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Mini Review

Short-Peptides May be the Key to Long Life

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Abstract

Harnessing the bioactive components of peptides is playing an increasingly important role in biotechnological applications. Unlike the larger polypeptide counterparts (i.e. proteins), bioactive peptides, are low molecular weight, organic substances formed by amino acids joined by covalent bonds also known as amide or peptide bonds. The bioactivity of the peptide is determined by the amino acid composition and sequence once that they are released from the precursor protein. Emerging research in stem-cell-derived peptides presents a promising avenue for enhancing longevity and combating age-related decline. These peptides, such as Nano-organo Peptides (NOP) and Mito-organo peptides (MOP), have been identified as key regulators of cellular homeostasis, influencing multiple physiological pathways critical to aging and metabolic health. These peptides exert effects across five major domains: mitochondrial function, proteostasis, cellular senescence, immunogenicity, and metabolic regulation. By optimizing mitochondrial function, they enhance cellular energy metabolism and reduce oxidative stress, a major driver of aging. Their role in proteostasis ensures proper protein folding and degradation, preventing the accumulation of misfolded proteins linked to neurodegenerative diseases. Furthermore, these peptides modulate cellular senescence, delaying the accumulation of senescent cells that contribute to chronic inflammation and tissue dysfunction. Importantly, they also influence immunogenicity, fine-tuning immune responses to mitigate excessive inflammation while preserving immune surveillance. Additionally, their impact on metabolic regulation promotes insulin sensitivity, glucose homeostasis, and lipid metabolism, thereby reducing the risk of age-related metabolic disorders such as type 2 diabetes. The integration of stem-cell-derived peptide therapy into longevity interventions holds immense potential for delaying aging, improving metabolic resilience, and preventing degenerative diseases. Future research will focus on optimizing their therapeutic delivery, understanding individual variability in response, and exploring synergies with other longevity-enhancing strategies. This review summarizes some of the therapeutic approaches in the progressing field highlighting how peptide-based interventions may redefine regenerative medicine and aging therapeutics, offering novel solutions for promoting healthy lifespan extension.

Keywords: Peptides, Longevity, Nano-organo Peptides (NOP), Mito-organo peptides (MOP)

Introduction

Harnessing the bioactive components of peptides is playing an increasingly important role in biotechnological applications. Unlike the larger polypeptide counterparts (i.e. proteins), bioactive peptides, are low molecular weight, organic substances formed by amino acids joined by covalent bonds also known as amide or peptide bonds. The bioactivity of the peptide is determined by the amino acid composition and sequence once that they are released from the precursor protein [1]. Commercial interest in bioactive peptides was originally in the food industry where they were shown to prevent oxidation and microbial degradation of food products. Subsequently, significant attention was given to bioactive peptides, often derived from natural sources such as food proteins, for the impact on human health and their use in the prevention of certain diseases [2].

As the recognition of bioactive peptides for their role in modulating physiological functions, including immune response, metabolism, and neuroprotection was enhanced, these peptides were explored for their potential in treating chronic diseases [1,2]. However, therapeutic use was limited by stability, bioavailability, and specificity challenges. Advances in peptide engineering and nanotechnology led to the development of nanopeptides, which are ultra-short peptides designed for improved stability, targeted delivery, and enhanced tissue penetration. Nanopeptides demonstrated superior pharmacokinetics and the ability to cross biological barriers, allowing for more effective intervention in age-related diseases by modulating cellular repair, autophagy, and inflammation. Building upon this foundation, mito-organo peptides (MOP) emerged as the next frontier, specifically engineered to target mitochondria and other organelles to optimize energy metabolism, reduce oxidative stress, and enhance organellar communication. These peptides are designed to restore mitochondrial homeostasis, regulate mitophagy, and counteract organelle dysfunction, addressing key hallmarks of aging at their root cause. The evolution from general bioactive peptides to nanopeptides [3] and mito-organo peptides represents a paradigm shift in peptide-based therapeutics, offering a highly precise and systemic approach to longevity and age-related disease management. As research advances, these specialized peptides hold great promise for extending healthspan and combating degenerative conditions at a cellular and organellar level.

Nanopeptides, short-chain peptides typically under 50 amino acids in length, have emerged as a promising therapeutic approach to longevity due to their ability to regulate key biological processes at the molecular level. Due to their small size, nanopeptides can be designed to specifically interact with specific cellular targets, allowing for precise modulation of biological pathways [3]. These bioactive peptides can modulate cellular signaling pathways involved in aging, including those related to mitochondrial function, autophagy, inflammation, and genomic stability. Some nanopeptides exhibit antioxidant properties, reducing oxidative stress, a major contributor to cellular senescence, while others enhance proteostasis by promoting protein folding and degradation of damaged proteins. Additionally, nanopeptides can act as epigenetic modulators, influencing gene expression to support cellular repair and regeneration. Research is exploring NOP for various longevity-related targets. In aging, NOP have been linked to autophagic regulation, telomere maintenance, epigenetic modifications and mitigation of oxidative stress [4]. Advances in synthetic biology and peptide engineering have further enabled the design of nanopeptides with enhanced stability and specificity for aging-related pathways. As research progresses, nanopeptides hold significant potential for extending healthspan by delaying age-related diseases, improving metabolic resilience, and supporting tissue homeostasis, making them a compelling area of study in the field of longevity therapeutics (Figure 1).

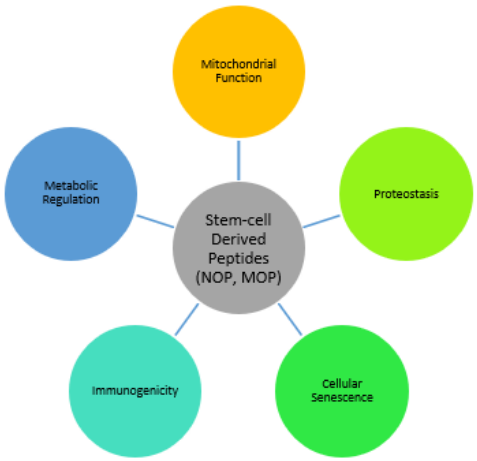

Figure 1: At the center, the green circle represents stem-cell-derived peptides, which influence five key biological processes: Mitochondrial Function Enhances cellular energy production and regulates oxidative metabolism; Proteostasis– Maintains protein homeostasis, ensuring proper protein folding and degradation; Cellular Senescence– Modulates aging-associated pathways and prevents premature cell deterioration. Immunogenicity– Regulates immune response and minimizes immune rejection; Metabolic Regulation– Influences glucose homeostasis and insulin sensitivity for improved metabolic health.

Mito-organelle peptides. Given the inextricable link between mitochondrial dysfunction and the normal aging process, it is not surprising that mitochondrial-derived peptides, essential components of mitochondria that activate signaling pathways and modulate nuclear gene expression, have emerged a therapeutic approach to extend longevity. Mito-organo peptides (MOP), a specialized class of peptides targeting mitochondrial and organellar function, represent a cutting-edge therapeutic strategy for promoting longevity by addressing cellular aging at its core. These peptides are designed to enhance mitochondrial bioenergetics, optimize oxidative phosphorylation, and mitigate reactive oxygen species (ROS) production, key factors in aging and age-related diseases. By modulating mitochondrial dynamics, such as fission, fusion, and mitophagy, MPO can help maintain mitochondrial quality control, preventing the accumulation of dysfunctional mitochondria that contributes to cellular senescence and metabolic decline. Additionally, these peptides can regulate mitochondrial unfolded protein response (UPRmt), a crucial stress response pathway that preserves proteostasis and supports cellular resilience. Some MOPs also exhibit the ability to restore calcium homeostasis and lipid metabolism within organelles like the endoplasmic reticulum and lysosomes, further enhancing cellular health and longevity. Advances in peptide engineering have enabled the development of highly stable and targeted MOP capable of crossing biological membranes and localizing specifically to mitochondria or other organelles. By addressing multiple hallmarks of aging, including mitochondrial dysfunction, proteostasis failure, and chronic inflammation, MOP hold great promise for extending healthspan and delaying the onset of age-related diseases. As research and clinical development progress, these peptides could become a powerful tool in the next generation of longevity therapeutics.

- Mitochondrial Function- Mitochondrial Quality Control (MQC) maintains mitochondrial function and biogenesis. Increasing evidence suggests that Reactive Oxygen Species (ROS) drive mitochondrial dynamic changes and promote the buildup of oxidized by-products through mitochondrial proteases and the UPRmt [5]. Mitochondrial-derived vesicles serve as the first line of MQC, aiding in the removal of oxidized components. Additionally, mitophagy plays a crucial role in eliminating partially damaged mitochondria to maintain mitochondrial health and functionality. Excessive activation or suppression of any MQC pathway may exacerbate abnormal energy metabolism and accelerate mitochondrial dysfunction-induced senescence [5]. Maintaining optimal mitochondrial function is a feature of health. Mitochondrial damage triggers mitophagy, the removal and recycling of damaged mitochondria and regulates the biogenesis of new, fully functional ones preserving healthy mitochondrial functions and activities. Reactive oxygen species and inflammation also induce detrimental effects considered pivotal in aging and disease development. The cytokines interleukin-1 (IL-1), IL-4, IL-10, and tumor necrosis factor alpha (TNFα) can also act as triggering signals. These processes ultimately disrupt protein tertiary structure and impact post-translational modification and concurrently impair mitophagy. ROS induce mitochondria damage, necessitating the involvement of key factors across various pathways to reinstate balance. Impaired mitophagy negatively affects cellular health and contributes to age-related chronic diseases. As such, restoration of age-related decline in mitophagy represents an avenue towards extending lifespan.

- Metabolic Regulation- Aging beta cells have increased ER stress, defective autophagy, and accumulation of DNA damage markers. Insulin sensitivity, enhanced insulin signaling, and enhanced glucoregulatory control are associated with reduced ER stress and inflammation [6]. Mitophagy is an adaptive cytoprotective response to chronic inflammation. Mesenchymal Stem Cells (MSCs) maintain the capacity to increase mitophagy flux and preserve regenerative capacity. Inflammation impairs nutrient uptake and suppresses cellular metabolism, whereas inflammation-mediated mitophagy engagement preserves metabolic adaptation. Stem cell-derived MOPs offer a promising approach to mitigating age-related pathologies by restoring mitochondrial function and reducing cellular senescence. These specialized peptides, designed to target mitochondrial and organellar health, can enhance mitophagy, improve ATP production, and decrease ROS accumulation, thereby alleviating oxidative stress and inflammation. Additionally, by modulating key pathways involved in mitochondrial quality control, such as PINK1/Parkin-mediated mitophagy and the UPRmt, these peptides help maintain cellular homeostasis and resilience. Stem cell-derived MOP also has the potential to rejuvenate aged stem cell populations by improving their metabolic efficiency and reducing senescence-associated dysfunction, thereby promoting tissue repair and regeneration.

- Proteostasis- Loss of protein homeostasis (proteostasis) is one of the key hallmarks of aging. Proteostasic pathways, such as the heat shock response and aggregation of metastable proteins, play a critical role in the development of neurodegenerative protein misfolding diseases in humans [7]. Under shock conditions, changes occur in signaling pathways enhance immune inflammatory responses, and result in organ damage. Further, the downregulation of proteostsic pathways reduce protein expression, and accelerate metabolic reprogramming.

- Cellular Senescence- A typical somatic cell undergoes a limited number of division cycles, with surveillance checkpoints halting cell division in response to stressors such as oxidative stress from excess free radicals, oncogene-induced abnormalities, genotoxic damage, and telomere shortening. When exposed to such stress, the cell cycle temporarily pauses to allow repair mechanisms to take effect. The type and severity of stress determines whether the cell undergoes repair or enters a state of permanent arrest. Depending on whether the stress is temporary or long-lasting, cells either enter quiescence or senescence, respectively. Quiescence is a reversible state that enables damaged cells to undergo repair before re-entering the normal cell cycle. In contrast, senescent cells remain permanently arrested, accumulating with age and con-

tributing to inflammation and various age-related diseases [8]. Cellular senescence, a hallmark of aging, has been implicated in the pathogenesis of many major age-related disorders, including neurodegeneration, atherosclerosis, and metabolic disease. Therefore, investigating novel methods to reduce or delay the accumulation of senescent cells during aging may attenuate age-related pathologies. Impaired mitophagy, cellular senescence, and longevity are intricately linked through mitochondrial dysfunction, a key driver of aging and age-related diseases. Mitophagy, the selective degradation of damaged mitochondria, is essential for maintaining cellular homeostasis and preventing the accumulation of dysfunctional mitochondria that produce excessive ROS. When mitophagy is impaired, damaged mitochondria persist, leading to oxidative stress, chronic inflammation, and metabolic decline, all of which contribute to cellular senescence, a state of irreversible cell cycle arrest characterized by the secretion of pro-inflammatory factors known as the Senescence-Associated Secretory Phenotype (SASP) [9]. Senescent cells accumulate with age, promoting tissue dysfunction and systemic inflammation, which accelerates aging and shortens lifespan. This cascade of mitochondrial dysfunction, senescence, and inflammation adversely affects longevity. Enhancing mitophagy and reducing cellular senescence are therefore critical strategies for promoting longevity and delaying age-associated decline.

- Immunogenicity- For dying cells to trigger adaptive immune responses, cell death must occur under adaptive stress conditions, involve antigen presentation not covered by thymic tolerance, and be accompanied by immunostimulatory endogenous molecules. The microenvironment must support Antigen-Presenting Cell (APC) recruitment, maturation, and migration, as well as cytotoxic T Lymphocyte (CTL) activation, while the absence of any of these factors can lead to local inflammation, immune tolerance, or antigen-specific CTL expansion without effector responses. Longevity necessitates preservation of the efficient capacity to trigger immune responses [10]. In addition, in the immune system, aging is characterized by an excess of innate immune cells and a shortage of adaptive immune cells. The age-associated imbalance in immune cell abundance arises from the aging of MSCs. With age, MSCs undergo multiple impairments in functions are associated with molecular changes, including DNA damage, epigenetic remodeling, translation defects, and alterations in extracellular signaling. Identification of stem cell derived components underlying the onset of immune aging provides potential cellular and molecular targets for therapeutic interventions to delay aging.

The immune response is a core component of the significant age-related changes that occur during aging leading to a chronic low-grade inflammatory state. The low-grade inflammatory state represents a major risk factor for multiple chronic age-related dysfunctions and/or diseases. A decade ago, *Lee, et al* [11] suggested mitochondria may actively regulate metabolic homeostasis at the cellular and organismal level via peptides encoded within their genome. Today, through enhanced understanding of the molecular pathogenesis involved in mitochondrial function, plausibly the core construct linking metabolic regulation, proteostasis, immunogenicity and cellular senescence, it has been possible to develop therapeutic approaches targeting extending lifespan (e.g. longevity) [12]. In particular, stem cell therapy offers great promise for a myriad of age-related diseases via paracrine effect on cytokines, modulation of the immune system, and trans differentiation. The recent observation that stem cells can donate healthy mitochondria to injured cells to rescue aerobic respiration and recover their metabolism capability promoted consideration of stem-cell derived mitochondrial peptide as a new therapeutic strategy for tissue damage of the aging process. The via restoration of cellular function, MOP provide a cytoprotective therapy, while promoting senolytic elimination of dysregulated cells. Plausibly, MOPs could make the senescent cells more apt to be cleared by the immune system or more sensitive to senolytics.

European Wellness (EW) and the BioPep Research Group developed two distinct peptide therapy products made of organ-specific cellular extracts and peptide molecules, MOP and Nano Organo Peptides (NOP), which are produced through a proprietary parallel-extraction process from mammalian precursor stem cells and rabbits bred in closed colonies under good manufacturing practices conditions. The UPRmt is a coordinated interaction between the nucleus and the mitochondrial network, activating chaperones and proteases to maintain proper protein quality control. Upregulation of UPRmt-related genes helps restore mitochondrial stability and counteracts adverse conditions, including mtDNA mutations, mitochondrial protein imbalances, altered membrane permeability, respiratory chain dysfunction, and protein aggregate buildup. Given the wide distribution of Mitochondria-Derived Peptides (MDPs) through various tissues and their role in cryoprotection roles through maintaining cell viability and mitochondrial function under both pathological and normal conditions, EW conducted a study to determine whether the administration of stem-cell derived MOP twice-weekly to non-obese diabetic (NOD) mice through intramuscular injections over 17 weeks delays or prevents the onset of the destruction of the insulin-secreting beta cells in pancreatic islets of Langerhans. Specifically, the stem-cell derived MOP were obtained from thymus and pancreatic extracts to target the regions of the beta cells and T-cell maturation [13,14]. It was found that NOD MO treated mice had a lower blood glucose concentration than NOD saline treated mice on average. In conjunction, at the end of week 17, there was a 33% larger non-diabetic population within the MOP treated group versus the saline treated group. These studies will help understand the mechanisms of immunological protection in type 1 diabetes and may serve as a model for other autoimmune disorders. Importantly, this is the first in a continuum of our studies demonstrating MOP as a promising therapeutic approach for treating diseases, particularly metabolic disorders [15].

Cardiac aging is a multifaceted process that contributes to the

rising prevalence of Cardiovascular Diseases (CVDs), the leading cause of mortality worldwide. As populations age, structural and functional changes in the heart, including myocardial stiffness, reduced cardiac output, and endothelial dysfunction, predispose individuals to conditions such as hypertension, heart failure, atrial fibrillation, and coronary artery disease. These diseases not only shorten life expectancy but also diminish quality of life by causing fatigue, physical limitations, and increased disability. Genetic, environmental, and lifestyle factors influence the progression of cardiac aging, making early detection, lifestyle modifications, and pharmacological interventions essential for mitigating its effects. Understanding the molecular and cellular mechanisms of cardiac aging is vital for developing innovative strategies to enhance longevity and quality of life in older adults. MOP play vital roles in protecting the heart from ischemic injury, oxidative stress, and mitochondrial dysfunction. MOP enhance metabolic homeostasis by activating AMP-activated protein kinase (AMPK), improving mitochondrial biogenesis [16], glucose metabolism, and myocardial energetics while reducing fibrosis and remodeling. MOP have demonstrated potential in preclinical and clinical studies, showing improvements in left ventricular function, infarct size reduction, and enhanced myocardial regeneration. By targeting mitochondrial health, these peptides represent a novel and promising approach to mitigating cardiovascular diseases and improving cardiac function [17].

The capacity to improve mitochondrial function, provide restorative capacity in metabolic dysregulation associated with obesity, a key determinant of shortened life expectancy [18]. Thus, MOP represent a potentially critical factor in improving obesity-related mitochondrial dysfunction by reducing oxidative stress, enhancing energy production, and promoting fatty acid oxidation. MOs play pivotal roles in modulating metabolic dysfunction associated with obesity and related diseases, including insulin resistance type 2 diabetes, and Nonalcoholic Fatty Liver Disease (NAFLD). Various MOP have demonstrated consistent metabolo-protective properties, improving glucose tolerance and insulin sensitivity in rodent models through different mechanistic pathways. In addition, skeletal muscle appears to be a major target organ [19]. MOPs have also been theorized to enhance lipid oxidation and thermogenesis in adipose tissues, promoting weight loss. MOPs have also been shown to exhibit neuroprotective and insulin-sensitizing effects by modulating apoptotic pathways and enhancing insulin receptor signaling, with its analogs improving glucose metabolism and reducing fat accumulation. Clinical trials investigating MOP therapies, particularly for type 2 diabetes, obesity, and NAFLD, are underway. These peptides represent promising candidates for addressing metabolic stress and improving outcomes in metabolic diseases [20].

A key area of interest is whether MOP levels decline with age due to mitochondrial dysfunction, potentially caused by accumulated mtDNA mutations that compromise MDP coding sequences and reduce their functional production, which could also help identify novel biomarkers for aging and age-related diseases. Despite the numerous studies highlighting the therapeutic effectiveness of NOP and MOP and the established procedures documented on obtaining them, little is known of the exact makeup of these formulations. Mass spectrometry has been shown to identify and quantify analytes in complex solution [21] and therefore is thought to be able to identify the population of peptides derived from peptide cocktail formulations. The mass spectrometer produces a readout of peaks plotted in relative abundance against the mass-to-charge ratios. By searching the experimentally derived peaks against a database of known proteins, it is possible to identify the peptides. Our results indicated that there were no statistically significant differences in protein concentration (ug/mL) between batches but were statistically significant differences between sample types ($p<0.05$). These results are in line with our experimental expectations as both the NOP and MO samples are cellularly derived solutions that contain a heterogenous mixture of molecules and peptides that will vary depending on the tissue that they are recovered from. Between batches, however, relative protein concentrations were expected to remain consistent as they were procured from the same tissue samples and processed in the same manner. In addition to the consistency between batches found in the protein concentration assay, consistency was also demonstrated between batches during our preliminary MS experiment. Although our preliminary data relied upon LC-MS/MS based peptide sequencing techniques to produce chromatograms and deconvolute our data, we utilized Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS identification techniques for our in-depth analysis due to several calculated benefits [15]. Comparisons of experimental MS data with that of well-established open-source databases provided the capacity to identity of the molecules, peptides, or proteins found within a solution, at lower cost and rapid efficiency. In brief, our use of the technique of using MALDI-TOF, a protein fingerprinting method in which the sample is digested by a proteolytic enzyme was used to generate an MS spectrum that can be searched against existing databases, which can subsequently ranked according to a scoring method in which the candidate protein that contains more proteolytic peptides has a higher score. In general, this represents the most probable protein/peptide. Using MALDI-TOF, eleven major peptide products of interest were identified (five in batch one [14,969 Da, 15,300 Da, 8,449 Da, 8,294 Da and 4,618 Da], six in batch two [four of the same peptides– 14,969 Da, 15,301 Da, 8,294 Da, 8,449 Da in size– and two additional peptides of 5,436 Da, and 6,214 Da in size). We further evaluated the peptides to identify the stability and significance in peptide therapy conducting analyses to assess the impact of temperature storage and duration of storage on peptide stability. We tested the acidic peptide N-06 D, seven acidic peptide combination (N-18A), a 7-peptide combination (N-18A) stored at 4°C, N-06D peptides in liver samples stored at 4°C over one- three-and six months. extracted from liver samples stored at 22°C for one-, three-, and six- months. Overall, the collected data suggested that acidic peptides stored at 22°C experience degradation over time, with a clear reduction in both peak intensities and overall peptide stability by six months of storage. The results of our study suggest that while some peptides remain

stable, there are notable changes in the peptide profiles over time. Slight differences in peptide products between batches are likely due to the heterogeneous nature of cellularly-derived solutions and differences that occurred during the extraction process. This approach lays the groundwork to identifying potential adverse effects on stability, and therefore therapeutic potential to ensure the safe application of stem cell technologies in clinical and research settings. Understanding these risks is essential for advancing stem cell science while safeguarding public health and promoting the responsible development of stem cell-based therapies.

Conclusions

Peptides are vital physiological mediators that are attractive therapeutic candidates with their high potency, specificity, and low toxicity. NOP and MOP are emerging as promising therapeutic strategies for promoting longevity and combating age-related diseases. Recent trends highlight their potential in cellular rejuvenation, tissue repair, and metabolic optimization. NOP play a crucial role in modulating inflammation, enhancing tissue regeneration, and improving cellular communication. These peptides are increasingly being explored for their ability to activate endogenous repair mechanisms and enhance mitochondrial function, which declines with aging. MOP, such as humanin and MOTS-c, have gained attention for their role in cellular metabolism, stress resistance, and inflammation reduction. By improving mitochondrial efficiency and protecting against oxidative damage, these peptides help maintain cellular homeostasis and delay age-related functional decline. Current therapeutic strategies include direct peptide supplementation, genetic modulation to enhance endogenous peptide expression, and cell-based therapies leveraging stem cell secretomes. The benefits of these approaches include improved energy metabolism, reduced cellular senescence, enhanced stress resilience, and potential protection against neurodegenerative and metabolic disorders. As research advances, these peptides hold promise for novel longevity interventions, offering a targeted approach to age-related decline and chronic disease management.

Acknowledgement

None.

Conflict of Interest

None.

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