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Protective and multi-organ effects of MOTS-c and other mitochondrial-derived peptides in the endocrine system

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Abstract

The discovery of mitochondria-derived peptides has facilitated a comprehensive understanding of their protective effects on various organs. One of such peptides, Mitochondrial ORF of the 12S rRNA type-C (MOTS-c), was initially characterized in 2015 as a bioactive molecule that regulates gene expression and cellular metabolism via 5'-adenosine monophosphate-activated protein kinase (AMPK).

MOTS-c has exhibited notable protective effects across diverse organs, including protection against diabetes, cardiovascular diseases, alleviating the impacts of ageing, and regulating the immune response. Despite these well-established functions, the precise role of MOTS-c in the endocrine system remains elusive. However, recent research emphasizes the increasing significance of MOTS-c and other mitochondrial-derived peptides in regulating endocrine system function and addressing metabolism-related diseases. Therefore, this review aims to summarize the current information on the action of MOTS-c and other mitochondrial-derived peptides in various endocrine system organs.

Running title: MOTS-c and other MDPs in the endocrine system

Keywords: MOTS-c, MDPs, AMPK, endocrine system, metabolism

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Introduction

In recent years, the notable role of mitochondria in the regulation of the endocrine system and body's metabolism has been extensively documented [1,2]. Mitochondria, organelles derived from symbiotic bacteria in a co-evolutionary relationship with their host, exhibit a semi-autonomous nature due to the encoding of several mitochondrial proteins in the nuclear genome [1,2]. In contrast, the mitochondrial genome encodes mitochondrial-derived peptides (MDPs) that affect the activity of nuclear genes. Moreover, MDPs have been described as proteins with a key role in the body's metabolism [3–5]. The presence of MDPs in individual organs of the endocrine system has also been confirmed; however, their general role in the endocrine system has not yet been described. Mitochondria are responsible for the process of cellular respiration, which makes them play a crucial role in the metabolism of the cell and the whole organism [6]. Moreover, mitochondria control intracellular calcium metabolism and signaling, regulate thermogenesis, generate most cellular reactive oxygen species (ROS), and regulate cell apoptosis [7,8]. There is also an association between mitochondrial diseases and endocrine system dysfunction, suggesting that mitochondria play a relevant role in regulating the endocrine system [1,2]. Mitochondria-related disorders include neurodegenerative diseases, growth hormone deficiency, hypothyroidism, exocrine pancreatic insufficiency, diabetes, primary adrenal insufficiency, premature ovarian failure, hypogonadism and hypergonadism [2]. The above diseases are related to the dysregulation of hormone production by specific organs of the endocrine system. Given that all steroid hormones are synthesized in the mitochondria, mitochondrial dysfunction and thus reduced ATP generation can lead to impaired hormone production [9]. Genetic mutations also play an important role in the development of endocrine dysfunction. In particular, large-scale rearrangements of mtDNA such as Kearns-Sayre syndrome are associated with a high incidence of endocrine disorders [10,11]. The relationship between the mitochondria and the endocrine system is interdependent. On one hand, mitochondria can influence hormone secretion by regulating metabolism and ATP production. On the other hand, the endocrine system can affect the functioning of this organelle through glucocorticoids (GCs) and their receptors present in the mitochondria [12]. GCs are steroid hormones predominantly produced in adrenal glands. One of the main functions of GCs is their anti-inflammatory role, which allows usage of GCs in treatment of autoimmune diseases and cancer [13]. However, GCs are predominantly used only to help patients tolerate side effects of the treatment, rather than as a chemotherapeutic targeting the cancer itself [14]. GCs also play a role in the regulation of mitochondrial energy metabolism with effects dependent on the dose and exposure duration [12]. Low doses or short duration of administration of glucocorticoids have a neuroprotective effect and improve mitochondrial oxidation, mitochondrial potential, and calcium holding capacity. The opposite effect is observed with prolonged exposure to high doses of glucocorticoids [15]. It was reported that regulating mitochondrial functions by glucocorticoid receptors (GRs) is mediated by interaction of GRs with a cytoprotective protein Bcl-2 and translocating into mitochondria in response to corticosterone [15]. GRs export induced by an anti-inflammatory drug dexamethasone in the C6 mouse glioma cell line was also associated with elevated expression of the mitochondrially-encoded cytochrome oxidase-1 (*COX-1*) gene, which suggests that the mitochondrial GRs may regulate mitochondrial transcription [16]. Other properties of GCs include regulation of lipid and glucose metabolism; maintenance of normal blood pressure through regulation of plasma volume, electrolyte retention, epinephrine synthesis, and angiotensin levels; regulation of nervous system and stress; and regulation of secretion of other hormones of the endocrine system [17–21]. Specifically in mitochondria GCs act in two ways depending on the time of exposure. Short-term exposure to GCs serves as a protective mechanism which is associated with induction of mitochondrial biogenesis and increase of enzymatic activity of the respiratory chain. However, prolonged exposure to GCs leads to respiratory chain dysfunction, decreased ATP production, increased ROS generation, mitochondrial structural abnormalities, dysregulated mitochondria biogenesis, decreased mitochondrial membrane potential, increased sensitivity to cell death, and telomere attrition [22–25].

This article focuses on the role of MOTS-c and other MDPs in various organs of the endocrine system, their functions in endocrine-related metabolic diseases and the potential of MDPs in treatment of those diseases.

Mitochondrial-derived peptides

Mitochondria can communicate with the rest of the cell's organelles and the whole organism through MDPs, whose genes are encoded in the mitochondrial genome by short open-reading frames (sORFs). Although all their functions are not yet known, these small, bioactive proteins play an essential role in metabolism regulation, especially in glucose metabolism, obesity, and aging [4,26]. Moreover, MDPs are known for their cytoprotective effects and for preserving proper mitochondrial function and cell viability under stress conditions [27]. The first MDP discovered in 2001 was Humanin which was described to suppress cell death initiated by Alzheimer's disease-related damage in neuronal cells [28–30]. Humanin is the most stud-

ied MDP and is believed to activate various receptors involved in immune response, such as WSX-1, CNTFR, and gp130; therefore, activating ERK1/2, AKT, and STAT3 signaling pathways that regulate cell proliferation, apoptosis, and cell metabolism [5,31]. Another MDPs are small Humanin-like peptides (SHLP1 – SHLP6) which are a group of peptides encoded by the 16S rRNA gene of the mitochondrial genome. These peptides differ in their functions; however, SHLP2 and SHLP3 were the most studied because of their similar and Humanin-like protective effects [32]. The most recently discovered MDP is MOTS-c, which is a 16 amino acid peptide encoded by a short open reading frame within the 12S rRNA region of the mitochondrial genome (**Fig. 1**) [33,34]. Mitochondria are semi-autonomous organelles containing mitoribosomes which allow for translation of mitochondrial genes inside the mitochondria [35]. However, a polyadenylated transcript of MOTS-c is believed to be exported from mitochondria to the cytoplasm of the cell, where the translation process takes place [34]. Furthermore, under metabolic stress conditions MOTS-c peptide translated in the cytoplasm can translocate to the cell nucleus where it can regulate expression of nuclear genes in an AMPK-dependent manner [26]. MOTS-c was described as a bioactive peptide regulating gene expression and cellular metabolism, mainly targeting skeletal muscles as its primary organ. Cellular actions of MOTS-c depend on inhibition of the folate cycle and the associated de novo purine biosynthesis, resulting in AMPK activation [34]. Moreover, MOTS-c is responsible for maintaining the body's metabolic homeostasis; therefore, the most known actions of this peptide are its ameliorating effects on insulin resistance and aging related pathologies [34,36]. Receptors for MOTS-c have not been described yet; however, the effects of MOTS-c in HEK293 cells are known to be mediated by an increase in 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) levels and activation of AMPK [34]. In addition, MOTS-c regulates the expression of other proteins and the activation of various signaling pathways regulating metabolism and immune response such as: ERK1/2 [37], Nrf2/ARE and NF-κB [38], TGF-β/Smad [39],

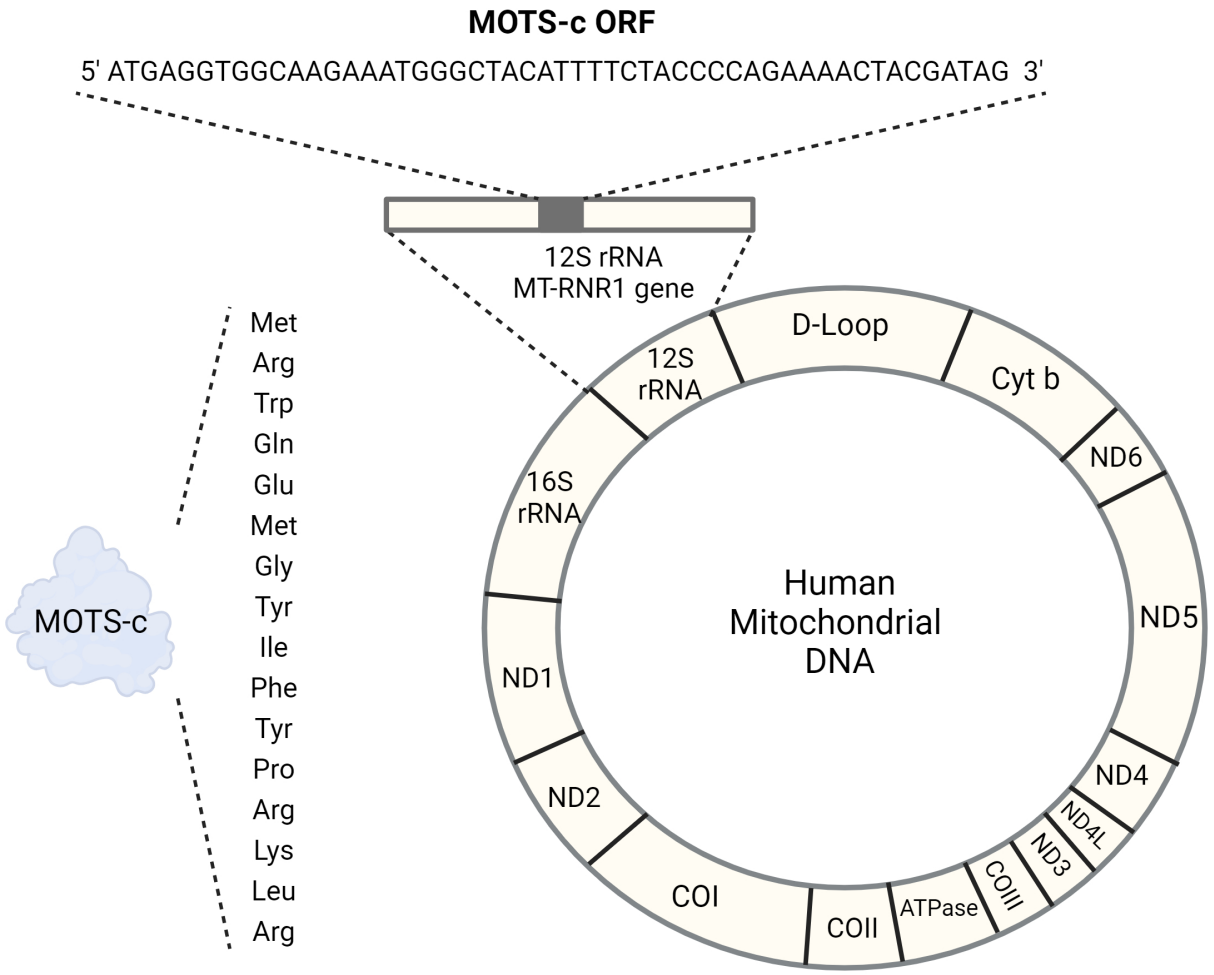

FIGURE 1 Location of MOTS-c ORF and amino acid sequence of MOTS-c peptide. Based on NCBI Nucleotide database (https://www.ncbi.nlm.nih.gov/nuccore/KP715230). Figure created with BioRender.com

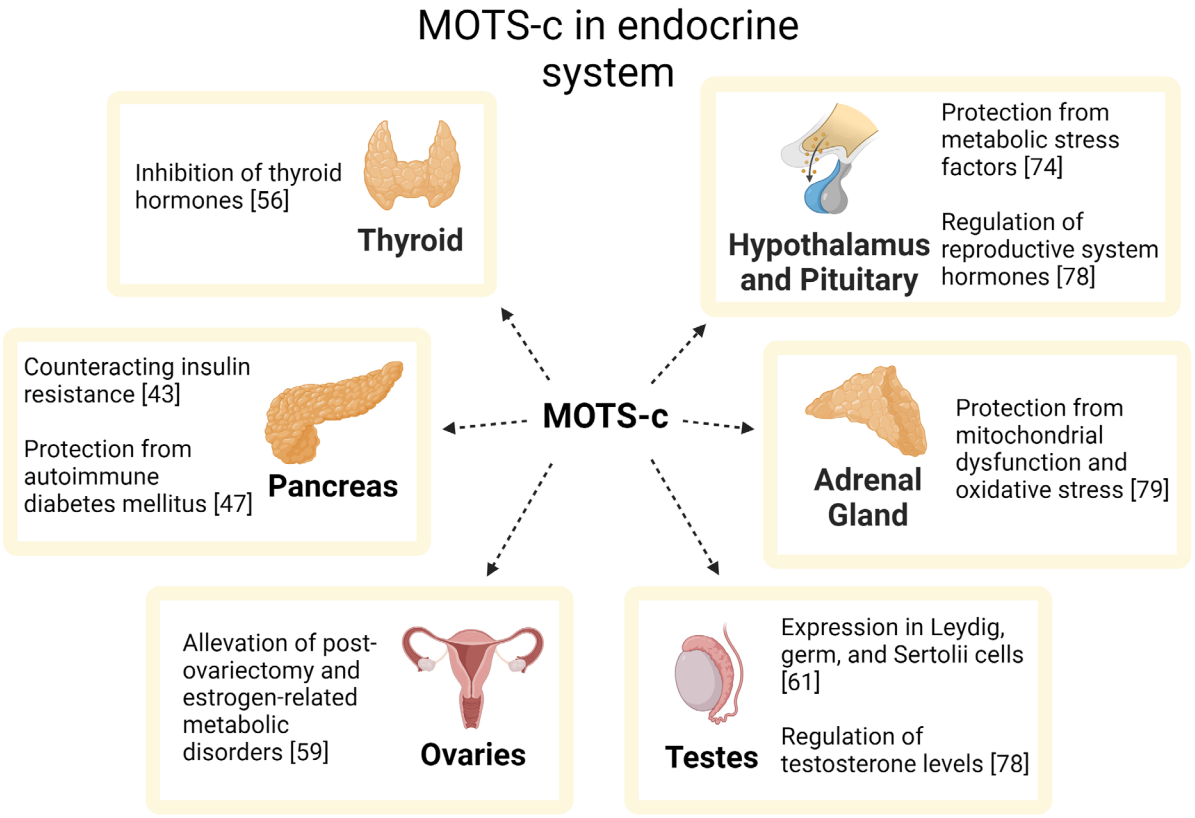

FIGURE 2 Functions of MOTS-c in various organs of the endocrine system. Figure created with BioRender.com

mTORC2 and PTEN [40], and PI3K/AKT [34]. The influence of MOTS-c on the key signaling pathways in the regulation of metabolism and the mitochondrial origin of this peptide suggests that MOTS-c may play a relevant role in regulating the endocrine system and various metabolic disorders associated with this system (**Fig. 2**).

Mitochondrial-derived peptides in endocrine organs and disorders

Pancreas

The major role of the pancreas is regulating glucose metabolism in the body by secreting glucagon and insulin by alpha and beta cells, respectively of pancreatic islets [41]. It is well known that MOTS-c counteracts insulin resistance in diabetic patients [34]. MOTS-c levels have also been observed to be reduced in type 1/2 diabetes and gestational diabetes mellitus (GDM) patients, indicating the protective properties of this peptide [42,43]. The effect of MOTS-c on the regulation of glucose metabolism is mediated by activation of the AMPK/AKT signaling pathway, which is crucial for metabolic stress response. Treatment of GDM mice with MOTS-c resulted in increased AMPK and AKT phosphorylation followed by an increase in Glucose transporter type 4 (GLUT4) expression in skeletal muscle [43]. MOTS-c treatment of GDM mice was also associated with reduced blood glucose levels and reduced offspring mortality compared to GDM controls without administered MOTS-c [43]. It is worth noting that administration of insulin in adult female Sprague–Dawley rats leads to a significant decrease in MOTS-c protein levels in both uterine and placental tissues [44,45]. Moreover, lipid infusion significantly increases plasma MOTS-c in healthy women and patients with polycystic ovary syndrome (PCOS); however, insulin administration suppresses lipid-induced increase of MOTS-c protein levels in plasma [46]. In addition to the glucose metabolism-regulating effect of MOTS-c, this peptide has a protective role in autoimmune diabetes. This effect relies on preventing the destruction of pancreatic islets by protecting β cells and regulating T-cell differentiation [43,47]. MOTS-c can bind to Raptor, a major component of the mammalian target of rapamycin (mTORC1), a protein complex regulating cell growth and proliferation, transcription, and translation processes. Activation of mTOR is considered to be strongly related to cancer, obesity, aging, and autoimmune disorders like type 1 diabetes [48]. Upregulated mTORC1 signaling leads to increased Th1 differentiation of T cells [49]. Furthermore, mTORC1 can be inhibited by MOTS-c through AMPK, an important mediator of MOTS-c's functions, which may partially explain the protective role of MOTS-c in diabetes [34,50].

Thyroid

The thyroid, consisting of two lobes, constitutes an integral component of the endocrine system. The thyroid also belongs to the hypothalamic-pituitary-thyroid axis, which is regulated by hormones secreted by successive glands of this axis and has the ability to self-regulate through negative feedback loop [51]. Thyroid hormone secretion is regulated by the thyroid-stimulating hormone (TSH), which enhances iodide uptake and further leads to increased secretion of the triiodothyronine (T3) and thyroxine (T4). Thyroid hormones can affect the entire body, and their main role is the regulation and increase of metabolic rate and thermogenesis. Thyroid hormones are responsible for increased heart rate, stimulation of respiratory centers and increased oxygenation, increased development of type II muscle fibers, and increased oxygen consumption in different tissues [52]. Considering the role of the thyroid gland in the metabolism regulation, one may wonder whether MOTS-c, a peptide that regulates cell metabolism and maintains its homeostasis, is related to changes in thyroid function. The thyroid is prone to metabolic disorders such as hypothyroidism and often is connected to a metabolic syndrome in patients [53,54]. Studies that focused on examining the relationship between MOTS-c and hormonal changes in the thyroid showed a decrease in the concentration of MOTS-c in maternal blood and cord blood in patients with hypothyroidism in comparison to a group of mothers with obesity; however, there were no changes in MOTS-c protein level between patients with hypothyroidism and healthy group [55]. Another study examining the effect of intracerebroventricular MOTS-c intake on thyroid hormones using male Wistar Albino rats showed that MOTS-c infusion increased food consumption but did not cause any changes in the body weight [56]. Administration of MOTS-c peptide was also shown to decrease serum levels of TSH, T3, and T4 hormones and to increase expression levels of mitochondrial uncoupling proteins, responsible for the regulation of thermogenesis, fatty acid metabolism, and insulin secretion – UCP1 and UCP3 in peripheral tissues [56,57]. Expression of UCP1 mRNA was upregulated in white and brown adipose tissue, and UCP3 expression was upregulated in muscle.

Reproductive organes

Within the endocrine system, the ovaries and testes emerge as pivotal organs responsible for the synthesis and release of sex hormones. These hormones have a broad field of activity through cellular and molecular processes and can affect sexual differentiation, reproduction, and action of the immune system [58]. Little is known about how exactly MDPs interact with those organs. However, studies are reporting protective properties of MDPs in both ovaries and testes [59–61]. Ovaries, through their hormones, mainly estrogens, also play an important role in regulating metabolism and maintaining lipid and glucose homeostasis [62]. Disturbance and inhibition of the ovaries as a result of menopause or ovariectomy lead to several metabolic disorders, including glucose and lipid metabolism, weight gain, and insulin resistance, which causes the development of type 2 diabetes. Moreover, ovariectomized female Wistar rats which were already diabetic before the operation showed exacerbated effects of the disease, abnormal lipid profile, higher HOMA-IR value, hyperinsulinemia, and higher leptin concentration and lower adiponectin concentration [63]. Leptin and adiponectin are appetite-regulating hormones whose altered concentrations also play a role in insulin resistance [64]. There is a noticeable connection between metabolic disorders caused by impaired or lack of ovarian activity and the protective effect of the MOTS-c peptide, which is confirmed by several studies [36,59,60]. MOTS-c treatment in mice mitigated ovariectomy-induced obesity and decreased plasma lipid and hepatic triacylglycerol. Moreover, MOTS-c treatment led to significant suppression of genes related to lipogenesis (*Fasn*, *Scd1*), reduced adipocyte size, weakened adipose-inflammatory response, and enhanced lipid catabolism [59]. The above changes induced by the administration of MOTS-c indicate that it causes a significant alleviation of the effects of ovariectomy-induced and estrogen-related adipose metabolic dysfunction. Moreover, the impact of MOTS-c manifesting only in ovariectomized mice and its reduction or absence in healthy controls suggests the protective role of the peptide in the event of stress on the body and its metabolism. Estrogen is also a regulator of bone metabolism and affects key cells in this process. Estrogen is responsible for inhibiting bone remodeling and resorption, while the deficiency of this hormone leads to bone loss and osteoporosis [65–67]. Regulation of bone formation occurs through the activation of AMPK, which mediates the action of the MOTS-c peptide, suggesting that MOTS-c also affects bone metabolism [68]. The role of MOTS-c in ovariectomy-induced bone loss was confirmed by Ming et al. who discovered that administration of MOTS-c represses osteoclast differentiation *in vitro* and decreases bone loss in mice with ovariectomy-induced osteoporosis [60]. The above study shows that the protective function of MOTS-c on lipid and glucose metabolism extends to bone metabolism as well, and that AMPK is a key mediator of the protective effects of MOTS-c. MDPs, including MOTS-c and SHLP-2, are also present in the testes; however, the main mitochondrial peptide in this organ is Humanin. The expression of MOTS-c and Humanin has been described in Leydig cells, but Humanin is also present in germ cells and seminal plasma [61]. In Leydig cells in vitro, Humanin showed protective properties by promoting cell

survival and interacting with IGF-I to stimulate DNA synthesis and steroidogenesis [69]. Considering the anti-apoptotic properties of Humanin and its presence in male germ cells it was hypothesized that Humanin might be involved in preventing apoptosis in human sperm and testis and; therefore, play a role in improving sperm quality and preventing infertility in males [70]. It has been shown that the anti-apoptotic effect of Humanin takes place only in the presence of a stressor such as gonadotropin-releasing hormone antagonist (GnRH-A), where it weakens the apoptotic effect of this factor. However, Humanin has no effect on apoptosis in non-stressed cells [71]. The Humanin effect was mediated by phosphorylation of STAT3 – a transcriptional factor that is stimulated in response to cytokines and growth factors. Moreover, exogenous Humanin attenuated activity of p38 MAPK – the key stress kinase that regulates male germ cell apoptosis [71].

Hypothalamus and pituitary

The hypothalamus secretes hormones that govern the functioning of other organs within the endocrine system, by regulating the secretion of hormones from the pituitary gland [72,73]. Currently, there are few studies focusing on the relationship of mitochondrial-derived peptides with the hypothalamus and pituitary activity. However, Kang et al. conducted research on mitohormesis and stress-related changes in pro-opiomelanocortin (POMC) neurons in the hypothalamus, which sheds light on the role of MOTS-c in this organ [74]. This study showed that severe mitoribosomal stress in POMC neurons caused by homodeficient *Crif1* depletion leads to maturity-onset obesity in both males and females. On the other hand, mild mitoribosomal stress in *Crif1* heterodeficient POMC neurons promotes a high-turnover metabolism, resistance to diet-induced obesity, glucose tolerance, and insulin sensitivity. Moreover, MOTS-c peptide expression was significantly increased in hypothalamic neuronal cells of *Crif1* heterodeficient mice; however, MOTS-c expression in mouse pituitary POMC cells was negligible [74]. These results indicate that mitoribosomal stress stimulates MOTS-c expression in hypothalamic POMC neurons and that MOTS-c possibly mediates the body's protection against the effects of the stressor on metabolism. Moreover, it was indicated that elevated MOTS-c in coordination with STAT3 transcriptional regulator can influence and promote *Pomc* transcription [74,75]. On the other hand, Rattin which is a homologous peptide of Humanin in rats was shown to be expressed in pituitary cells, negatively regulated by estrogens, and its expression levels were lower in females than in males; however, Rattin was not regulated by estrogens in pituitary tumor cells. [76]. Humanin also showed its cytoprotective action by protecting anterior pituitary cells from TNF-α induced apoptosis in female rats; however, silencing of Humanin in pituitary tumor cells lead to increase in number of apoptotic cells, slowed tumor growth and enhanced survival rate [76,77]. These results are an example of cytoprotective properties of the mitochondrial-derived peptide Humanin and suggest an involvement of this peptide in pathogenesis and potential treatment of pituitary tumors. In addition to the protective effects of MOTS-c, it was also shown to play a role in the regulation of the reproductive system by affecting Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels in male rats [78]. Moreover, a MOTS-c infusion increased gonadotropin-releasing hormone (GnRH) mRNA expression, upregulated GnRH protein expression, increased serum testosterone levels, and elevated LH and FSH levels in both obese and non-obese male rats. However, LH and FSH levels were more upregulated in the non-obese group [78]. These results show that MOTS-c can stimulate the hypothalamus and pituitary to release respective hormones and regulate reproductive behavior.

Adrenal gland

Currently, there is a lack of publications regarding the direct impact of MOTS-c on the secretory activity of the adrenal cortex; however, there are studies indicating the influence of MOTS-c on rat adrenal medulla pheochromocytoma (PC12) cell line. The study showed the protective effect of MOTS-c by alleviating effects of mitochondrial dysfunction and oxidative stress [79]. MOTS-c protein expression was alleviated after treatment of the cells with rotenone to induce cellular stress. MOTS-c peptide was also observed to be translocated from mitochondria and cytoplasm to the nucleus in PC12 cells under stress conditions. Moreover, pre-treatment of the cells with MOTS-c increased their viability and improved mitochondrial membrane potential and ATP content while inhibiting the formation of reactive oxygen species (ROS) induced by the stress factor [79]. The above effects suggest protective effects of MOTS-c treatment in case of cellular stress in adrenal medulla pheochromocytoma cells.

AMPK as the main mediator of MOTS-c's function

One of the main mediators of MOTS-c action is AMPK, which is also involved in hormonal signaling (**Fig. 3**) [26,80,81]. AMPK is an important factor in metabolism of various tissues and organs like skeletal muscle, fat, myocardium and liver, which reacts to stress stimuli like fasting, physical exercise, and metabolic diseases such as obesity and diabetes [50,82]. Moreover, AMPK has a dual effect in cancer treatment. On one hand it is known to act as a metabolic tumor suppressor; therefore, activation of AMPK is a potential target for cancer prevention [83]. On the other hand; however, after the occur-

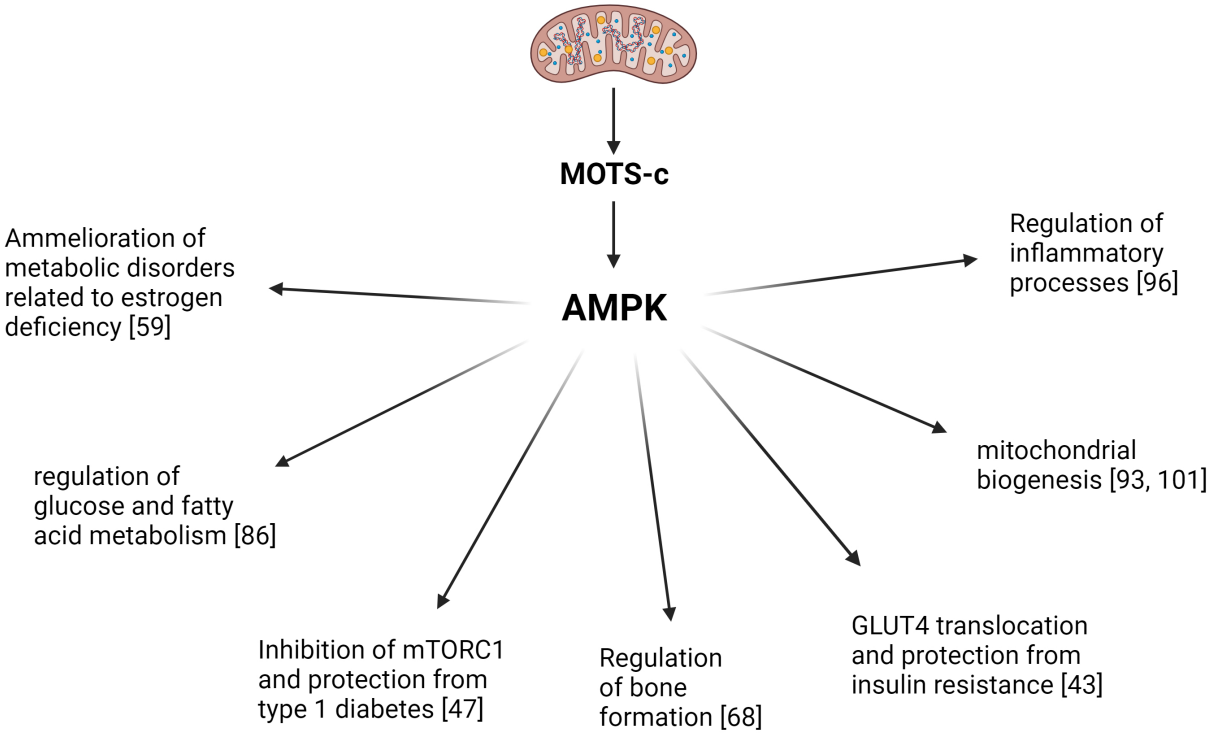

FIGURE 3 Functions of MOTS-c mediated by AMPK. Figure created with BioRender.com

rence of cancer, AMPK can act as a tumor promoter improving survival and resistance to stress of cancer cells [84,85]. The general function of AMPK relies on stimulating catabolic processes to produce ATP and inhibiting anabolic processes which consume ATP. AMPK acts as a cellular energy sensor and is activated by disruption of energy homeostasis due to an imbalance in the AMP:ATP ratio. Due to this function, increased levels of AMP and ADP are the main factors activating AMPK [86]. Processes stimulated by AMPK activation include fatty acid oxidation, glucose uptake, mitochondrial biogenesis, and autophagy, while processes suppressed by AMPK are mainly focused on synthesis of fatty acids, proteins, and cholesterol [86]. Activation of AMPK can lead to phosphorylation and inhibition of ACC1 and HMG-CoA, which; therefore, decreases expression of fatty acid synthase (FAS) and activates malonyl-CoA carboxylase leading to inhibited fatty acid and cholesterol synthesis [82]. AMPK can inhibit mTOR which regulates cell growth and is essential in development; however, inhibition of mTOR in later stages of life suppresses tumor development and regulates energy balance [87–89]. AMPK can be activated by AICAR in an insulin-independent manner and influence glucose metabolism by increasing GLUT4 translocation and glucose transport [90–92]. Moreover, AMPK plays a relevant role in the process of mitochondrial biogenesis by stimulating expression of CaMK IV and PGC-1α in response to chronic energy deprivation [93]. Both CaMK IV and PGC-1α are transcriptional regulation factors crucial for proper mitochondrial functioning [94,95]. AMPK is also a vital mediator of several metabolic hormones and plays a role in both metabolic syndrome and inflammatory processes [82,96]. Above functions show the importance of AMPK in endocrine system and considering that MOTS-c is a peptide with a protective and multi-organ effect mediated by AMPK activation, it further supports MOTS-c as an important regulator of metabolism and endocrine function [43,47,59,60,97–99]. Moreover, it was indicated that AMPK overexpression can stimulate PGC-1α expression in skeletal muscle and improve mitochondrial biogenesis leading to enhanced MOTS-c secretion and/or production in skeletal muscle cells [99–101]. Therefore, it suggests a potential positive feedback loop between MOTS-c and AMPK. Another interesting and worth mentioning discovery in context of the protective effect of MOTS-c on diabetes and insulin resistance are studies that have shown that the action of AMPK can be inhibited by insulin itself [46,102]. Insulin stimulates AMPK Ser485/491 phosphorylation through Akt in hepatocytes, myotubes and incubated rat skeletal muscle leading to reduction of AMPK activity. Considering the fact that AMPK is a main mediator of MOTS-c activity, that discovery may counterintuitively suggest the potential inhibitory role of insulin in MOTS-c action.

Conclusions

The role and exact effects of MOTS-c in organs of the endocrine system are not fully known yet. However, MOTS-c has shown to be an important

regulating factor in maintaining homeostasis in the body, especially in terms of glucose metabolism. Moreover, protective effects of MOTS-c in post-ovariectomy females make this peptide a potential factor in the treatment of estrogen-dependent metabolic disorders in post-ovariectomy and post-menopausal women. MOTS-c has protective and multi-organ impact that, if studied further, may contribute to better treatment of various metabolic diseases and cancer.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest

The authors declare they have no conflict of interest.

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