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An Overview on Sirtuins in Aging

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Abstract

Aging is a universal process that began with the origination of life about 3.5 billion years ago. Accumulation of the diverse deleterious changes produced by aging throughout the cells and tissues progressively impairs function and can eventually cause death. Aging changes can be attributed to development, genetic defects, the environment, disease, and an inborn process—the aging process. Various cellular and molecular changes occur in the constituents of the brain (for example, neurons, microglia, astrocytes and oligodendrocytes) during the ageing process. Functional alterations, such as cognitive decline, mental deficits, sleep disruption and circadian dysfunction, are induced by these cellular and molecular changes. Sirtuins have crucial roles in the regulation of brain function during the ageing process. Activation of microglia, possibly caused by reduced sirtuin activity, induces prolonged neuroinflammation, resulting in synaptic damage and neuronal death. Age-associated decline in hypothalamic function, which is probably due to reduced SIRT1 activity, mediates ageing at a systemic level and ultimately affects longevity in mammals. Peripheral tissues communicate with the brain via a range of hormones and circulating factors, which have been characterized by parabiosis experiments, thus affecting the pathophysiology of brain ageing.

Keywords: Sirtuins, aging, elderly.

Mini review article **Corresponding Author*, e-mail: *ahalkolaly@gmail.com*

1. Introduction

Ageing is a conserved phenomenon across all species and imposes an ever-increasing risk of dysfunction and death in older organisms. Growing evidences have shown that sirtuins are essential factors those delay cellular senescence and extends organismal lifespan through the regulation of diverse cellular processes. Therefore, in review, we summarize evidences and controversies regarding the roles of different sirtuins on aging and lifespan extension, and systematically elucidate functions and pathways of sirtuins on aging and lifespan extension [1]. The link between sirtuins and longevity was first established 20 years ago in yeast, in which complex of *Sir2/3/4* extended replicative lifespan of S. cerevisiae Research interests increased after a report showed that extra copies of *Sir2*, a member of sirtuins in budding yeast Saccharomyces cerevisiae, extended the lifespan by 30% by preventing the formation of extrachromosomal DNA circles. Subsequently, more and more research shows that sirtuins can regulate longevity in numerous lower organisms, especially yeast *Sir2* and its homologues, which extend lifespan of budding yeast *S. cereviseasae*, worms *C. elegans*, fruit flies D. melanogaster, and mice [2].

So far, prolongevity effect of *sir2* has confirmed in higher organisms, while mechanisms of exerting prolongevity effects are different from that in yeast, including changes in mitochondrial function & biogenesis, suppression of inflammation, and regulation of genomic stability [3]. Though several reports have challenged this theory, sirtuins have long recognized as regulators of ageing, and overexpression of some sirtuins has shown to extend lifespan in several organisms. The suppression of cellular senescence by sirtuin is mainly mediated through delaying age-related telomere attrition, sustaining genome integrity and promoting DNA damage repair. According to reports, *sirt1* deacetylates histones H3, H4 and H1 and more than 50 non-histone proteins, including DNMT1, transcription factors and DNA repair proteins. *Sirt1* and *sirt6* were shown to be recruited to the damaged sites and promote DNA repair through deacetylating the repair proteins such as poly (ADP-ribose) polymerase (PARP)-1, Ku70, NBS, and Werner (WRN) helicase [4]. In mammals, sirtuin upregulation can work in a context-, tissue-, and particular sirtuin-dependent manner, and not all laboratories have managed to repeat initial life span extending effect of sirtuins upregulation.

In addition, sirtuins are found to especially interact with all major conserved longevity pathways, such as AMP-activated protein kinase (AMPK), insulin/IGF-1 signaling (IIS), and target of rapamycin (TOR), and forkhead box O (FOXO). Of these, FOXO transcription factor is the most fascinating target of sirtuin. In *C. elegans*, the extension of

lifespan by elevation of sir-2.1 was shown to be dependent on daf-16, the homologue of FOXO in worms. Considering that FOXO is a major component in the IIS cascade to promote lifespan extension and stress resistance, several evidences have reported the association of the IIS pathway with the prolongevity effect of sirtuin. In *C. elegans*, the deletion of sir-2.1 had no effect on the lifespan of a long-living daf-2 mutants [5]. In mammals, the relationship of IIS and sirtuin has also been well investigated. *Sirt1* is reported to play a crucial role in metabolic homeostasis and IIS. AMPK signaling belongs to the protein kinase family and restores cellular energy levels. Increased AMPK activity is known to extend the lifespan of some model organisms. The mutation of AMPK (aak-2) in *C. elegans* abrogated the lifespan extension by sir-2.1 expression, indicating that AMPK also contributes to the sirtuin-induced lifespan extension.

Sirt1 activates AMPK through direct deacetylation of LKB1, regulator of AMPK. In addition, AMPK contributes to prolongevity effect of IIS, suggesting that these longevity pathways intricately cross-talk with each other. Apart from these, several other molecules are also reported to mediate lifespan extension by sirtuin overexpression, including 14-3-3, kat-1, hcf-1, and cts-1 in *C. elegans* [6]. In addition, a study of mutant screening reported that loss-of-function mutations of ketoacyl thiolase (kat-1) resulted in premature aging and fully suppressed the lifespan extension exerted by overexpression of sir-2.1. Also, host cell factor-1 (hcf-1), a nuclear co-repressor of FOXO, was shown to act downstream of sir-2.1 to modulate the lifespan in C. elegant. Furthermore, mitochondrial regulators such as cts-1 and fzo-1, and the mitochondrial unfolded protein response (UPRmt) gene hsp-6, were reported to be increased by sir-2.1 overexpression, and the knock-down of UPRmt regulator ubl-5 using RNAi almost completely suppressed lifespan extension by sir-2.1 overexpression. [1]. among mammalian sirtuins, *sirt1* has most extensively characterized for its role in aging.

Although much of the attention has gone to *sirt1* and its protective effects against the onset of chronic diseases, its effect on longevity remains unconvincing. Sirtuins other than *sirt1* are also reported to exert a prolongevity effect. Recently, *sirt2* has been found to be a key modulator of ageing, and it extends lifespan in the BubR1 mice model. Additionally, *sirt3* is the only sirtuin that has shown to be associated with human aging; some (but not all) studies have linked polymorphisms in *sirt3* genomic locus to survival in elderly individuals [7]. However, no pan- or tissue-specific transgenic animal models overexpressing *sirt3* to determine whether *sirt3* overexpression confers lifespan extension or protects against age-associated pathologies have described in literature currently, and some newer studies failed to confirm these correlations in other populations. In contrast, recent work on *sirt6* suggests that this sirtuin might hold most potential for actual life-span extension. Loss of *sirt6* causes severe metabolic defects and rapid aging. In addition, global *sirt7* depletion contributes to premature ageing, especially in backbone, white adipose tissue and heart [8].

2. Sirtuins and ageing-related diseases

Although there has been emerging debate on the role of sirtuins in ageing and lifespan extension, mounting evidence suggests that sirtuins are indeed critical modulators of ageing and aging-related diseases via different signaling pathways. Human sirtuin isoforms, *sirt1*-7, are considered attractive therapeutic targets for ageing-related diseases included diabetes, metabolic syndrome, cardiomyopathies, non-alcoholic hepatic steatosis, hyperinsulinism-induced dyslipidaemia, chronic inflammation, neurodegenerative diseases, and some types of cancer [1].

3. Sirtuins and metabolic diseases

Furthermore, declines in basal metabolic rate and physical activity contribute to an elevated incidence of insulin resistance, obesity, and metabolic syndrome with age. Sensing of the metabolic state and regulation of the sirtuin function and expression are critical components of metabolic machinery. Thus, activation of pathways that restores insulin sensitivity and improves the utilization of glucose and fatty acids would be of benefit in stemming the pathologies associated with age-related metabolic dysfunction [9]. Many studies have indicated that *sirt1* is an important target for mitigating metabolic dysfunction. *Sirt1* is directly involved on metabolic pathways such as lipogenesis, stimulation of fatty acid β-oxidation, & gluconeogenesis. Its overexpression is thought to be beneficial and generates phenotypes in mice similar to calorie restriction conditions. All the major mitochondrial processes including the krebs cycle, the fatty acid metabolism, the antioxidant response, the amino acid catabolism, and so on, are regulated by the balance of N"-lysine acetylation/deacetylation. Several transgenic models have shown that heightened *sirt1* activity protects against the metabolic derangement associated with obesity [10].

Sirt1 and *sirt1* activators can prevent and reverse insulin resistance and diabetic complications, and have been proven to be promising therapeutic targets for type 2 diabetes (T2D). In addition, the protective effects of *sirt1* may occur through attenuation of inflammatory responses, as *sirt1* overexpression mitigates HFD-induced hepatic steatosis and adipose tissue specific inflammation [11]. Compared to *sirt1*, *sirt2* is abundant in adipocytes. Current evidence suggests a role for *sirt2* in regulating adipose tissue development and function. *Sirt2* activates the PEPCK via deacetylation and enhances gluconeogenesis during times of glucose deprivation. Meanwhile, recent studies have proposed that, with regard to insulin sensitivity, *sirt2* may act in opposing roles in different tissues. Thus, *sirt2* activation may prove to be protective against obesity, and its role in metabolic homeostasis deserves further exploration [12]. *Sirt3* may regulate cellular energy status both at transcriptional level in the nucleus and by posttranscriptional mechanisms in mitochondria, and its expression is higher in metabolically active tissues including brain, liver, heart, brown adipose tissue and skeletal muscle.

Sirt3 functions by activating important enzymes during CR, such as 3-hydroxy-3-methylglutaryl- CoA synthase 2 for generation of ketones and long chain acyl-CoA dehydrogenase for oxidation of long-chain fatty acids. *Sirt3* also activates glutamate dehydrogenase (GDH), facilitating gluconeogenesis from amino acids [13]. In addition, *sirt3* indirectly destabilizes transcription factor HIF1α and subsequently inhibits glycolysis and glucose oxidation. Intriguingly, recent studies have shown that *sirt3* levels in pancreatic islets are reduced in patients afflicted with type 2 diabetes, and *sirt3* overexpression in pancreatic β-cells promotes insulin secretion and abrogates endoplasmic reticulum (ER) stress is connected to β-cell dysfunction and apoptosis [14]. In contrast to *sirt3*, hepatic *sirt4* expression

declines slightly during caloric restriction (CR) and increases in genetic models of diabetes. Little is known about physiological relevance of *sirt4* and its role in metabolism.

In addition to GDH, a diverse range of *sirt4* targets are identified in regulation of insulin secretion, including ADP/ATP carrier proteins, insulin-degrading enzymes, ANT2 and ANT3. A study showed that *sirt4* promoted lipid synthesis and inhibition of fatty acid oxidation by deacetylation of malonyl CoA decarboxylase [15]. In contrast to other sirtuins, *sirt5* displays deacetylase and NAD^+ dependent demalonylase and desuccinylase activities. *Sirt5* facilitates glycolysis by demalonylating glycolytic enzyme glyceraldehyde phosphate dehydrogenase (GAPDH). A study proposed that *sirt5* might be positively correlated with insulin sensitivity, biological significance of which still remains to be confirmed [16]. The indication of connection b/w *sirt6* and *Sirt4*, initially reported as a unique ADP ribosyltransferase, appears to blunt insulin secretion by reducing GDH activity.

metabolism was first provided by Sebastian et al. who showed that *sirt6*-deficient mice had a loss of subcutaneous fat, lymphopenia and acute hypoglycemia. Conversely, one recent study revealed *sirt6* overexpression protects mice from diet-induced obesity, showing increased glucose tolerance and reduced fat accumulation. *Sirt6* may positively mediate glucose stimulated insulin secretion and overexpression of *sirt6* enhances insulin sensitivity in skeletal muscle and liver, which implicates *sirt6* may act as an attractive therapeutic target for T2D [17]. In addition, *sirt7* knockout mice resistant to glucose intolerance, and insulin sensitivity improved in *sirt7* knockout mice receiving a high-fat diet [18], revealing a novel role for *sirt7* in glucose metabolism.

Table 1. Some age-related diseases in elderly population [1].

	Aging and age-related disease
Neurodegenerative diseases	Presbyophrenia, Huntington's disease, Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis
Cardiovascular and cerebrovascular diseases	Hypertension, Coronary disease, Cardiomyopathies, Elder valvular heart disease, Arrhythmia, Cardiac failure, Cerebral infraction, Atherosclerosis
Metabolic related diseases	Diabetes, Metabolic syndrome, Osteoporosis, Hyperinsulinism-induced dyslipidaemia, Uarthritis, Non-alcoholic hepatic steatosis,
Others	Scapulohumeral periarthritis, Chronic bronc, Chronic inflammation, Cancer

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