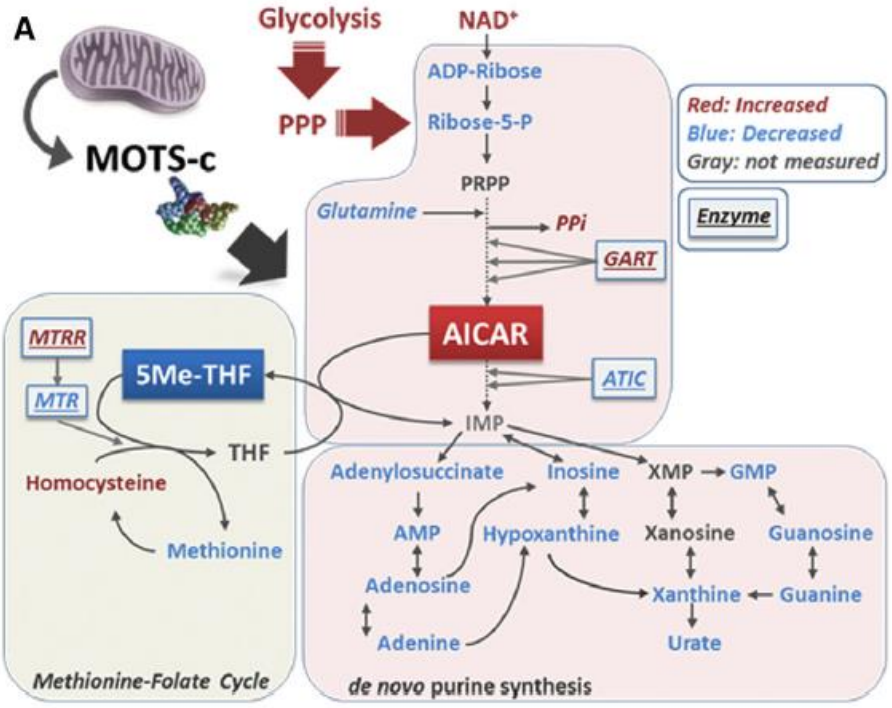
MOTS-c is a peptide encoded as a sORF in the mtDNA that is metabolically and developmentally regulated, which has endocrine-like effects on muscle metabolism, insulin sensitivity, and weight regulation, establishes its role as a member of a new class of mitochondrial signals which can be called MDPs (Lee et al., 2013). The MDP humanin similarly acts in a systemic fashion to protect neuronal and vascular systems from disease processes and toxic insults (Cohen, 2014; Lee et al., 2013).

MOT-C is a short open reading frame (sORF) that encodes a signaling peptide inside the mitochondrial DNA (mtDNA). Mitochondrial 12S rRNA encoding a 16-amino-acid peptide named MOTS-c (mitochondrial open reading frame of the 12S rRNA-c) that regulates insulin sensitivity and metabolic homeostasis. Its primary target organ appears to be the skeletal muscle, and its cellular

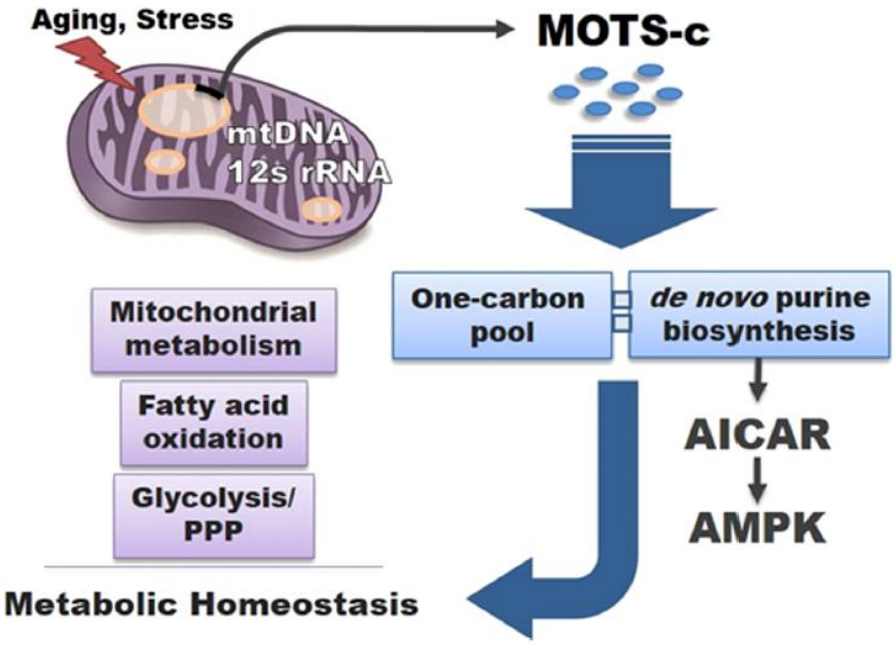
actions inhibit the folate cycle and its tethered de novo purine biosynthesis, leading to AMPK activation.

MOTS-c Targets the Methionine-Folate Cycle, Increases AICAR Levels, and Activates AMPK



MOTS-c Targets the Methionine-Folate Cycle, Increases AICAR Levels, and Activates AMPK. A well-described role of AICAR is to activate AMPK and stimulate fatty acid oxidation via phosphorylation-induced inactivation of acetyl-CoA carboxylase (ACC) that consequently alleviates allosteric inhibition of carnitine palmitoyltransferase 1(CPT-1), and also enhance glucose uptake in muscle (Steinbergand Kemp, 2009).

Regulation of the Folate-AICAR-AMPK Pathway

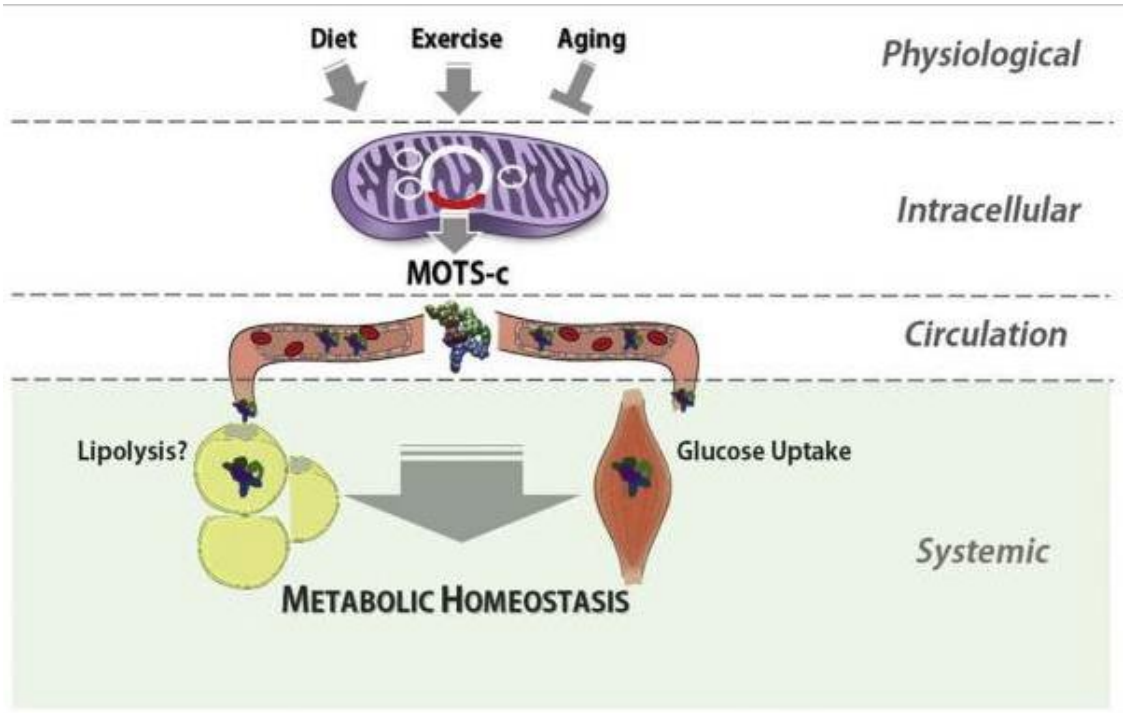


- **MOTS-c Is a Bioactive Peptide that Regulates Gene Expression and Cellular Metabolism**.
- **MOTS-c appeared to stimulate glucose utilization evidenced by increased glucose clearance and lactate accumulation in culture media.**
- **MOTS-c Coordinates Cellular Glucose, Mitochondrial, and Fatty Acid Metabolism**
- **MOTS-c prevents HFD-induced obesity by increasing energy expenditure, including heat production, and improving glucose utilization and insulin sensitivity. Reduced fat accumulation may be a result of robust carbohydrate usage that reduces fatty acid synthesis, but the possible**

involvement of increased fatty acid oxidation, as observed in vitro

The Mitochondrial-Derived Peptide MOTS-cPromotes Metabolic Homeostasisand Reduces Obesity and Insulin Resistance

MOTS-c has been shown to target the skeletal muscle and enhance glucose metabolism. As such, MOTS-c has implications in the regulation of obesity, diabetes, exercise, and longevity, representing an entirely novel mitochondrial signaling mechanism to regulate metabolism within and between cells.



MOTS-c: A novel mitochondrial-derived peptide regulating muscle and fat metabolism.