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MOTS-c: an equal opportunity insulin sensitizer

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MOTS-c is a 16-amino acid peptide encoded from 12S rRNA region of the mitochondrial DNA [1]. Multiple publications support the notion that MOTS-c plays an important role in regulating metabolism and insulin action and it has been suggested that MOTS-c exerts exercise mimetic effects in rodents [2]. In this issue of the Journal of Molecular Medicine, Lu et al. [3] revealed an important new role of MOTS-c as a hormone capable of preventing negative metabolic effects associated with menopause in an ovariectomized mouse model. These investigators found that MOTS-c treatment reduced both the weight gain as well as the insulin resistance associated with experimental menopause. Furthermore, they found that MOTS-c also suppressed the increase in inflammatory markers such as IL-1ß and IL-6 in adipose tissue. This anti-inflammatory effect may be key in the health-promoting effects of MOTS-c.

It is well known that postmenopausal women exhibit physiological alterations including weight gain, changes in adipose tissue distribution, and deterioration of insulin secretion, and sensitivity [4, 5]. These changes predispose them to develop type 2 diabetes [4]. Furthermore, decreased levels of estrogen are associated with non-alcoholic steatohepatitis, osteoporosis, and cardiovascular diseases [6-8]. These menopausal-associated metabolic abnormalities and health problems can be alleviated by exercise, whose benefits are obtained via diverse mechanisms including decreased inflammatory mediators, increased activity of antioxidants, and improved endothelial function [9, 10]. A recent meta-analysis on the effects of programmed exercise on insulin sensitivity-related outcomes in postmenopausal women revealed that exercising for three to four months significantly lowers insulin levels, and improves HOMA-IR, BMI, waist circumference, and body fat mass [11]. Exercise, which induces muscle remodeling, is beneficial not only for menopause but also for multiple other chronic diseases. Previous studies have shown that regular aerobic exercise such as walking, running, or high physical fitness has protective effects against obesity, type 2 diabetes, and cardiovascular disease [12-14]. Given the sedentary lifestyle in western societies, developing exercise mimetics offers a promising therapeutic strategy for chronic diseases [15].

The development of such exercise mimetic drugs requires a better understanding of the molecular mechanisms involved in exercise-induced muscle remodeling. Muscle is not only

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a locomotive organ but also an endocrine organ. Muscle releases multiple myokines during exercise, and these myokines likely mediate many of the systemic effects of exercise [16].

Mitochondria not only provide muscle with the necessary fuel, but also release and integrate exercise-induced signaling. AMPK, SIRT1, and PGC1α are central to exercise-induced signaling and are activated in skeletal muscles during exercise, leading to fatty acid oxidation and mitochondrial biogenesis [17]. These processes are followed by muscle remodeling that leads to exercise endurance and metabolic improvements. Indeed, small molecules and naturally occurring compounds that activate AMPK and SIRT1 exert exercise mimetic effects including insulin sensitization protect against diet-induced metabolic dysfunction in mice [18].

MOTS-c has been proposed to be a mitochondrial-derived exercise-mimetic myokine [1]. MOTS-c is expressed in skeletal muscles and other tissues and is detected in plasma. MOTS-c increases endogenous AICAR levels and activates AMPK [1]. In addition, MOTS-c increases NAD+ levels, and SIRT1 is partially involved in MOTS-c actions [1]. MOTS-c also increases insulin sensitivity in skeletal muscle from aged, and high-fat fed, mice [1]. Furthermore, MOTS-c dramatically decreases weight gain during high-fat-diet-induced obesity in mice, and prevents fat accumulation in liver, making it a potential target in NASH (Figure-1) [1, 19]. The paper by Lu and colleagues, suggests that brown adipose tissue (BAT) may also be a direct target of MOTS-c, affecting mitochondrial number and function in this tissue [3]. Lu et al. also show that MOTS-c administration also prevents ovariectomy-induced obesity and insulin resistance in mice via the AMPK pathway. Previous studies revealed that MOTS-c prevents ovariectomy-induced osteoporosis in mice and that it promotes differentiation of bone mesenchymal stem cell to osteoblasts in a rat model [20, 21].

Taken together, MOTS-c is a mitochondrial derived exercise mimetic affecting a variety of chronic diseases of aging, but remarkably, as Lu et al. as well as Lee et al. showed, has no effect on rodents that aren't metabolically challenged (Table-1). In addition, MOTS-c assays could emerge as biomarkers of metabolic dysfunction. Plasma MOTS-c levels are lower in obese male children and adolescents, and are negatively correlated with markers of insulin resistance [22, 23]. MOTS-c levels are also positively correlated with coronary endothelial function in humans, and MOTS-c improves endothelial function in rats [24]. However, the metabolic beneficial effects were observed only in male mice but not in pre-menopausal female mice [22]. Further studies understanding this sexual dimorphism of MOTS-c will extend our understanding of its biology.

MOTS-c directly connects the mitochondria to exercise-induced signaling. Mitochondria are semiautonomous organelles with the capacity to transcribe and translate 13 large proteins and multiple mitochondrial-derived peptides (MDPs) including MOTS-c [25]. MDPs are a group of peptides with potent biological activities and effects on mitochondrial functions and systemic metabolism [25, 26]. MDPs modulate mitochondrial respiration, mitochondrial biogenesis, and mitochondrial ROS production [27-30]. Humanin, the first MDP discovered, has been extensively characterized as a cytoprotective molecule that can attenuate Alzheimer's disease-related pathology, endothelial dysfunction, and macular degeneration

[30-32]. The discovery of humanin represented a paradigm shift in the field of genetics, which has led to discoveries of multiple bioactive peptides encoded by small open reading frames in nuclear and mitochondrial DNA including the family of small humanin like peptides 1-6 (SHLPs), MOTS-c and more such peptides are likely to be discovered and characterized [33, 35].

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References

1. Lee C, Zeng J, Drew BG, et al. (2015) The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab 21:443–454. doi: 10.1016/j.cmet.2015.02.009 [PubMed: 25738459]
2. Lee C, Kim KH, Cohen P (2016) MOTS-c: A novel mitochondrial-derived peptide regulating muscle and fat metabolism.Free Radic Biol Med100:182–187. doi: 10.1016/j.freeradbiomed.2016.05.015 [PubMed: 27216708]
3. Lu H, Wei M, Zhai Y et al. (2019) MOTS-c peptide regulates adipose homeostasis to prevent ovariectomy-induced metabolic dysfunction J Mol Med 10.1007/s00109-018-01738-w
4. Szmuilowicz ED, Stuenkel CA, Seely EW (2009) Influence of menopause on diabetes and diabetes risk. Nat Rev Endocrinol 5:553–558. doi: 10.1038/nrendo.2009.166 [PubMed: 19687788]
5. Paschou SA, Anagnostis P, Pavlou DI, et al. (2018) Diabetes in menopause: risks and management. Curr Vasc Pharmacol 16:1–8. doi: 10.2174/1570161116666180625124405
6. Watts NB (2018) Postmenopausal Osteoporosis: A Clinical Review. J Womens Health (Larchmt) 27:1093–1096. doi: 10.1089/jwh.2017.6706 [PubMed: 29583083]
7. Venetsanaki V, Polyzos SA (2018) Menopause and Non-Alcoholic Fatty Liver Disease: A Review Focusing on Therapeutic Perspectives. Curr Vasc Pharmacol 16:1–10. doi: 10.2174/1570161116666180711121949
8. Khoudary El SR, Thurston RC (2018) Cardiovascular Implications of the Menopause Transition Endogenous Sex Hormones and Vasomotor Symptoms. Obstet Gynecol Clin North Am 45:641–661. doi: 10.1016/j.ogc.2018.07.006 [PubMed: 30401548]
9. Farah C, Kleindienst A, Bolea G, et al. (2013) Exercise-induced cardioprotection: a role for eNOS uncoupling and NO metabolites. Basic Res Cardiol 108:389. doi: 10.1007/s00395-013-0389-2 [PubMed: 24105420]
10. Golbidi S, Badran M, Laher I (2012) Antioxidant and anti-inflammatory effects of exercise in diabetic patients. Exp Diabetes Res 2012:941868–16. doi: 10.1155/2012/941868 [PubMed: 22007193]
11. Bueno-Notivol J, Calvo-Latorre J, Alonso-Ventura V, et al. (2017) Effect of programmed exercise on insulin sensitivity in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause 24:1404–1413. doi: 10.1097/GME.0000000000000936 [PubMed: 28654627]
12. Carnethon MR, Sternfeld B, Schreiner PJ, et al. (2009) Association of 20-year changes in cardiorespiratory fitness with incident type 2 diabetes: the coronary artery risk development in young adults (CARDIA) fitness study. Diabetes Care 32:1284–1288. doi: 10.2337/dc08-1971 [PubMed: 19324945]
13. Chen LY, Zmora R, Duval S, et al. (2018) Cardiorespiratory Fitness, Adiposity, and Heart Rate Variability: The CARDIA Study. Med Sci Sports Exerc Publish Ahead of Print:1. doi: 10.1249/MSS.0000000000001796
14. BLAIR SN, KOHL HW, PAFFENBARGER RS, et al. (1989) Physical-Fitness and All-Cause Mortality - a Prospective-Study of Healthy-Men and Women. JAMA 262:2395–2401. [PubMed: 2795824]

15. Carlson SA, Fulton JE, Schoenborn CA, Loustalot F (2010) Trend and prevalence estimates based on the 2008 Physical Activity Guidelines for Americans. Am J Prev Med 39:305–313. doi: 10.1016/j.amepre.2010.06.006 [PubMed: 20837280]
16. Huh JY (2018) The role of exercise-induced myokines in regulating metabolism. Arch Pharm Res 41:14–29. doi: 10.1007/s12272-017-0994-y [PubMed: 29177585]
17. Cantó C, Auwerx J (2009) PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure.Curr Opin Lipidol20:98–105. doi: 10.1097/MOL.0b013e328328d0a4 [PubMed: 19276888]
18. Fan W, Evans RM (2017) Exercise Mimetics: Impact on Health and Performance. Cell Metab 25:242–247. doi: 10.1016/j.cmet.2016.10.022 [PubMed: 27889389]
19. GRINDSTAFF K, MAGNAN R, SHANG R, et al. (2018) CB4211 Is a Potential Treatment for Metabolic Diseases with a Novel Mechanism of Action—Sensitization of the Insulin Receptor. Diabetes 67:233–LB. doi: 10.2337/db18-233-LB
20. Ming W, Lu G, Xin S, et al. (2016) Mitochondria related peptide MOTS-c suppresses ovariectomy-induced bone loss via AMPK activation. Biochem Biophys Res Commun 476:412–419. doi: 10.1016/j.bbrc.2016.05.135 [PubMed: 27237975]
21. Hu B-T, Chen W-Z (2018) MOTS-c improves osteoporosis by promoting osteogenic differentiation of bone marrow mesenchymal stem cells via TGFβ/Smad pathway. Eur Rev Med Pharmacol Sci 22:7156–7163. [PubMed: 30468456]
22. Du C, Zhang C, Wu W, et al. (2018) Circulating MOTS-c levels are decreased in obese male children and adolescents and associated with insulin resistance. Pediatr Diabetes. doi: 10.1111/pedi.12685
23. Cataldo LR, Fernández-Verdejo R, Santos JL, Galgani JE (2018) Plasma MOTS-c levels are associated with insulin sensitivity in lean but not in obese individuals. J Investig Med jim–2017–000681. doi: 10.1136/jim-2017-000681
24. Qin Q, Delrio S, Wan J, et al. (2018) Downregulation of circulating MOTS-c levels in patients with coronary endothelial dysfunction. International Journal of Cardiology 254:23–27. doi: 10.1016/j.ijcard.2017.12.001 [PubMed: 29242099]
25. Yen K, Lee C, Mehta H, Cohen P (2013) The emerging role of the mitochondrial-derived peptide humanin in stress resistance. J Mol Endocrinol 50:R11–9. doi: 10.1530/JME-12-0203 [PubMed: 23239898]
26. Kim SJ, Xiao J, Wan J, et al. (2017) Mitochondrially derived peptides as novel regulators of metabolism. J Physiol (Lond) 595:6613–6621. doi: 10.1113/JP274472 [PubMed: 28574175]
27. Paharkova V, Alvarez G, Nakamura H, et al. (2015) Rat Humanin is encoded and translated in mitochondria and is localized to the mitochondrial compartment where it regulates ROS production. Mol Cell Endocrinol 413:96–100. doi: 10.1016/j.mce.2015.06.015 [PubMed: 26116236]
28. Sreekumar PG, Ishikawa K, Spee C, et al. (2016) The Mitochondrial-Derived Peptide Humanin Protects RPE Cells From Oxidative Stress, Senescence, and Mitochondrial Dysfunction. Invest Ophthalmol Vis Sci 57:1238–1253. doi: 10.1167/iovs.15-17053 [PubMed: 26990160]
29. Kim SJ, Mehta HH, Wan J, et al. (2018) Mitochondrial peptides modulate mitochondrial function during cellular senescence. Aging (Albany NY)10:1239–1256. doi: 10.18632/aging.101463 [PubMed: 29886458]
30. Nashine S, Cohen P, Chwa M, et al. (2017) Humanin G (HNG) protects age-related macular degeneration (AMD) transmitochondrial ARPE-19 cybrids from mitochondrial and cellular damage. Cell Death Dis 8:e2951. doi: 10.1038/cddis.2017.348 [PubMed: 28726777]
31. Hashimoto Y, Niikura T, Tajima H, et al. (2001) A rescue factor abolishing neuronal cell death by a wide spectrum of familial Alzheimer's disease genes and Abeta. Proc Natl Acad Sci USA 98:6336–6341. doi: 10.1073/pnas.101133498 [PubMed: 11371646]
32. Oh YK, Bachar AR, Zacharias DG, et al. (2011) Humanin preserves endothelial function and prevents atherosclerotic plaque progression in hypercholesterolemic ApoE deficient mice. Atherosclerosis 219:65–73. doi: 10.1016/j.atherosclerosis.2011.06.038 [PubMed: 21763658]

33. Cobb LJ, Lee C, Xiao J, et al. (2016) Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers. Aging (Albany NY) 8:796–809. doi: 10.18632/aging.100943 [PubMed: 27070352]

34. Zhai D, Ye Z, Jiang Y, et al. (2017) MOTS-c peptide increases survival and decreases bacterial load in mice infected with MRSA. Molecular Immunology 92:151–160. doi: 10.1016/j.molimm.2017.10.017 [PubMed: 29096170]

35. Rathore A, Martinez TF, Chu Q, Saghatelian A. Small, but mighty? Searching for human microproteins and their potential for understanding health and disease. Expert Rev Proteomics. 2018 12;15(12):963–965. [PubMed: 30415582]

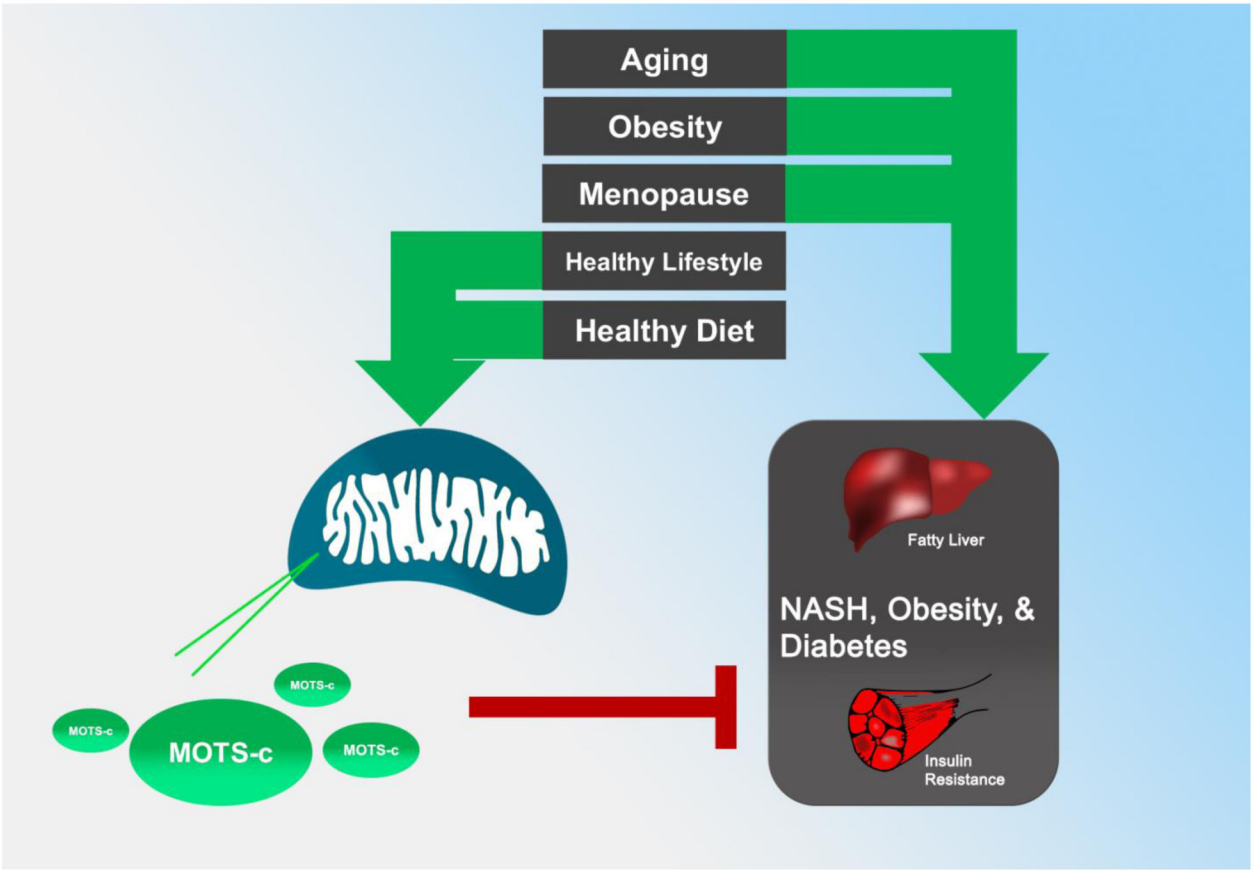

Figure 1.
MOTS-c ameliorates various multiple resistant states.

Table 1.

MOTS-c alleviates various pathological conditions

Pathological conditions	MOTS-c action	References
Aging-associated insulin resistance	Increases glucose uptake in skeletal muscles in aged mice.	[1]
High-fat diet (HFD)-insulin resistance	Increases insulin sensitivity in HFD-fed mice. Increases GLUT-4 expression in skeletal muscle in HFD-fed mice.	[1]
Obesity-associated insulin resistance	Plasma MOTS-c levels are lower in obese male children and adolescents and negatively correlated with markers of insulin resistance and obesity.	[22, 23]
Nonalcoholic steatohepatitis	Decreases hepatic fat accumulation in HFD-fed mice. MOTS-c analogues prevent NASH in a STAM model	[1,19]
Endothelial dysfunction	Improves endothelial function in rats. Plasma MOTS-c levels are lower in human subjects with impaired coronary endothelial function.	[24]
Menopause-associated conditions	Prevents ovariectomy-induced obesity and insulin resistance. Alleviates ovariectomy-induced osteoporosis.	[3, 20]
Osteoporosis/Osteopenia	Alleviates bone loss in ovariectomy-induced osteoporosis via AMPK. Promotes rat bone mesenchymal stem cells differentiation to osteoblasts via TGF-β pathway.	[20, 21]
Sepsis	Improves survival in mice during MRSA infection. Enhances bactericidal capacity of macrophages in MRSA-infected mice.	[34]