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Telomeres, Sirtuins and NAD+ ---- The Genetic Communication at the Ends

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Abstract

Telomeres, Sirtuins and NAD+ are all implicated in the aging process. Telomeres are repeating nucleoprotein sequence found at the ends of chromosomes. Sirtuins regulate telomere length by localizing to telomeres. A decrease in NAD+ level as aging progresses has been demonstrated by many clinical studies. An understanding of shortening of telomere leads to suppression in Sirtuin activity as well as decrease in NAD+ and *vice versa*, suggesting interlinking of their pathways. The positive effects of NAD+ on the aging phenotype are partially assumed to be attributed to Sirtuins. Data was collected by selecting 43 articles by searching through keywords; Telomeres, p53, Sirtuins, NAD+, aging, age-related diseases, genomic stability, Sirtuin activation, in search engines like google scholar and PubMed. The purpose of this review was to find out the functional linking among telomeres length Sirtuins and NAD+, which can help in future studies to improve the therapy options for possible age associated diseases.

Keywords: Telomeres, p53, Sirtuins, NAD+, aging, age-related diseases, genomic stability, Sirtuin activation.

1. INTRODUCTION

Sirtuins and telomere length (TL), both are known for causing aging and disease but relationship between them is not well understood. Some early research has shown that Sirtuins regulate TL by localizing to telomeres. A little understanding has come from a study which reported that shortening of telomere leads to suppression in Sirtuin activity and *vice versa*, suggesting interlinking of their pathways [1]. Sirtuins by researchers have been shown to have anti-aging and disease-prevention properties [2].

Recent study [3] has found nicotinamide adenine dinucleotide (NAD+), an essential regulator of Sirtuins activity in aging. Numerous age-related diseases have been linked to deficiencies in nuclear and mitochondrial function caused by NAD+ depletion which is shown in (Fig. **1**). The positive effects of NAD+ on the aging phenotype are partially assumed to be attributed to Sirtuins [3].

Because of the significant role of this protein family in the cellular biology, such as those related to inflammation, metabolism, oxidative stress, apoptosis and reduced nitric oxide (NO) production [4] its therapeutic role is being explored as a possible target in a number of diseases, including cancer, cardiovascular disease (CVD), respiratory disorders, and other ailments [5].

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Increase in disease associated with repression in NAD+, SIRTUIN protein for TL is a concerning trend. Although Sirtuins and telomeres are separately linked to aging and disease, however; there is dearth of data on their combine effect on human health and aging. The purpose of this review was to find out the functional linking among TL, Sirtuins and NAD+ which can help in future studies to improve the therapy options for possible age associated diseases.

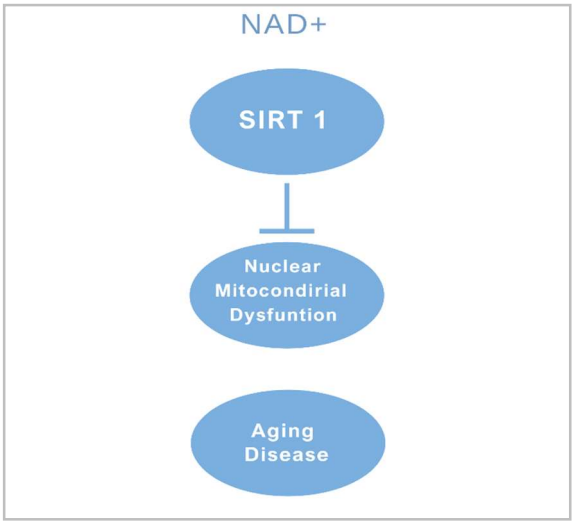

Figure 1: Age-related diseases have been linked to deficiencies in nuclear and mitochondrial function caused by NAD+ depletion.

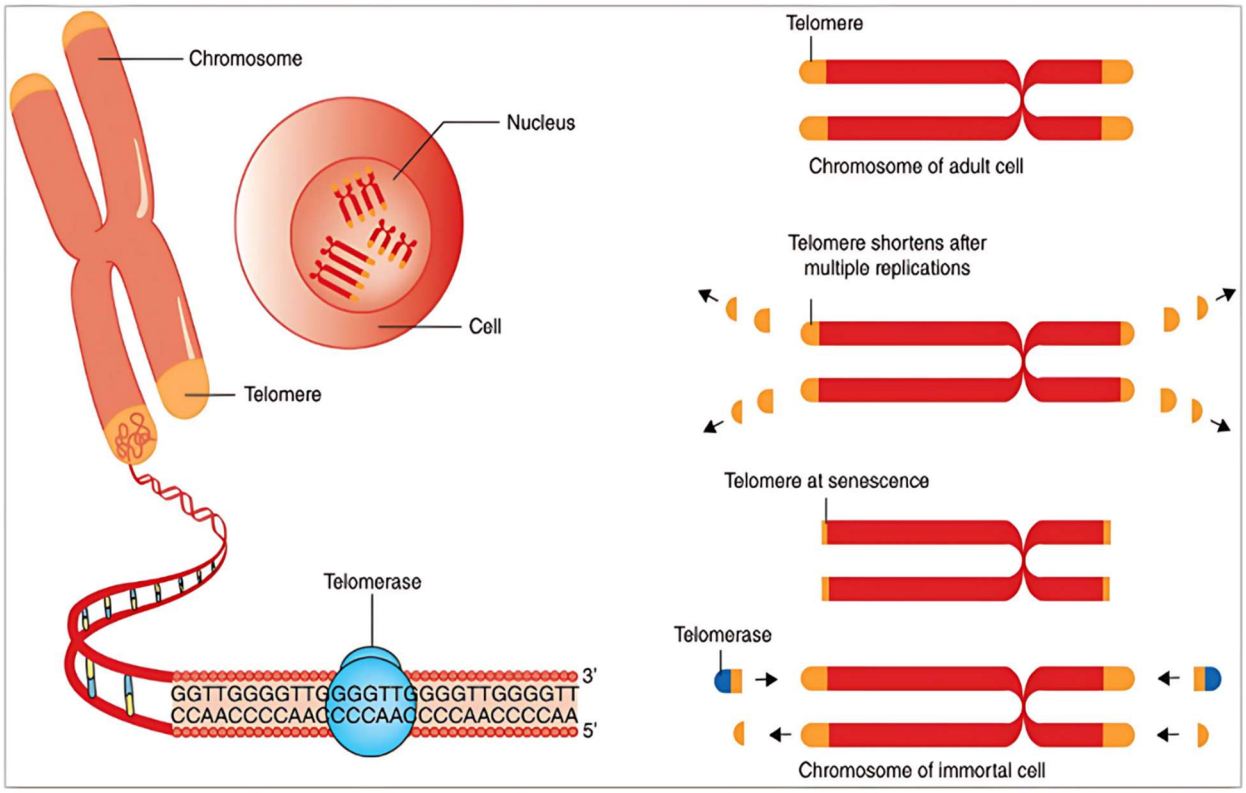

Figure 2: Shortening of telomere with each cell division.

2. DISCUSSION

Studies have shown that NAD+ has a life sustaining and longevity promoting role through its vital function as DNA repair facilitator and its benefits are enhanced by caloric restriction and exercise [5]. Sirtuins participated in plenty of biological processes, played an important role in aging and longevity [4]. Telomeres shorten with age and rate of telomere shortening may indicate the pace of aging [6]. How reduction in NAD+ level lead to decline in Sirtuin and have negative influence on lifespan through its impact on telomere is discussed in detail as follows:

2.1. Telomeres

Telomeres are repeating nucleoprotein sequences found at the ends of chromosomes that are made by the specialized RNA-dependent DNA polymerase, telomerase. Telomere shortens with each cell division and becomes "senescent", when a certain TL is reached which prevents cellular replication, which is shown in (Fig. **2**). During every cell division, telomeres shorten 30 to 200 base pairs (bps) till it reaches the stage of senescence. In order to reverse this shortening, telomerase is essential [7].

Most human cells gradually shorten their telomere and have insufficient telomerase activity, which is closely associated with aging and disease.

Telomeres have drawn attention as a possible health diagnostic. A reduction in immunocompetence, the onset of chronic diseases (e.g., diabetes, obesity, inflammatory diseases, depression), anomalies in the structure and function of the brain, and an earlier death rate have all been linked to shorter TL. As a result, scientists have worked to identify factors that may be important indicators of health by accelerating the process of telomere attrition. It is believed that a person's TL at birth determines their starting TL [8] and subsequent attrition rate, hence affecting their lifetime telomere biology.

The majority of research show that lifestyle factors, including nutrition, stress management and exercise, have a significant impact on the rate of biological aging. Both smoking and being overweight hasten the aging process and telomere shortening as shown in (Fig. **3**). Lifestyle and regular physical activity are believed to positively alter the TL. Hence, lengthening the human lifespan [9].

The DNA damage response and its primary transducer tumour protein p53 (TP53, also referred to as p53), have been found to play a significant role in a number of model organisms. Even though knowledge of the pathogenic pathways driving telomere-dependent disease and aging is still inadequate, these processes induce cellular senescence, growth arrest, and apoptosis [1].

2.2. Sirtuins

So far SIRT1 to SIRT7 are known. Nuclear Sirtuins, which include SIRT1, SIRT6, and SIRT7, have been linked to

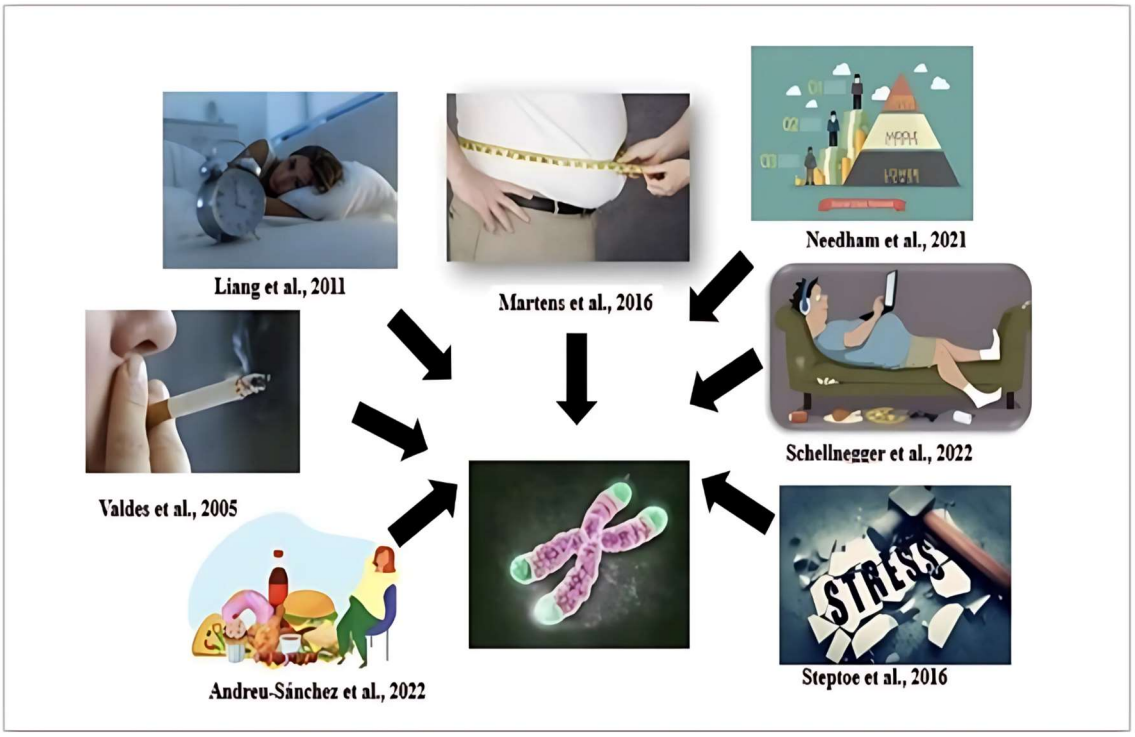

Figure 3: Risk factors affecting telomere length.

DNA repair [10]. SIRT1 is involved in the recombinant repair of DNA breaks [11]. SIRT6 in base excision repair of damaged DNA [12] as well as double-strand breaks in DNA [13]. SIRT7 is used in the repair of double strand breaks through non-homologous end joining [14]. The SIRT2 is mostly present in the cytoplasm, however, the SIRT3, SIRT4, and SIRT5 are located in the mitochondria [4]. With 9 exons, the human SIRT1 gene is found on chromosome 10q21.3. It encodes a protein with 747 amino acid (aa) residues [15, 16].

The subcellular location of SIRT1 changes according to the type of tissue or cell, degree of stress, and interaction with other molecules. SIRT1 is widely expressed in a variety of human tissues and cells [16]. It's the most widely researched member of Sirtuin. The expression of SIRT1 influenced several downstream cellular proteins, such as PPAR-γ, eNOS, AMPK, FoxO subgroup, protein tyrosine phosphatase, NF-κB, and p53, as well as Peroxisome proliferator- activated receptor- gamma coactivator (PGC-1$^{\alpha}$) [4], which are all related to the occurrence of aging and age-related diseases.

2.3. SIRT1

Animal studies have shown that SIRT1 is required for the maintenance of TL during aging and overexpression of SIRT1 increases TL in mice [17].

According to the research from USA on animal model, Sirtuins are downstream targets of defective telomeres, and telomere stabilisation and mitigation of telomere-dependent diseases can be achieved by raising SIRT activity either by itself or in conjunction with other Sirtuins [18].

Data from China revealed that SIRT1 overexpression or drug-induced activation decreased TPP1 and PTOP degradation in lung fibroblasts and suppressed telomeric DNA damage and cellular senescence. These effects were countered by SIRT1 inhibition. Therefore, SIRT1 overexpression or activation may be able to decrease the onset and progression of age-related respiratory conditions, since SIRT1 can diminish telomere shortening through a variety of ways [19].

An Australian study declared that the shorter telomeres and decreased SIRT1 expression in leukocytes are characteristics of long-term type 1 diabetes survivors. Hyperglycemia and triglycerides may be contributory factors. The factors' relationship to coronary heart disease (CHD) in diabetic individuals may be a reflection of both their influence and the aging process in the development of atherosclerosis, and they may also serve as novel biomarkers for diabetes and CVD [20].

A Cross-sectional study from Norway reported: TL and dynamics have been linked to CVD and are now recognized as a biomarker of aging. Patients with a history of Atrial Fibrillation (AF) had considerably lower SIRT1 levels than those without [21].

Korean study reported the primary mechanisms via which Sirtuin-induced cellular senescence is suppressed are

telomere attrition prevention and DNA damage repair promotion. Because they respond to DNA damage, repair and help maintain the normal chromatin condensation state, Sirtuins are essential for preserving genome integrity. In particular, the nuclear form of Sirtuins, which stabilise the chromatin structure and function as transcriptional regulators to restrict gene expression, includes SIRT1, SIRT6, and SIRT7 [22].

2.4. Other Sirtuins

SIRT2 and SIRT3 have been found to be associated with neurodegenerative disorder [23, 24]. SIRT4 and SIRT6 act as tumor suppressors [25, 26]. SIRT5 has a role in homeostasis [27]. SIRT7 which has a link in CVS and bone diseases is the least studied human Sirtuin [28].

In addition to lowering the risk of telomere attrition rate, a healthy lifestyle will also aid to reduce oxidative stress by raising Sirtuin levels. Study from Australia reported that it's critical to maintain an active lifestyle and eat a diet high in antioxidants and Sirtuin activators, which include polyphenols like resveratrol and Sirtuin co- factors like NAD+ [29].

2.5. Nicotinamide Adenine Dinucleotide (NAD+)

The Metabolic benefits of Nicotinamide riboside are gradually becoming an eye opener for the researchers around the world. NAD+, a well-known co-factor in cell ***energy*** transfer, is essential for sustaining life in virtually all living cells, playing a critical as well as a vital role [30]. The life sustaining and longevity promoting roles are currently being realized by its vital function in DNA repair facilitation. Furthermore, NAD+ cellular functions are enhanced by restricting calories or fasting as well as exercise. Thus a decrease in NAD+ levels have a negative influences on the life-span, whereas, reinstating NAD+ levels promote longevity. Number of studies, ranging from simple worms to mammals like mice, have proved that supplements of NAD+ or its precursor i.e. ***nicotinamide riboside*** promote longevity [31-33]. NAD+ is crucial for promoting longevity through various mechanisms, such as DNA repair. Studies have shown that restoring NAD+ levels can extend lifespan in mice by the human equivalent to 4 years, indicating its importance in healthy aging. As scientists delve deeper, they are uncovering new ways in which NAD+ supports longevity. With age; NAD+ levels decline significantly, leading to an energy deficit that impairs the body's ability to maintain youthful function. By age 50, the typical person may only have half the NAD+ levels they had in their youth, and by age 80, NAD+ levels can drop to just 1-10% of youthful levels.

2.5.1. *Role of NAD+ in Anti-Aging Process*

NAD+, virtually found in all living cells, also contributes to longer telomere through facilitating the function of Sirtuins, by maintaining the critical telomeres that reach a perilously short length, virtually stopping **cell renewal** which accelerates aging or death of the cell [34].

2.5.1.1. ***NAD+ is Essential for Longer Telomeres***

NAD+ is essential for the functioning of Sirtuins, proteins that aid in longevity by maintaining the length of telomeres. Telomeres gradually shorten with each cell replication, likened to a burning fuse, and once they become critically short, cell renewal slows down, accelerating the aging process or leading to cell death. Shortened telomeres serve as markers of cellular aging and predictors of reduced lifespan. Researchers are exploring interventions such as exercise and weight loss to lengthen telomeres. Additionally, nutrients like resveratrol may activate Sirtuins to promote longevity, but evidence suggests Sirtuins work best with ample NAD+ supply. Extending TL through NAD+ offers, promise for slowing aging and improving longevity, as it supports Sirtuin activity, preserving TL and promoting overall health and longevity [35, 36].

2.5.1.2. ***Role of NAD+ in DNA Repair***

Despite the protective shelter of chromosomes, DNA remains highly susceptible to damage, leading to broken strands and mutations in critical genes. This accumulated DNA damage is a contributing factor to aging and can predispose individuals to lifespan-shortening diseases like cancer and compromised immune function. When DNA damage occurs, an enzyme called PARP-1 is activated to conduct DNA repair within cells [37]. However, this process consumes significant amount of NAD+, and as NAD+ level declines, PARP-1's ability to repair DNA is impaired [38]. Fortunately, replenishing NAD+ levels in cell can restore DNA repair processes and prevent cell death during periods of stress [38]. Studies involving animal models of neurodegenerative diseases have shown that increasing cellular NAD+ can mitigate the severity of these disorders, normalize neuromuscular function, delay memory loss, and extend lifespan. In summary, enhancing DNA repair with NAD+ supplementation has the potential to decelerate cellular aging, reduce the persistence of mutations leading to cancer, and play a crucial role in preventing inflammatory conditions such as atherosclerosis [38-40].

2.5.1.3. ***NAD+ for Combating Immune-Cell Signaling***

Autoimmune system becomes overly active during old age, increasing susceptibility to infections. NAD+ activity is closely linked to immune senescence, and plays a crucial role in regulating immune and inflammatory pathways, including those involving the cytokine TNF-alpha, which is essential for signaling within the immune system [41].

2.5.1.4. ***NAD+ is Essential for Sirtuin Activation***

Sirtuin proteins known for their significant role in regulating cellular aging, influence crucial processes such as DNA repair, inflammatory responses, and cell survival pathways. Activating Sirtuins is highly sought after as a means to slow down aging, with compounds like resveratrol and quercetin showing promise as Sirtuin activators [42]. However, it's important to note that NAD+ is essential for Sirtuins to carry out their function effectively. Without sufficient NAD+, the potential benefits of Sirtuin activation in combating CVD and preserving brain function in aging may be limited. In

summary, while Sirtuin activation holds great promise for longevity and health, it relies heavily on adequate levels of NAD+ for optimal functioning.

3. CONCLUSION

Sirtuins are involved in major regulation of cellular aging as they fundamentally function in inflammatory response, DNA repair and apoptosis. Two compounds have been discovered by researchers, **resveratrol** and quercetin, which have been found as **Sirtuin activators** and are evaluated as promising [43]. NAD^+ and Sirtuins promote genome maintenance by stabilizing telomeres, by playing a crucial role in gene expression and cell proliferation pathways. These include nucleic acid metabolism regulation, genome stability preservation, as well as cellular DNA damage response.

As aging is the attenuation of physiological functions that comes with time and, eventually,leads to cell death. Sirtuins and telomeres are both linked to aging and disease. However,despite these insights, the precise mechanisms governing the relationship among Sirtuins, NAD+, telomeres, and their collective impact on age related p rocesses remain incompletely understood. Genetic variations of different races may result in varying functions in different populations. Sirtuin is linked to longevity and it is involved in DNA repair therefore, it is linked with TL. This can aid in identifying the new genetic connection that may lead to an emergence of a novel marker. Also unraveling this association will elucidate novel therapeutic avenues to mitigate age-related decline and associated diseases as well as in evaluating therapeutic implications.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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AUTHOR'S CONTRIBUTION

Not applicable.

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