Mitochondria-Derived Peptides in Age-Related Diseases: A Review

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Abstract: Mitochondrial—derived peptides (MDPs) are new kinds of peptides, which are small open reading frames in circular mitochondrial DNA that encode a variety of microproteins, including humanin(HN), SHLPs 1-6, and MOTS-c. It is found that it can regulate mitochondrial bioenergy and mitochondrial metabolism, and has many biological effects such as helping to maintain mitochondrial function and cell viability under stress conditions, giving play to cell protection and improving metabolic markers.In this paper, we review recent research progress in MDPs, examines the biological effects of MDPs and focus on the role of MDPs in age-related diseases(ARDs), including mechanism of action and therapeutic potential.

Keywords: Mitochondria-Derived Peptides; Oxidative Stress; Genome; Mutation; Cell Aging

1. Introduction

Aging is usually accompanied by chronic degenerative diseases [1]. Mitochondria are important organelles involved in various human metabolisms and are a major source of reactive oxygen species (ROS) [2]. Mitochondrial dysfunction and increased production of ROS are considered to be one of the main markers of ARDs [1, 3, 4]. Therefore, mitochondrial modifications are considered an important target for the treatment of ARDs. Mitochondria-derived peptides (MDPs) are newly identified retrograde signaling entities from mitochondria[5]. Recent studies have found that the levels of MDPs are strongly associated with ARDs [6, 7]. We will review the functions and characteristics of MDPs and their relation with geriatric diseases in order to provide new ideas for diagnostic and therapeutic studies of age-related diseases.

2. MDPs in ARDs

2.1 humanin (HN)

HN is the first discovered member of the MDPs and the most studied of them.HN is a linear polypeptide encoding 24 amino acids.It has certain anti-inflammatory[8], anti-apoptosis [9] and neuroprotective effects [10], and regulates metabolism related to aging. HN also acts as a cell protective molecule in type 2 diabetes, cardiovascular disease, atherosclerosis and cancer[11], and its levels generally decline with age and is associated with increased healthspan and lifespan[12].

2.2 MOTS-c

MOTS-c is a linear polypeptide that is encoded by the mitochondrial 12SrRNA open reading frame[13].The main target of action of MOST-c is skeletal muscle, and it is thought to be the 1st peptide in MDP to regulate gene expression in the nucleus by interacting with transcription factors, leading to the production of retrograde signaling molecules[14]. Recent

studies have demonstrated that MOST-c exerts its effects by increasing glucose utilization, fatty acid oxidation, altering mitochondrial function and nucleotide metabolism in the organism, which in turn improves muscle metabolism, increases insulin sensitivity, and regulates lipid metabolism. Because of these important cellular functions, MOTS-c has been shown to be beneficial in ARDs.[15, 16].

2.3 SHLP1-6

SHLP1-6 is another six small peptides similar to HN found in HN's 16SrRNA gene.Among them, SHLP2 and SHLP3 have been extensively studied and have HN-like cytoprotective effects on apoptosis and metabolism.Current studies have shown that SHLP2 has an anti-oxidative stress effect and it improves insulin sensitivity in both central and peripheral systems. Moreover, circulating SHLP2 levels have been found to decrease with age, Indicate that it is associated with the progression of ARDs [17].

3. MDP and ARDs

3.1 Diabetes

The global incidence of diabetes is increasing year by year [2]. Oxidative stress is an important factor in the progression of diabetes [18]. Current studies have found that mitochondrial dysfunction is closely related to diabetes mellitus. MDPs improve the prognosis of diabetic patients by improving insulin resistance, suppresses inflammatory response and anti-apoptosis [19]. At present, MOTS-c and HN are the main MDPs associated with diabetes and its complications. Yang et al[20] found that MOTS-c regulates the expression of PGC-1α in mice through AMPK signaling pathway, reduces insulin resistance, promotes glucose metabolism and thus improves the clinical outcome of diabetic patients. MOTS-c also protects pancreatic β cells from streptozotocin mediated damage[21] . SHEN M et al. found that HN analogues (HNG) inhibited endothelial cell apoptosis induced by high glucose, providing a new direction for HN-related biologics to treat various types of diabetes-related vascular complications[22].

3.2 Cardiovascular disease

More and more research have shown that MOTS-c and HN in MDP are closely related to coronary artery disease (CAD). Patients with coronary artery disease (CAD) endothelial dysfunction have both low MOTS-c and HN levels[23]. Ya Wear, E. et al. found a strong correlation between MOTS-c level and CAD. Therefore, MOTS-c can help distinguish CAD patients for early preventive treatment[24]. And HN plays a key role in CAD. CAI et al. found that low circulating HN is an independent risk factor for CAD[25].

3.3 Neurodegenerative disease

HN has been increasingly studied in neurodegenerative diseases.Sandra et al. found in a rat model of surgical menopause that HN prevented synaptic loss in hippocampal neurons and reduced inflammation in astrocytes[26].Niikura et al. recently discovered the mechanism behind the antagonistic effect of HN on cognitive deficits - HN can directly promote neuronal regulation of exocytosis, thereby promoting improvement in cognitive function [27].Kelvin et al. found that ginsenosides improved metabolic health span parameters and reduced inflammatory markers in middle-aged mice treated with ginsenoside analogs (HNG) twice a week[12].

4. Conclusion

To sum up, we mainly introduce MDPs in ARDs, hoping to draw attention to the potential value of MDPs in the

diagnosis and treatment of ARDs. Although studies have proved that MDPs have the effects of anti-apoptosis, regulating metabolism and protecting cells in many diseases processes, and their possible mechanisms have been preliminarily explored, the existing studies are scattered and unsystematic, and most of them are limited to animal experiments, so there are still many gaps that need to be further explored.

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