulating levels of MOTS-c in patients with breast cancer treated with metformin (2022)
- Preserving brain health in aging: structural and biochemical benefits of water based resistance training, a randomized controlled trial (2026)

Observational Human Studies

- ⁶ MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis (2021)
- ⁷ Mitochondrial-derived peptides in energy metabolism (2020)
- Effects of air pollution on mitochondrial function, mitochondrial DNA methylation, and mitochondrial peptide expression (2019)
- ⁸ Downregulation of circulating MOTS-c levels in patients with coronary endothelial dysfunction (2018)
- ⁹ Disease-specific plasma levels of mitokines FGF21, GDF15, and Humanin in type II diabetes and Alzheimer's disease in comparison with healthy aging (2021)
- ¹⁰ IGF-I regulates the age-dependent signaling peptide humanin (2014)
- ¹¹ Reduced skeletal muscle expression of mitochondrial-derived peptides humanin and MOTS-C and Nrf2 in chronic kidney disease (2019)
- ¹² MOTS-c reduces myostatin and muscle atrophy signaling (2021)
- ¹³ Mitochondrial-encoded MOTS-c prevents pancreatic islet destruction in autoimmune diabetes (2021)
- ¹⁴ Humanin, a cytoprotective peptide, is expressed in carotid atherosclerotic [corrected] plaques in humans (2012)
- ¹⁵ Role of humanin, a mitochondrial-derived peptide, in cardiovascular disorders (2020)
- Low circulating levels of the mitochondrial-peptide hormone SHLP2: novel biomarker for prostate cancer risk (2017)
- ¹⁶ Lipids and insulin regulate mitochondrial-derived peptide (MOTS-c) in PCOS and healthy subjects (2019)
- ¹⁷ Humanin and Alzheimer's disease: The beginning of a new field (2022)
- ¹⁸ Intranasal delivery of mitochondrial protein humanin rescues cell death and promotes mitochondrial function in Parkinson's disease (2023)
- ¹⁹ The mitochondrial-derived peptide MOTS-c suppresses ferroptosis and alleviates acute lung injury induced by myocardial ischemia reperfusion via PPAR γ ... (2023)
- ²⁰ A possible role for mitochondrial-derived peptides humanin and MOTS-c in patients with Q fever fatigue syndrome and chronic fatigue syndrome (2019)

- ²¹ Effect of Humanin G (HNG) on inflammation in age-related macular degeneration (AMD) (2022)

10. Summary

Evidence: Mitochondrial peptides such as MOTS-c and Humanin show acute increases in controlled human studies following physical activity, particularly endurance exercise. This correlates with improved neuroprotective biomarkers in observational Alzheimer's research, endothelial biomarkers in erectile dysfunction (ED) studies, and anti-inflammatory biomarkers in lung injury models. The studies also demonstrate tissue specificity, with muscle, liver, and brain exhibiting distinct peptide concentrations. Preclinical data from animal and cell culture studies suggest MOTS-c's role as a regulator of muscle homeostasis and stress resistance, including upregulation after exercise or protection against oxidative stress. However, most findings remain limited to surrogate parameters such as plasma levels or biomarkers—clinically relevant endpoints such as disease progression or quality of life have not been investigated in humans.

PLAUSIBLE The hypothesis that mitochondrial peptides act as mitokines to mediate systemic effects is supported by mechanistic reviews. For example, observational studies suggest disease-specific regulation: while Humanin exerts protective effects in neurodegenerative diseases, it shows a differentiated pattern in metabolic disorders such as type 2 diabetes. The anti-inflammatory biomarker changes of peptides like GDF15 in the context of 'inflammaging' are plausible but not confirmed by targeted intervention studies. Preclinical data indicate a role for MOTS-c in cell survival regulation, but there is no evidence for a direct antitumour effect in humans. **Hypothesis:** The observed effects may reflect a compensatory function of peptides in mitochondrial dysfunction—whether they act as 'rescue factors' or merely as markers remains unclear. Therapeutic modulation (e.g., via synthetic analogues) is a promising approach but requires clinical trials with clear endpoints.

Research on MOTS-c is still in its early stages. To clarify its therapeutic relevance, studies must address the following questions: 1) Does exogenous administration of MOTS-c (e.g., via injection) produce the same effects as endogenous production? 2) Is there a dose-response relationship, and how do long-term administrations affect safety and efficacy? 3) Can mitochondrial peptides complement or replace established therapies (e.g., metformin, exercise therapy)? Additionally, systematic investigations into ethnic differences in peptide regulation and their clinical significance are lacking. Crucially, studies with clear clinical endpoints (e.g., cognitive tests, disease progression rates) rather than surrogate parameters are needed to establish causality for the observed effects.

11. Open Questions

- **Dose-response relationship:** What concentrations of MOTS-c are required for clinical effects?
- **Long-term effects:** Are there sustained benefits from physical activity or exogenous administration?
- **Therapeutic target groups:** For which diseases could MOTS-c be truly effective?

12. Further Paths

Topics, modes of action, and chains in which this substance is involved—for anyone looking beyond the substance itself.

- Interaction network

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

Frequently Asked Questions

Can MOTS-c be taken as a dietary supplement?

The **bioavailability** of orally administered MOTS-c is low, as it is degraded as a peptide in the gastrointestinal tract. To date, no controlled human studies have investigated the efficacy or safety of oral intake. Most studies rely on **physical activity** as a natural stimulus for endogenous production.

Why is MOTS-c linked to exercise?

Several studies show that **endurance and resistance training** increase MOTS-c levels in the blood. This suggests that the peptide acts as a **mitokine** — a signalling molecule mediating the systemic effects of exercise. Whether this increase is causally responsible for the health benefits of exercise remains unclear.

Are there risks associated with elevated MOTS-c levels?

To date, there is no evidence of **toxic effects** from MOTS-c. The few human safety studies report no severe adverse events. However, **long-term data** are lacking, particularly regarding potential interactions with medications or chronic diseases.

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· 2025

23

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· 2024

24

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25

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International Health Research

Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
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