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MINI-REVIEW

Effect of Calorie Restriction on the Expression of Sirtuin1 as an Antiaging Biomarker

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Abstract

Calorie restriction (CR) is the most effective method for delaying aging and preventing the onset of age-related diseases. Sirtuins constitute a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases. Their activity can be regulated by NAD^+/NADH levels, which are influenced by nutrient intake, a variable acted upon by CR. This review elaborates on the link between CR and sirtuin1 (SIRT1). It retrieved articles from several sources, such as ClinicalKey, PubMed, and ScienceDirect. It discusses the up-to-date knowledge of how SIRT1 acts as a nutrient sensor and regulator of molecular mechanisms. These mechanisms include the control of the cell cycle, enhancing mitochondrial quality control, activating fatty acid oxidation, and stimulating anti-inflammatory effects. Disruptions in the aforementioned mechanisms are the basis of aging. CR increases the expression of SIRT1, which enhances the biogenesis and dynamics of mitochondria, resulting in an antiaging effect. In CR, SIRT1 is activated and stimulates different pathways, especially those related to mitochondrial activity and effectiveness, leading to an antiaging effect in collaboration with other antiaging biomarkers.

Keywords: antiaging, calorie restriction, sirtuin1

Introduction

The elderly population is continuously increasing, and this trend has a substantial effect on the healthcare sector because additional effort is required to optimize this particular population [1]. A statistical review by the US Census Bureau predicted that the proportion of the global elderly population would double in 35 years between 2015 and 2050. Within the same period, the elderly population aged 80 and above is expected to increase thrice [2]. In Indonesia, the number of people aged 60 years and over has also increased and may reach 44.9% (30,162,000 people) in 2010–2035, as indicated by population census data [3]. Aging is a multifactorial degenerative process that involves genetic and environmental influences with considerable complexity. A multidisciplinary approach is required to achieve what is known as "healthy aging." Nutrition is a factor to be considered because it is not only a basic need of living beings but also a massive influence on physiological function, well-being, and overall quality of life [4].

The concomitant increase in life expectancy with the expansion of the aging population can be seen as a positive change because it would provide considerable benefits and opportunities in all aspects to the elderly and their families and society. However, the quality of aging itself is being questioned. Health is a factor that significantly influences how much a person can enjoy such extended advantages. Diet and nutrition are undoubtedly a part of health and thus affect how a person ages. Studies have shown different correlations between diet and aspects of aging, particularly the genes that participate in aging [4].

Given the numerous theories on the mechanism underlying the complex aging process, no single aging mechanism may exist. An idea proposed by Kirkwood that is widely accepted is that the underlying mechanism contributing to aging starts at the molecular level and involves the gradual build-up of molecular damage, such as telomere shortening and mutations, which leads to defects at a cellular level, including dysfunctions in

mitochondria and repair mechanisms. These cellular defects would result in tissue damage that proceeds to the organ system level [5, 6].

Although aging is inevitable, it can be modulated by different approaches. A particular diet regimen known as calorie restriction (CR) is highlighted in this research. CR is defined as reducing calorie intake below ad libitum without causing malnutrition and can be mimicked through numerous ways, including prolonged fasting (PF) and intermittent fasting (IF) [7]. One way by which CR participates in decelerating aging is by triggering the expression of sirtuin1 (SIRT1) in numerous organs, such as the liver, muscle, heart, and kidney. Reduced calorie intake would increase the nicotinamide adenine dinucleotide (NAD), the metabolic substrate of sirtuins, eventually resulting in the activation of additional SIRT1 [7–10]. The health-promoting effects associated with CR are believed to be mediated by the increased activity of SIRT1. SIRT1, along with other sirtuins, is a NAD^+-dependent deacetylase. As a metabolic sensor, SIRT1 acts to mediate responses to nutrient availability.

As a proteome regulator, SIRT1 targets histones to regulate epigenomic and nonhistone proteins. At a cellular level, SIRT1 counteracts the hallmarks of aging, such as genomic instability, epigenetic alteration, telomere shortening, proteostasis imbalance, cellular senescence, and mitochondrial dysfunction. Through these activities, SIRT1 can delay aging and extend lifespans, it can also extend health spans by delaying the onset of aging-related diseases, including cancer, cardiovascular diseases, inflammation, and neurodegeneration [9, 10].

Increased SIRT1 in the liver improves insulin sensitivity and reduces fat gain. At a molecular level, SIRT1 regulates the metabolic transcription of cholesterol and fatty acids in hepatocytes. Thus, SIRT1 protects against pathologies, including inflammation, glucose intolerance, and liver steatosis, typically induced by a fat-rich diet [7, 8]. Moreover, SIRT1 participates in bile acid metabolism and transport by modulating the bile acid farnesoid X receptor. Bile acids are important signaling molecules and regulators of glucose and lipid homeostasis. SIRT1 further extends its role in the liver by promoting fat mobilization and regulating liver regeneration. However, with age, the level of SIRT1 in the liver and other organs decreases, and molecular hallmarks of aging, such as DNA damage, increase simultaneously [7, 8].

Previous studies have shown the benefits of restricting calorie intake, especially its positive effect on lifespan, in animals of low evolutionary complexity, such as yeast, *Drosophila*, and mice. In particular, IF and PF have attracted the interest of researchers because they are easier to follow than traditional CR. Myriad studies have proven that IF and PF trigger pathways similar to those triggered by CR by downregulating nutrient-sensitive signaling pathways and simultaneously activating stress-resistant pathways. In yeast, gene silencing due to histone deacetylation prevents recombination between rDNA repeats and the accumulation of extrachromosomal rDNA circles. In mice, SIRT1 gene overexpression results in a significantly extended lifespan along with the occurrence of phenotypes associated with delayed aging, including enhanced physical activity and oxygen consumption. In addition, mice with an extra copy of the SIRT1 gene have less DNA damage and lower p16 levels than nontransgenic mice [8, 9].

This review provides in-depth insight into sirtuins, specifically SIRT1, and then discusses the dietary regimen known as CR, which exerts a well-established influence on lifespan. Moreover, the correlation between SIRT1, CR, and longevity is discussed.

Definition of Sirtuin

Sirtuins are a family of proteins that primarily act as histone deacetylases. Their activity is dependent on NAD^+. The first sirtuin was discovered in *Saccharamyoces cerevisae* through genetic screening and was named silent information regulator 2 (Sir2). Sir2 became the basis for identifying the remaining members of the sirtuin family, which is evolutionarily conserved across various organisms. Sir2 is a gene-silencing protein. It represses gene transcription at particular loci known as HM mating-type loci during the initial stages of yeast development but later moves to ribosomal DNA, where it acts to prevent DNA damage as yeasts age. Sir2 became the foundation for identifying the rest of the sirtuin family, which is evolutionarily conserved across various organisms, from yeast to humans [10, 11].

Mammalian sirtuins consist of seven members (SIRT1–SIRT7), which, through phylogenetic analysis, are classified into four classes: class I consists of SIRT1, 2, and 3; class II contains SIRT4; class III comprises SIRT5; and class IV includes SIRT6 and 7. They differ in localization, substrate targets, and functions. Sirtuins are found in different cellular compartments, allowing them to act on various substances and metabolic reactions. Studies have shown that mammalian sirtuins have crucial advantages in life processes, such as stress response, longevity, and aging. At a molecular level, sirtuins regulate gene transcription, DNA repair, cell survival, inflammation, and energy metabolism [10, 11].

Among sirtuins, SIRT1 in humans has the highest sequence homology with Sir2 in yeast. It is also the subtype that is most extensively studied. In addition to deacetylating histones, SIRT1 acts on DNA repair proteins, such as poly-ADP-ribose polymerase 1, and transcription factors, including p53, nuclear factor κ-light-chain-enhancer of activated B cell, and peroxisome proliferator-activated receptor γ coactivator 1-α. The

ability of SIRT1 to shift its location from the nucleus to the cytosol diversifies its possible activities because SIRT1 can interact with proteins in either the nucleus or cytoplasm [12, 14].

SIRT2 is mainly cytosolic but can also switch to the nucleus, where it modulates cell cycle control by binding to chromatin during mitosis. SIRT3 is a mitochondrial protein. However, when stimulated by stress, it can transfer to the nucleus. SIRT4 and SIRT5 are also located in the mitochondria, where they regulate metabolic enzymes and managing oxidative stress. SIRT6 is localized in the heterochromatic region, whereas SIRT7 is found in the nucleoli; both function in nuclear mechanisms, such as DNA repair and gene expression [11, 14].

Location and Structure of SIRT1

SIRT1 mainly localizes in the nucleus. However, a small amount of SIRT1 can be found in the cytoplasm. Such a localization pattern expands the variety of possibilities for SIRT1 because it can interact with proteins in the nucleus or the cytoplasm. The factors that determine the location of SIRT1, however, remain unknown, with stress level and molecular interactions thought to be among them [15].

SIRT1 consists of 747 amino acids and comprises a catalytic core, an N-terminal region, a C-terminal region, and an allosteric site. The catalytic core is conserved in mammals, and the terminal domains vary in length and sequence. The N- and C-terminal domains are not arranged in a fixed manner. Instead, they are dynamic and can undergo conformational changes, enabling the attachment of a myriad of regulators. This property accounts for the different functional roles of SIRT1 [16, 17]. The core of SIRT1 consists of two subdomains: a large NAD^+-binding site and a small domain. The small domain comprises a helical module and a Zn^+-binding module that are bonded through a hydrophobic interface and are also connected to the NAD^+-binding domain. The binding cleft that forms from the interaction between the two subdomains creates a binding site for a substrate during a catalytic reaction. Despite being structurally consistent throughout the sirtuin family, the catalytic core shows some differences in charge distribution, influencing its hydrophobicity [15, 16]. In addition, the two important segments of SIRT1 are the nuclear localization signal (NLS) and the nuclear export signal (NES). Two NLSs and one NES are part of the N-terminal region, and another NES is found in the core [15, 17].

Functions of SIRT1

SIRT1 participates in various physiological and pathological processes. The enzymatic activity of SIRT1 involves deacetylation. SIRT1 targets histone and nonhistone substrates. SIRT1 regulates the transcription of histones H3 (H3K9ac and H3K14ac), H4 (H4K16ac), and H1 (H1K26ac) through deacetylation. The deacetylation of these histone tails is one way SIRT1 epigenetically regulates genes [18,19]. Another function of SIRT1 is to control metabolic homeostasis. When the level of SIRT1 increases, the deacetylation of PGC-1a increases. PGC-1a thus becomes activated. Given that PGC-1a regulates numerous genes involved in metabolic processes, such as thermogenesis, mitochondrial biogenesis, and gluconeogenesis, its activation increases mitochondrial activity and glucose metabolism [19].

Stress, such as carcinogens and hypoxia, can damage various intracellular molecules, including DNA. When DNA damage occurs, cells respond in numerous ways, one of which is to promote the acetylation and activation of p53. If the damage exceeds a certain threshold, the cells undergo p53-dependent apoptosis; however, SIRT1 activation represses p53 and simultaneously enhances the repair mechanism, thereby promoting longevity. The deacetylation of Ku70, a DNA repair protein, by SIRT1 can stimulate DNA repair and prevent Bax-mediated apoptosis. However, some findings on the effects induced by SIRT1 are contrary to what is already known. For example, when PGC1a is deacetylated, cells become prone to another form of apoptosis, namely, TNFα-induced apoptosis. Therefore, SIRT1 can be said to exert a proapoptotic as well as an antiapoptotic influence on cells [18, 19].

In the context of pathology, SIRT1 activation is neuroprotective and protects against the development of neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, mainly by deacetylating PGC-1 and HSF-1. PGC-1 deacetylation by SIRT1 promotes mitochondrial biogenesis and its activity, which protects dopaminergic neurons from oxidative stress and protein aggregation, thereby preventing the onset of Alzheimer's and Parkinson's diseases [20]. Moreover, the deacetylation of HSF-1 by SIRT1 activates Hsp70 transcription, thereby reducing α-synuclein aggregation, which is exacerbated in Alzheimer's and Parkinson's diseases [21]. SIRT1 is also involved in cardiovascular disease and tumors [5, 22]. SIRT1 inhibits atherosclerosis by reducing NF-ĸB activity and inducing endothelial nitric oxide synthase [23].

Modulation of SIRT1

The numerous positive effects of SIRT1 activation on metabolic and gene expression regulation and stress response have piqued the interest of researchers investigating the modulation of SIRT1 to maximize its benefits. Among sirtuin modulators, sirtuin-activating compounds (STACs) have a higher therapeutic potential than sirtuin-inhibiting compounds (STICs). Some advantages of STACs over STICs include high specificity

for the target molecule because activators tend to act on the allosteric site and thus conserve the catalytic core. Another benefit is that activators induce few side effects [24, 25].

The most well-known STAC is resveratrol, a polyphenol that is naturally found in the skin of red grapes, peanuts, berries, and red wine. Although other classes of polyphenols have been discovered, resveratrol is of particular importance due to its high potency: it can increase SIRT1 levels by up to 10 times. However, the mechanism underlying this process is still unknown. A study used peptide microarrays to analyze 6802 acetylation sites of SIRT1 in the presence of resveratrol. It proved that adding resveratrol increased the peptide deacylation of factor SF38A by SIRT1 [26]. In mice, resveratrol prolonged lifespan through mitochondrial improvements. Clinical trials were and are being performed to demonstrate the potential of resveratrol as a therapy for many diseases, such as type 2 diabetes mellitus and other metabolic disorders, in humans [18, 20]. Deng et al. recently investigated the effect of resveratrol on osteoarthritis (OA) and found that resveratrol increased SIRT1 levels in a dose-dependent manner and exerted the effects of SIRT1 modulation on chondrocytes and numerous metabolic pathways, leading to the inhibition of OA progression [24, 25].

However, this natural activator has some drawbacks. They include poor specificity for sirtuin family members and low bioavailability. These drawbacks led to the development of a synthetic STAC known as SRT1720. SRT1720 is structurally different from resveratrol but has high potency. Since then, additional synthetic alternatives have been investigated, with SRT2104 being the most advanced [24, 25].

In some cases, the therapeutic effect of sirtuin modulation is achieved by inhibiting sirtuin activity. Splitomicin was the first sirtuin inhibitor to be discovered. It was identified through the screening of Sir2 inhibitors in yeast. Although splitomicin is effective only against yeast sirtuin and not against human sirtuin, its discovery led to the identification of additional inhibitors through different approaches, including structure-based, mechanism-based, or virtual screening methods [18, 19]. Given that the research on sirtuin inhibitors is more extensive than on sirtuin activators, more inhibitors than activators have been discovered [27].

Some inhibitors are classified as mechanism-based inhibitors. They include nicotinamide, which is a product of sirtuin deacetylation and hence can be considered a natural inhibitor. Other mechanism-based inhibitors are compounds containing thioacyllysine, which inhibits sirtuin by forming the 1′-*S*-alkylimidate intermediate during deacetylation. These compounds occupy the catalytic core, preventing full deacetylation. However, despite their high potency, these thioacyl peptides have poor selectivity. Further modifications are required to increase their specificity for a target sirtuin [24, 25].

CR

The first evidence for a correlation between CR and metabolism was observed 100 years ago in yeast. Upon the induction of CR, the lifespan of yeast was extended. Specifically, calorie intake was reduced by 30%–50% in yeast. The ideal amounts of CR in mice and humans are 30% and 15%, respectively [9].

Numerous studies have demonstrated the potential beneficial effects that can be induced by fasting. These effects include cellular metabolism regulation, which enables resistance against oxidative stress by increasing the efficiency of energy production and decreasing the production of reactive oxidative species. Fasting also has other protective effects that have been validated in the rat brain and mouse liver and kidney. It also prevents carcinogenesis. The mechanisms by which fasting can cause the aforementioned effects are believed to be similar to those stimulated by CR [9].

Understanding the mechanism by which CR promotes longevity could provide deep insights into whether aging can be modulated through behavioral or pharmacological changes. CR is a direct intervention feasible in real life, so it has fascinated the general public and the scientific community. Since the first study on yeast by McCay et al., numerous works have been performed to acquire additional discoveries about this particular diet and its underlying mechanism. Aging is a universal experience. Thus, considerable efforts have been made to delay or improve the quality of aging. Thus far, CR is said to be the most successful mechanism that not only decelerates aging but also reduces the risk of acquiring diseases that are often seen in the elderly. CR decreases cardiovascular risk factors more than drug administration [28]. It is generally accepted to influence the body in all aspects—from the biochemical to cellular to physiological—thus promoting CR's prolongevity effect [9, 29]. However, most people find maintaining a lifestyle with CR difficult in the long term. This situation increases the need to develop natural and synthetic molecules that can mimic the effects of CR without reducing food intake. Such molecules are known as CR mimetics (CRM) and include resveratrol. Their effects have been tested in mice and humans. Recent studies compared the antiaging effects of CR and resveratrol and found that CR and resveratrol have similar activities on SIRT1 mRNA levels, increasing the protein expression of FOXO 3a. Therefore, in in vivo and in vitro studies, CR and resveratrol produce antiaging effects similarly [30].

The factor behind CR has been challenged by the initial assumption that a decrease in calorie intake alone is

responsible for the effects of this intervention. However, vigorous research on reducing individual macronutrients demonstrated that calorie level is the primary driving factor of the benefits of CR, with lipids and proteins affecting the effectivity of CR [29, 31]. Daily fasting, regardless of the composition of nutrients in the diet, can activate the same mechanisms that CR stimulates [31, 32].

Sirtuin, CR, and Aging

Aging is multifactorial and involves changes at all organismal levels, from organs to cells. Over time, senescent cells accumulate in various tissues, impairing proper tissue function by influencing the surrounding cells through various mechanisms, such as cytokine, chemokine, and inflammatory mediator secretion. This phenomenon can induce low-grade inflammation, observed in the aging population, causes the further senescence of neighboring cells and increases the risk of tumor progression. In addition to their secretory phenotype, these senescent cells have other enhanced features, including but not limited to cell cycle inhibition, granulation, and DNA damage. DNA damage is hypothesized to be the primary cause of cellular senescence and results from the impairment of the DNA repair system as a person ages. DNA damage has a detrimental effect on the normal functioning of cells, and the ability to repair DNA is crucial for preventing the accumulation of DNA damage. The indispensable role of sirtuins in DNA repair, inflammation control, and antioxidative defense indicates that sirtuins are a good antiaging/antisenescence target [33–35].

The level of SIRT1 in the liver decreases with age due to the reduction in NAD^+ availability and the simultaneous increase in the accumulation of DNA damage. The overexpression of SIRT1 increases the expression of PPARα and activates PGC-1α; both effects improve oxidative metabolism and regulate lipid metabolism as a response to nutrients and hormonal signals [33–35].

Furthermore, SIRT1 levels in the arteries have decreased, suggesting that SIRT1 participates in cardiovascular system aging. Reduced SIRT1 expression promotes the expression of the genes responsible for aging. As such, the enhancement in SIRT1 activity is proven to be beneficial. SIRT1 inhibits the activation of NF, thus reducing oxidative stress and inflammation in the vascular endothelium. In an experiment by Herrnaz et al., mice induced with an extra copy of the SIRT1 gene presented reduced hallmarks of aging, such as DNA damage and p16 levels. The overexpression of SIRT1 in the cardiac muscle decreases the area affected by myocardial infarction, thus facilitating recovery [33, 36].

The decline in nutrient intake with CR is perceived as metabolic stress by the body's metabolic sensors. This perception then stimulates changes at the molecular and physiological levels. Three sensors exist, namely, the mammalian target of rapamycin (mTOR), adenosine monophosphate-activated protein kinase (AMPK), and sirtuins [37]. One function of these sensors is controlling the ratio between catabolic and anabolic processes to achieve metabolic homeostasis, the interruption of which is related to age-related diseases and aging as a whole [36–37].

CR decreases the activity of mTOR while simultaneously activating sirtuin (via the increase in NAD^+/NADH ratio) and AMPK (via the increase in AMP/ATP ratio). In addition, the inhibition of mTOR activates sirtuin further and vice versa. AMPK phosphorylates PGC-1α and mediates metabolism, including mitochondrial biogenesis and insulin response, whereas SIRT1 deacetylates PGC-1α, thereby activating PGC-1α. PGC-1α is crucial for mitochondrial dynamics and biogenesis and regulates oxidative phosphorylation. This process is summarized schematically in Figure 1. Given that SIRT1 has a variety of substrates, it has a broad effect. For example, APE1, a protein responsible for DNA damage repair and stimulates protein endonuclease activity, is a SIRT1 target. The accumulation of cellular damage, especially mitochondrial and genomic damage, is associated with aging and its related diseases. Hence, preventing such damage through activating SIRT1 and other antiaging biomarkers is widely accepted to lengthen lifespan and health span [37–40].

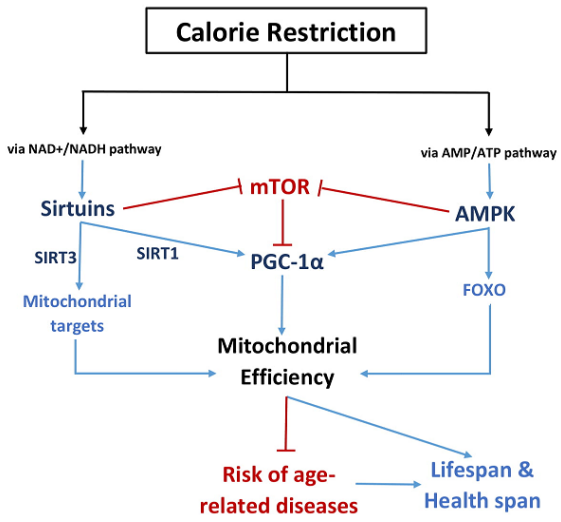

Figure 1. Effect of CR on Lifespan via SIRT1 Expression. CR Decreases the Activity of mTOR while Simultaneously Activating Sirtuin (via the Increase in NAD^+/NADH Ratio) and AMPK (via the Increase in AMP/ATP Ratio). AMPK Phosphorylates PGC-1α and Mediates Metabolism, Including Mitochondrial Biogenesis, whereas SIRT1 Deacetylates PGC-1α. The Activation of PGC-1α is Crucial for Mitochondrial Dynamics, which Plays a Role in Preventing Degenerative Diseases and Promoting Lifespan as Well as Healthy Aging

Conclusion

CR increases the expression of SIRT1, which enhances the biogenesis and dynamics of mitochondria, resulting in an antiaging effect. In CR, SIRT1 is activated and stimulates different pathways, especially those related to mitochondrial activity and effectiveness, inducing an antiaging effect in collaboration with other antiaging biomarkers. In addition, substances that mimic CR, such as resveratrol, can act as sirtuin modulators that enhance sirtuin activity. Such substances represent another area for exploration.

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