The Powerful Roles of Nad+ in Anti-Aging

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Abstract: In aging, we broadly define it as the time-dependent dysfunction that affects most organisms. In recent years, research on ageing has made unprecedented progress, especially with the discovery that the rate of ageing is controlled by genetic pathways. There are nine characteristics of aging, and there are new treatments to delay aging. A better understanding of NAD+ and it's precursors will help us to get more information about diseases related to aging. Here, we review the new research advances of aging hallmarks, anti-aging treatments and the powerful roles of NAD+ in anti-aging.

1. Introduction

Aging can be defined as a spontaneous and inevitable process of all living creatures, which is a complex natural phenomenon accompanied by structural and functional degeneration with the loss of adaptability and resistance. There are about nine different types of mainstreams, namely altered inter-cellular communication, genomic instability, telomere attrition, epigenetic alteration, loss of proteostasis, deregulated nutrient sending, mitochondrial dysfunction, cellular senescence and stem cell exhaustion, of promoting aging and deciding phenotype of aging [1].

Firstly, genomic instability is one of the driving forces of triggering aging. It was said that the accumulation of DNA damage contributes to a considerable number of premature senility diseases. That is to say, exogenous physical and chemical agents may exert detrimental influence upon the integrity and stability of DNA. In this sense, artificial induction can accelerate the process of aging [2, 3].

It should be noticed that after people get older, telomeres are more likely to become shortened, thus leading to telomere attrition and increasing the possibility of catching diseases related to the regeneration capacity of tissues. One experiment showed that the activation of telomerase can slow the progress of getting old, so this gives information about the intimate relationship between telomere and mortality risk [4].

Also, the majority of cells and tissues can be affected by epigenetic alternation. In the aspects of histone modification and transcription alternation, these give a solid evidence to show that aging can be attributed to epigenetic alternation and it can facilitate precocity. It is therefore altering or adding epigenome is inclined to treat diseases and lengthen lifespan [5].

Interestingly, loss of proteostasis may lead to some aging-related diseases such as Alzheimer's disease and Parkinson's disease. A number of animal experiments support a causative impact of chaperone decline on longevity so people can improve proteostasis and delay aging of mammals with the help of genetic engineering [6].

Dietary restriction can increase the life expectancy of all eucaryotic organisms. To some extent, strong anabolic signals can accelerate senescence and reduce nutrient signals may extend lifespan. What's more, rapamycin which can limit the usage of nutrients is possible to increase the lifespan of mouse [7].

Mitochondrial dysfunction has a sophisticated linkage to aging as aging can be faster if mitochondrial dysfunction becomes more and more serious. Endurance training and alternate-day fasting go a long way when they come to improving human kinds' lifespan as this a superior method to prevent mitochondrial dysfunction [8].

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Cellular senescence is advantageous to replacing damaged tissue and potential cancer cells, which can be defined as a beneficial compensatory response. Elimination of senile cells may pave the way for delaying senescence and cure diseases caused by aging from cardiovascular disease to glaucoma [9].

Stem cells play a crucial role in the growth of all living organisms, so stem cell exhaustion is one of a dominant causes of aging, which jeopardizes tissue regeneration and poor immune response. There is every likelihood that the flourishing of stem cells may reverse the phenotype of senility [10].

Inflammation is interrelated to altered intercellular communication, which can accelerate the process of aging. It is no exaggeration to say the change of tissue related to aging may contribute to specific deterioration of other types of tissues such as bone brittleness and muscle weakness. People have the opportunity to regulate aging since aging is related to intercellular communication [11]. In conclusion, these are those nine hallmarks that trigger aging.

2. Anti-Aging Treatments

The Insulin-like signaling pathway plays a vital role in lengthening people's lifespan. Two DAF genes which lie on the same pathway were discovered, affecting dauer lifetime and formation. The research based on the experiment of yeast and fruit flies gives solid evidence that the inhibition of component of ILS can lengthen people's lifespan. Rapamycin can not only limit the growth of cells or use in immune reaction, but also extend lifespan. TOR is a muti-functional protein which can be used in translation, transcription and mitochondrial functions. Sirtuins and NAD+ can, to some extent, block the way of aging. Sirtuins can regulate and limit energy as well as prevent getting some age-related diseases. The activity of NAD+ and sirtuins can decrease with the increase of age and fat-rich diet. Also, the circadian clock is one of the hallmarks of aging. Circadian clock is extremely essential to rhythmic activity and maintenance of neuronal, physiological and endocrine functions. The destruction of circadian clock may exert detrimental influence upon diseases related to aging such as neurodegeneration, obesity and diabetes. However, it is quite difficult to identify whether it is the main cause or the result of aging. We can confirm that modulation of respiration can longer our lifespan. The three main characteristics of senescent cells are the stagnated cell proliferation, anti-apoptosis and sophisticated senescence-related secretory phenotype. Senescent cells tent to have intimate relationship with aged-diseases from Alzheimer's Diseases to cardiovascular dysfunction. Chronic inflammation is also related to many diseases such as cancer and neurodegeneration. Inflammation is the biomarker which can accelerate aging as many factors can trigger chronic inflammation. With the increase of age, protein homeostasis may degenerate, thus leading to the acceleration of aging. The damage to proteostasis can be associated with Alzheimer's disease, Parkinson's disease and other phototoxic diseases [12].

There are many newly designed drugs that undergo clinical trial such as metformin, rapamycin analogues, senolytics, sirtuin activators and NAD+ precursors. Doing exercise is also one of the methods to prevent aging and increase standard of living. Diet includes intermittent fasting, diets that mimic fasting and time-restricted feeding may increase lifespan and regulate aging.

3. Nad+ Synthesis

Decades ago, NAD+ was described as the accessory factor for alcohol fermentation by Arthur Harden and Young (ref). After that, Otto Warburg who is a Nobel laureate discovered the key impact of NAD+ on transporting hydrogen in redox reaction (ref). In 1963, people found NAD+ was a co-substrate of adding polu-ADP-ribose to proteins (ref).

The synthesis of NAD+ can be classified into four different ways with the help of Trp, NA, NAM and NR. NAD+ can be produced by NA. This process is also known as Preiss- Handler. NA is converted to NAMN with NAPRT and PRPP, followed by processing ATP and NAMN using the enzyme called NMNAT1-3 to become NAAD. In the final step, NAAD is turned into NAD+ through the enzyme ADSYN. Another way to produce NAD+ is much more complicated. Using

Trp as a raw material, it is converted to N-formylkynurenine by IDO or TDO. After four enzymatic steps, ACMS is formed and it can become quinolinic acid through spontaneous cyclization. Interestingly, with the help of QPRT and PRPP, quinolinic acid can be converted to NAMN, and pass through the method mentioned before to form NAD+. From ACMS, AMS can be produced by ACMSD. There are two different reactions that AMS can go through. One is glutamate pathway, acetoacetyl-CoA can be formed in this process and it may finally become carbon dioxide, water and ATP through TCA cycle. For another reason, picolinic acid can be produced from AMS during a spontaneous reaction. Synthesis NAD+ from NAM is a more direct way. Using PRPP as a cosubstrate, NAM can be turned to NMN by NAMPT. NAD+ is produced through ATP and NMNAT1-3 from NMN. This process is called NAD+ salvage pathway. NMN can also be produced from NR with NRK1-2 and ATP.

NAMP has a huge influence on the regulation of pressure, exercise, nutrition and diurnal rhythm [13]. There are two responsible signaling proteins, namely sirtuins and PARPs, in mammals, which can be used as NAD+ substrate, releasing NAM. Some research shows that NAD+ precursors tend to regulate NAD+ production and mediate the role of signals between organs. NAD+ boosters have a positive impact on physiology and health. Upgrading NAD+ booster can increase both lifespan and stress resistance of yeast cells and fruit flies. We also learn that in the process of signaling NAD+, important enzyme can protect the liver, avoiding liver to suffer from fat accumulation, fibrosis and insulin resistance. The decline in level of NAD+ in kidney may likely cause renal dysfunction. The improvement of muscle function can be cured by NAD+ precursor. Increasing the production of ATP by improving mitochondri function can reduce inflammation and changeover the muscle fibrosis. NAD+ level is crucial for normal heart function and recovery from injury. Treatment of NAD+ precursors also improved cardiac function and both mitochondrial and cardiac function. Sufficient supply with elevated NAD+ vascular endothelial levels is an attractive approach to increase mobility in the elderly and to treat diseases exacerbated by decreased blood flow, such as ischemia-reperfusion injury, slowing wound healing, liver dysfunction and myopathy. One way to treat cancer is to increase the level of NAD+ as excessive NAD+ can promote mitochondrial respiration and regulate glycolysis, thus contributing to metabolism. There is growing evidence that precursors of NAD+ can have anti-inflammatory effects. NAD+ metabolism also plays an important role in host-pathogen interactions. Several pathogenic organisms are nutritionally deficient and therefore depend on the host for NAD+ precursors. The neuroprotective effect of the precursor of NAD+ was first revealed through the study of ischemia induced by the middle cerebral artery. Numerous studies have reinforced the idea that NAD+ levels are key to neuronal function and survival. In the past, the total NAD+ level was thought to be stable but it has recently been found that the amount of NAD+ continues to decline from yeast to human nature in all species [14, 15].

4. Nad+ Degradation

NAD+ is the cofactor of many enzymes and plays a key role in metabolism, aging and cell survival. The molecular structure describes the initial and final product and the by-product of each reaction. Several important proteins in family's enzyme acylation. The third group NAD+ consumption enzyme is represented by the circulation of ADP-ribosome. CD38 catalyzes the creation of a cycle ADP-ribose by converting NAD+ into NAM. More specifically, the acyl groups are removed from the substrate by using NAD+ as a subbase. NAD+ levels provide a reading of the energy state of the cell, and some sirtuin is thought to be a material sensor that can be adjusted for meiosis according to metabolic needs. PARP does not seem to be affected by NAD+ level fluctuations. Poland has an advantage over sirtuins in limiting competition for NAD+ resources. In addition to PARP, the effect of a small enzyme on single ADP nucleation was studied. CADPR synthase is another family of NAD+ consumers. CADPR is an important cytokine regulator for the production of CADPR by NAD+. In addition to sirtuin, other important NAD+ consumer enzymes were identified, namely circulating APD ribosome CD38 and CD157. The efficiency of synthesis is hundreds of times greater than that of CD38, which is known as the specific cell surface molecule of the immune system [13, 14, 16].

5. Nad+ Precursors

Construction of NAD+ levels in mammals is a challenge for which it is unclear. The most rational and effective method is philosophical method. NR and NN are endogenous molecules that can be biodegraded orally and are the first choices for animal and human clinical trials. In rodents, NR is more effective at promoting NAD+ than NA and NAM, probably due to increased intake. NAM is an uncharged molecule that spreads rapidly through plasma and mitochondria membranes, consistent with the fact that NA and NAM have an added effect on the increase of NAD+ in cells. NAD+ is the existing insert and extracellular space, and some data suggests that the same is true for NMN. This data implies that NAD+ precursors may be coordinating NAD+ biosynthesis and regulating signals between organs. The concentration of NAD+ and NNAM in extracellular fluid plasma is in the micromole range and can be increased by oral administration of NMN or NR. Little is known about the metabolism and biological distribution of NAD+ precursors in various tissues and cells [14, 15, 17].

6. The Roles of Nmn in Improving Healthspan and Lifespan

NMN is a nucleotide that is widely recognized for its role as NAD^+ synthetic intermediate. We know that NAD^+ boosters seem relatively safe and have excellent disease prevention and treatment capabilities. NMN has shown its potential in liver function, kidney function, skeletal muscle function, heart function and nerve function. NMN was also found to have a positive effect on immunity and inflammation. In aging and longevity, NR and NMN improve neuron and muscle function and prolong life. NAD^+ boosters like NMN appear to raise NAD^+ to a higher level than NA and NAM, although it has not yet been demonstrated [18-20].

In most mammals, female genital aging is characterized by a marked decline in the quality and quantity of follicles and oocytes. Low-quality oocytes are common and difficult to overcome in elderly women, and that is the main reason for poor reproductive outcomes. NAD^+ is a rich auxiliary factor involved in many aspects of cell metabolism. More recently, the importance of NAD^+ has expanded from the key elements of intermediate metabolism to the criticality of various physiological processes. It is reported that NAD^+ levels decrease with age and are associated with various senescence related diseases. In this study, the authors found that supplementation with NMN could restore the NAD^+ level of maternal mature oocytes and improve the maturation rate, fertilization ability and embryonic development potential. They showed that NMN increased the ovoid rate when injected into older mice. It was found that mother cell aging significantly reduced the number of oocytes and the number of mature oocytes, but increased the incidence of oocyte division. NMN supplementation can significantly improve the number and morphology of oocytes caused by aging. Long-term NMN supplementation may have a better effect on other stages of follicular growth. These observations suggest that NMN can partially restore the number and morphology of mature oocytes by increasing NAD^+ levels, and improve the reproductive ability of animals [21].

In another study, NMN was used to reduce metabolic damage in offspring of male mice from obese mothers. Although the World Health Organization now considers obesity to be a major health problem in the early 21st century, there has been no research to date on the effect on the NMN of obese male offspring. It is assumed that maternal obesity, combined with long-term weaning, may worsen the pathology and metabolism of men. The study showed that mothers carry children with HFD that weigh more than thin mothers carry. The effect of physical obesity was more severe in young mice eating HFD, and important interactions were observed between the mother and the weaned diet. Regardless of the maternal diet, HFD will increase weight. The male offspring of obese moths are much heavier than the offspring of thin mothers. Liver and abdominal fat mass, but muscle mass also significantly increased by HFD in pregnant women. When tissue weight was standardized as a percentage of body weight, dramatic dietary effects were observed in the liver, quadriceps muscle and regenerative fat. Eating HFD after weaning increases the ultimate body weight as well as liver, muscle and hip fat. These significant differences persist when the

percentage of tissue weight to body weight is standardized. The effects of HFD on glucose removal after weaning were observed. However, glucose tolerance has declined in those who eat HFD. Blood sugar is still high compared to the offspring of thin mothers. This suggests that male offspring of obese mothers are less resistant to glucose. The adverse effect of HFD on plasma glucose removal was significant in puerpera and after weaning. The glucose tolerance of mice treated with HFD after weaning significantly decreased in mice injected with NMN [22].

7. Discussion

From a global perspective, the nine age characteristics listed are primary, antagonistic and integrative. The common feature of the markers is that they are clearly negative, which is always related to DNA damage, telomere loss and protein deposition defects [1]. Antagonistic characteristics have more opposite effects depending on intensity. These markers can be seen as protecting organisms from damage or from nutritional deficiencies. Until recently, Potential preventive and therapeutic applications of NAD^+ enhancement strategies are needed to assess the bioavailability and effectiveness of different doses of precursors in human therapy [14]. The excitement is that we can imagine a NAD^+ booster being tested inside the body to gain the ability to energize, reduce all causes of death, and prolong healthy life. Preliminary human clinical trials seem promising, but there is still a long way to go. It is important for NAD^+ boosters to be widely used as drugs to understand their safety and to understand the basic aspects of NAD^+ biology and physiology, such as the tissue distribution of NAD^+ intermediates in the intestine, blood flow and plasma [23]. Ageing research is entering a new era with unique medical, commercial and social implications. Exercise can improve your health. It is important to note that exercise is like a truly effective protector for the elderly. There have recently been exciting developments in nutrition, such as intermittent fasting, a parody of fasting and time-bound feeding [12].

In the future, we need to establish effective diagnostic criteria for quantitative and qualitative to evaluate aging, as nowadays there is not a specifically defined standard to measure the level of aging. Besides, it is time for people to develop more anti-aging drugs or healthy products. We can use the available medicines nowadays and upgrade existing production processes. Also, we can also develop new drugs for currently reported targets and explore new targets for drug design. We are hoping to extend our lifespan and healthspan in the near future.

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