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PATH TO PEPTIDES

MITOCHONDRIAL PEPTIDES:

THE NEXT FRONTIER IN ANTI-AGING

An Educational Overview of Humanin, MOTS-c, and Elamipretide Research

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INTRODUCTION

Inside nearly every cell in your body are tiny structures called mitochondria. Think of them as cellular power plants — they convert food and oxygen into the energy your cells need to function. As we age, our mitochondria become less efficient, producing less energy and more waste products called reactive oxygen species (free radicals). This decline is now considered a central driver of aging itself.1

What makes mitochondria unique is that they have their own DNA — separate from the DNA in the cell nucleus. Researchers have discovered that mitochondrial DNA encodes several small peptides that appear to protect cells, improve metabolism, and slow aspects of aging. These "mitochondrial-derived peptides" (MDPs) are among the most exciting developments in anti-aging science.2

HUMANIN: THE SURVIVAL SIGNAL

Humanin was discovered in 2001 by Japanese researchers who found it in brain tissue that was resistant to Alzheimer's disease. It is a 24-amino-acid peptide encoded by mitochondrial DNA, and it appears to act as a cellular stress signal — essentially telling cells "do not die yet."3

Research published in Science Translational Medicine shows that humanin levels naturally decline with age, dropping by approximately 40% between ages 20 and 80. People with higher humanin levels tend to live longer, have better cardiovascular health, and show lower rates of age-related cognitive decline. Animal studies show that humanin supplementation improves insulin sensitivity, reduces inflammation, protects against atherosclerosis, and preserves cognitive function in Alzheimer's disease models.4,5

MOTS-C: THE EXERCISE MIMETIC

MOTS-c (Mitochondrial Open Reading Frame of the 12S rRNA-c) is a 16-amino-acid peptide discovered in 2015 by researchers at the University of Southern California. What makes MOTS-c remarkable is that it appears to mimic some of the metabolic benefits of exercise.6

A study published in Cell Metabolism showed that MOTS-c activates AMPK — the same metabolic sensor that exercise turns on. In aged mice (equivalent to roughly 65-year-old humans), MOTS-c injections improved physical performance, enhanced insulin sensitivity, and reduced obesity even without changes in diet or activity. MOTS-c levels decline with age but increase with exercise, suggesting it may be one of the molecular messengers that explains why exercise is so beneficial for aging.7

The Big Picture: MOTS-c does not replace exercise — nothing does. But it may eventually help explain why exercise works at the molecular level and could potentially help people who are unable to exercise due to injury, illness, or disability to still receive some metabolic benefits.

ELAMIPRETIDE: FROM LAB TO CLINICAL TRIALS

Elamipretide (also known as SS-31, MTP-131, or Bendavia) is a synthetic 4-amino-acid peptide designed to target the inner mitochondrial membrane. Unlike humanin and MOTS-c, which are naturally encoded, elamipretide was engineered specifically to stabilize cardiolipin — a specialized fat molecule that is essential for mitochondrial energy production.8

Elamipretide is the furthest along in clinical development. Stealth BioTherapeutics has conducted multiple Phase 2 and Phase 3 clinical trials for conditions including heart failure, Barth syndrome (a rare mitochondrial disease), and age-related macular degeneration. In 2023, elamipretide received FDA Orphan Drug Designation for Barth syndrome. While not all trials met their primary endpoints, the cardiac data has shown improvements in heart muscle function and exercise capacity.9,10

THE BIGGER PICTURE: MITOCHONDRIA AND AGING

MDP	Size	Key Function	Clinical Status
Humanin	24 amino acids	Cell survival signaling	Preclinical
MOTS-c	16 amino acids	Metabolic regulation	Preclinical
Elamipretide	4 amino acids	Mitochondrial membrane stabilization	Phase 2/3 trials
SHLP1-6	24-38 amino acids	Various cytoprotective	Early preclinical

The discovery of mitochondrial-derived peptides has reframed how scientists think about aging. Rather than viewing mitochondrial decline as an inevitable consequence of getting older, researchers now see it as a potentially modifiable process. If these peptides can be supplemented or their production enhanced, some aspects of cellular aging might be slowed or even partially reversed.11

CONCLUSION

Mitochondrial peptides represent a genuine frontier in aging research. Humanin's role in cell survival, MOTS-c's exercise-mimicking properties, and elamipretide's progress through clinical trials all point to a future where maintaining mitochondrial function could be a central strategy in healthy aging.

However, this field is still young. Most evidence is preclinical, and the path from promising animal data to approved human therapies is long and uncertain. What is not uncertain is that our cellular power plants play a far more important role in health and aging than we understood even a decade ago.

REFERENCES

1. Lopez-Otin C, et al. Hallmarks of aging: An expanding universe. Cell. 2023;186(2):243-278.
2. Kim SJ, et al. Mitochondrial-derived peptides in aging and age-related diseases. GeroScience. 2021;43:1113-1121.
3. Hashimoto Y, et al. A rescue factor abolishing neuronal cell death by a wide spectrum of familial Alzheimer's disease genes and
A-beta. PNAS. 2001;98(11):6336-6341.
4. Cobb LJ, et al. Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis. J Am Heart Assoc.
2016;5(10):e003646.
5. Muzumdar RH, et al. Humanin: a novel central regulator of peripheral insulin action. PLoS One. 2009;4(7):e6334.
6. Lee C, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metabolism. 2015;21(3):443-454.
7. Reynolds JC, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline. Nature
Communications. 2021;12:470.
8. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. Br J Pharmacol. 2014;171(8):2029-2050.
9. Stealth BioTherapeutics. Elamipretide Clinical Development Pipeline. 2025.
10. FDA. Orphan Drug Designation for Elamipretide (Barth Syndrome). 2023.
11. Merry TL, et al. Mitochondrial-derived peptides in energy metabolism. Molecular Metabolism. 2020;32:1-14.

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