

Mechanism of SIRT1-mediated Energy Deprivation (Calorie Restriction and Exercise) Against Sarcopenia

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Abstract: *BACKGROUND:* Sarcopenia is a symptom of muscle aging characterized by mass loss and strength loss. The disorder is the leading cause of fall incapacity/death in the elderly and the great enemy of healthy aging. Energy deprivation (calorie restriction and exercise) is the most effective means against aging and SIRT1 is a key mediator molecule. *OBJECTIVE:* The article summarizes and analyzes the mechanisms of SIRT1-mediated energy deprivation against sarcopenia/skeletal muscle aging. *METHODS:* Literature review. *CONCLUSIONS:* Exercise and Calorie restriction lead to intermittent and continuous energy deprivation in muscle, respectively, which may contribute to some differences in their effects and mechanisms. SIRT1 may reside centrally in energy deprivation against sarcopenia. AMPK/NAD⁺ is the bridge between energy deprivation and SIRT1 activation. SIRT1 downstream is mainly through four pathways (FOXO1/autophagy, PGC-1 α /mitochondrial generation, P53/apoptosis and DNA repair, and NF- κ B/inflammation) to antagonize muscle aging/sarcopenia. Future directions to focus on: (1) Difference between the mechanisms of SIRT1 under stresses of exercise and calorie restriction. (2) The role of non-transcription factor targets of SIRT1 such as eNOS, LKB1, etc. 3) Exact division of labor involved in several cellular event molecules simultaneously, such as FOXO1, NF- κ B and P53.

Keywords: SIRT1, Sarcopenia, Calorie restriction, Exercise, Skeletal muscle, Aging

1. Introduction

Aging is a complex process of progressive structural and functional decline. Loss of mass/strength is an important feature of skeletal muscle aging. The phenomenon /symptom is known as sarcopenia. Its occurrence is associated with changes in inflammation, mitochondria, motor endplates, satellite cells and hormones. As the most metabolically active tissue in the body, sarcopenia has far-reaching effects, worsening chronic diseases such as obesity, type II diabetes, osteoporosis, rheumatoid arthritis, atherosclerosis, Alzheimer's disease, malignancies, etc. It is also the "number one killer" of falls incapacitation/death in the elderly. Therefore, sarcopenia prevention and control has been a hot issue[1, 2].

The essence of sarcopenia prevention is skeletal muscle resistance to aging. Energy deprivation (both in the form of Calorie restriction and exercise) is the most effective non-pharmacological means against aging, while several interrelated events such as insulin/IGF-1 signaling, oxidative damage, autophagy/mitophagy, and inflammation are involved in the mediation of anti-aging functions, of which SIRT1, a core molecule of energy and metabolism, is the key mediator. This review focuses on SIRT1-mediated anti-aging mechanisms under energy deprivation in skeletal muscle.

2. Overview of SIRT1

Structurally, SIRT consists of an N-terminus, an allosteric part, a catalytic core and a C-terminus. The allosteric part and catalytic core constitute its active center, and the N-terminal and C-terminal have nuclear localization signals and output signals. Functionally, it is a class of NAD⁺-dependent histone deacetylases that shuttle through the cytoplasmic nucleus and perform signal transduction functions - activating/inactivating transcription factor activity through deacetylation and altering the function of non-histone proteins by deacetylating them. SIRT plays an important role in some cellular activities such as silencing and cell cycle regulation. There are seven SIRT species in mammals, the most intensively studied being SIRT1. Numerous ex vivo and in vivo studies have confirmed that SIRT (mainly referring to SIRT1) has a wide range of anti-aging effects in cells/tissues[3-5] – in aging tissues/organ (skeletal

muscle, heart, brain, lung, liver, kidney) and cells (endothelial cells, vascular smooth muscle cells, macrophages), SIRT1 decreases; SIRT1 overexpression ameliorates sarcopenia, diabetes, obesity, cancer, neurodegenerative diseases, cardiovascular diseases and prolongs lifespan in mice, and also blocks the pro-aging effects of UV, angiotensin II, oxidative stress on fibroblasts, human coronary artery endothelial cells, porcine aortic endothelial cells and lung cells.

3. Mechanisms of SIRT1 in energy deprivation against aging in muscle

3.1. Similarities and differences between Calorie restriction & exercise

Calorie restriction and exercise are two means of energy deprivation. The former is restriction of fasting (minus 15-55% of regular food intake) and the latter is regular physical training. Some studies have considered exercise as a calorie restriction analogue. This study considers that there is no subordination between the two and that they should both be considered as a form of energy deprivation. From an energy perspective, both two reduce cellular energy reserves. However, the two means of energy deprivation are somewhat different. Calorie restriction results in a chronic and persistent state of low energy, whereas the low energy caused by exercise is transient and intermittent. Exercise, such as full-speed running, boxing, and resistance training, the body often gets fatigued in seconds to tens of seconds, while even very low-intensity aerobic activities, such as jogging, often lasts no more than half an hour. After fatigue, people will spontaneously replenish the energy substrate. Frequent participants in exercise have an organism that is more frequently in a low-energy/high-energy transition. Intervals and duration may be the key to the differences in the effects of the two energy deprivation modalities. Studies have found that calorie restriction can present some problems that are less likely to occur with exercise, such as early menopause, depression, and stones. For aging prevention in muscle, the difference in the mechanism of effect between continuous and intermittent energy deprivation needs to be further investigated.

3.2. Energy deprivation, SIRT1 and resistance to aging in muscle

There have been many studies on SIRT1-mediated calorie restriction and SIRT1 anti-aging mechanisms [6, 7], and AMPK, NAD⁺, FOXO, PGC-1 α , NF- κ B P65, and P53 are considered to be the key downstream effector molecules of SIRT1 against aging [3, 8]. Most of such studies have targeted vascular endothelial cells, whereas SIRT1 function is tissue-specific. This study focuses on relative reports in skeletal muscle.

AMPK/ NAD⁺ is the link between energy deprivation and SIRT1. Energy deprivation leads to decreased ATP and increased ADP/ATP which in turn activates AMPK which is involved in many intracellular signaling through phosphorylation of other proteins. The disclosure of AMPK anti-aging effect predates SIRT1's, which is at least partially mediated by SIRT1. It was found that AMPK activity was reduced in aging muscle, whereas the AMPK agonists metformin and berberine both had an effect on preventing muscle atrophy, and low-calorie diets simultaneously upregulated AMPK, SIRT1 and PGC1 α in human muscle, whereas SIRT1 knockdown reduced the active effect of resveratrol (calorie restriction mimicry) on mitochondrial function in muscle [9-11]. The control of SIRT1 by AMPK is mediated by NAD⁺, a key cofactor in the maintenance of cellular energy metabolism, which activates the gene expression of SIRT1 and whose homeostasis is doubly regulated by the opposing roles of AMPK, CD38.

Downstream molecules of SIRT1, FOXO, PGC-1 α , NF- κ B P65 and P53, are closely involved in the intervention of important cellular events such as autophagy, mitochondrial function, DNA repair and apoptosis, inflammation, DNA damage [3], which are key effective links in low-energy stress/energy deprivation adaptation.

Autophagy is an important process of organelle phagocytosis, proteolysis, and cellular self-renewal. Excessive activation of autophagy can cause severe cell/tissue damage, such as muscle atrophy and dysfunction in cancer cachexia, but this is uncommon. In essence, the role of autophagy is protective - to maintain internal environmental homeostasis and prevent apoptosis/death by removing misfolded proteins and senescent, damaged organelles. In muscle SIRT1 activates autophagy in two main ways: (1) by deacetylation of the transcription factor FOXO1, which activates autophagy gene expression (encoding ATG5/6/7, LC3, etc.) (2) by activation in AMPK and inhibition in mTOR, which upregulates ULK1. The exact process is that SIRT1's deacetylation activates LKB1, followed by activated AMPK which in turn upregulates autophagic activity by directly activating ULK1 (at SER 317, 467, 555, 574,

637 and 777 sites), and by inhibiting mTOR (which inhibits ULK1-AMPK linkage upon activation).

Mitochondrial dysfunction/oxidative stress is one of the main causes of sarcopenia. Mitochondrial dysfunction leads to respiratory chain uncoupling, ROS upregulation/oxidative stress, followed by activation of the ubiquitin protease catabolic pathway (mediated by ROS) and apoptosis of the mitochondrial pathway (pro-apoptotic factor release), resulting in structural loss and functional decline. The transcriptional co-activator PGC-1 α which assists NRF1/2 (nuclear respiratory factor 1/2) in activating mitochondrial gene transcription is a master controller of mitogenesis. SIRT1 promotes mitogenesis and anti-apoptosis/anti-chronic-disease effect through upregulation of PGC-1. Mechanistically, it is generally believed that the main means of SIRT1 in regulation of PGC-1 α is activation (deacetylation), but SIRT1 is also able to upregulate PGC-1 α expression - activation of SIRT1 in C2C12 myotubes upregulates PGC-1 α , while PGC-1 α is reduced in skeletal muscle of SIRT1 knockout mice. Besides mitogenesis, mitophagy and mitochondrial division/fusion dynamics are also important determinants of mitochondrial function. Mitophagy is also a part of autophagy and will not be discussed further (see above). In terms of dynamics, PGC-1 α has a pro-fusion effect on mitochondria and therefore. Thereby, theoretically, its activator SIRT1 could be used to do the same. However, direct evidence in this regard is lacking and is to be investigated.

DNA damage and apoptosis are among the consequences of mitochondrial dysfunction. The former can directly lead to genetic mutations, which are associated with a variety of symptoms such as aging, inflammation, and tumors, while the DNA repair network, including the latter (apoptosis) can counteract DNA damage and maintain genomic stability. When its DNA damage can be repaired, P53 activates p21 (cell cycle arrest) expression, giving the cell more time to repair adequately and avoiding apoptosis; conversely, when damage is perceived as irreversible, P53 initiates apoptosis (upregulates Bax), removing the "irredeemable" individuals and maintaining the health of the whole. During calorie restriction or exercise, SIRT1 activation inhibits apoptosis by inactivating P53 (deacetylation) to avoid muscle fiber reduction, but does not initiate DNA repair. This suggests that the P53 duty in energy deprivation adaptation is not anti-tumor and anti-fatigue, but anti-muscle-loss. This may be related to the low incidence of skeletal muscle tumors and the fact that muscle fiber senescence is more beneficial to muscle than loss. Inactivated P53 also inhibits autophagy (by pink1), a mechanism that limits autophagy overactivation. In addition, SIRT1 can also participate in DNA repair (repair of DNA double-strand breaks) by deacetylation of KU70.

Inflammation is an important trigger for sarcopenia, which is enhanced in both directions with oxidative stress. NF- κ B is the master switch of the inflammatory response and is usually linked to the NF- κ B inhibitor protein inhibitor (I κ B) in the form of a p65/p50 dimer. p65/p50, when activated, can be activated and translocated to the nucleus to regulate the transcription of various downstream inflammatory factors (TNF- α , IL-1 β , IL-2, IL-6, IL-8, IL-12, INOS, COX2, chemokines, adhesion molecules, colony-stimulating factors, etc.). SIRT1 is an important inactivator (deacetylation inactivation) of NF- κ B (P65), so its anti-inflammatory effects are not unexpected. Some studies have shown that Sirtinol (SIRT1 inhibitor), and SRT1720 (SIRT1 activator) enhanced and inhibited release of pro-inflammatory cytokine in smoking-treated mice, respectively. The evidence for a direct SIRT1/ NF- κ B link includes: reduced SIRT1 expression led to NF- κ B signaling activation and CNS damage; upregulation of SIRT1 inhibited NF- κ B in microglia and attenuated the neurotoxic effects of β -amyloid (a mediator of dementia) in mouse brain; and carboxamide triazole inhibited activation in NF- κ B and SIRT1 and attenuated muscle atrophy in tumor-bearing mice[12].

4. Conclusions

SIRT1 may play a central role in energy deprivation against sarcopenia by the mechanism that is essentially cellular adaptation to a low energy state. Specific mechanisms include AMPK/NAD⁺ links between reduced energy reserves and SIRT1; SIRT1 antagonizes muscle senescence/sarcopenia by activating or inactivating FOXO1/autophagy, PGC-1 α /mitogenesis, P53/apoptosis and DNA repair, and NF- κ B/inflammatory pathways.

Future research needs to focus on (1) differences in the mechanisms and effects between exercise and Calorie restriction during energy deprivation, and the role of SIRT1 in this process; (2) the role of non-transcription factors downstream of SIRT1 such as eNOS and LKB1; (3) how the fine division of labor among AMPK, FOXO1, NF- κ B, P53, etc., which are involved in multiple cellular events, are governed by SIRT1. For example, FOXO1 is not only involved in autophagy but also in apoptosis; P53 is not only involved in apoptosis but also mediates glucose metabolism and mitochondrial respiration, and NF- κ B,

the master controller of inflammation, can also activate anti-apoptotic gene expression, etc.

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