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E-mail: jzus_b@zju.edu.cn

Review

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Research advances in the function and anti-aging effects of nicotinamide mononucleotide

Min WANG[1,2], Yuan CAO[3], Yun LI[1,2], Lu WANG[1,2], Yuyan LIU[1,2], Zihui DENG[4], Lianrong ZHU[5], Hongjun KANG[2,6]✉

[1]*Chinese PLA Medical School, Beijing 100853, China*
[2]*Department of Critical Care Medicine, the First Medical Centre, Chinese PLA General Hospital, Beijing 100853, China*
[3]*Department of Emergency, the Second Hospital of Hebei Medical University, Shijiazhuang 050004, China*
[4]*Department of Biochemistry, Chinese PLA Medical School, Beijing 100853, China*
[5]*Department of Clinical Nutrition, the First Medical Centre, Chinese PLA General Hospital, Beijing 100853, China*
[6]*Nephrology Institute of the Chinese People's Liberation Army, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing Key Laboratory of Kidney Disease Research, Department of Nephrology, the First Medical Center, Chinese PLA General Hospital, Beijing 100853, China*

Abstract: Aging and age-related ailments have emerged as critical challenges and great burdens within the global contemporary society. Addressing these concerns is an imperative task, with the aims of postponing the aging process and finding effective treatments for age-related degenerative diseases. Recent investigations have highlighted the significant roles of nicotinamide adenine dinucleotide (NAD^+) in the realm of anti-aging. It has been empirically evidenced that supplementation with nicotinamide mononucleotide (NMN) can elevate NAD^+ levels in the body, thereby ameliorating certain age-related degenerative diseases. The principal anti-aging mechanisms of NMN essentially lie in its impact on cellular energy metabolism, inhibition of cell apoptosis, modulation of immune function, and preservation of genomic stability, which collectively contribute to the deferral of the aging process. This paper critically reviews and evaluates existing research on the anti-aging mechanisms of NMN, elucidates the inherent limitations of current research, and proposes novel avenues for anti-aging investigations.

Key words: Nicotinamide mononucleotide (NMN); Anti-aging; Energy metabolism; Apoptosis; DNA repair

1 Introduction

The escalating trend of demographic aging presents serious challenges for managing age-related degenerative diseases, with the health burden of chronic ailments and disabilities resulting from aging affecting individuals, families, and society as a whole. Within contemporary medicine, there is a pressing need to advance research to mitigate the aging process. Numerous approaches have been identified to find methods that ameliorate aging, including nutritional intervention, physical conditioning, and pharmacological therapies. Among these, nutritional intervention has garnered widespread attention, particularly through the modification of dietary structure to influence metabolism and bodily function. In recent years, nicotinamide mononucleotide (NMN) has gained prominence as a new form of nutritional intervention, with evidence of improving various aspects of aging.

Nicotinamide adenine dinucleotide (NAD^+), a crucial coenzyme in redox reaction and energy metabolism, plays a pivotal role in numerous biological processes. It impacts essential cellular functions both directly and indirectly, including metabolic pathways, DNA repair, chromosomal remodeling, cell aging, and immunocyte function. These processes are critical for maintaining metabolic homeostasis and facilitating healthy aging (Covarrubias et al., 2021). Across a spectrum of organisms, NAD^+ concentrations generally decline with age, closely associated with physiological deterioration and age-related pathologies (Belenky

✉ Hongjun KANG, doctorkang301@163.com
Hongjun KANG, https://orcid.org/0000-0002-5269-9082
Min WANG, https://orcid.org/0000-0003-1865-9113

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et al., 2007). Therefore, restoring NAD^+ levels has become a pivotal aim to alleviate or even reverse functional decline and diseases.

However, direct supplementation faces challenges due to the limited ability of NAD^+ to penetrate cellular membranes and its vulnerability to digestive enzymatic degradation. These issues result in the low bioavailability and stability of NAD^+ within the body, along with potential side effects such as insomnia and fatigue (Poddar et al., 2019). As a result, researchers are actively exploring alternative methods to enhance NAD^+ levels, aiming for more effective anti-aging effects. Among these alternatives, supplementation with the NAD^+ precursor NMN has been considered noteworthy for impeding the aging process, as it has demonstrated the ability to alleviate and reverse age-related degenerative diseases by increasing NAD^+ levels (Okabe et al., 2019).

Once inside the body, supplemented NMN undergoes a series of biochemical reactions, leading to a substantial increase in cellular NAD^+ levels, NAD^+/NADH ratios, and the expression of sirtuin deacetylases. This supplementation further improves mitochondrial function and alleviates cellular aging (Wang et al., 2022). However, determining the precise mechanisms of anti-aging effects, optimal dosage, and treatment safety of NMN still requires elaborate investigations. In this review, we focus on elucidating the anti-aging mechanisms of NMN and address the current research limitations, providing references and suggestions for in-depth future studies into the anti-aging effects of NMN.

2 NMN biosynthesis and depletion

Various natural foods, such as beef, shrimp, legumes, nuts, and cereals, contain compounds related to vitamin B3, including nicotinamide (NAM), nicotinamide riboside (NR), nicotinic acid (NA), and NMN. These precursors undergo synthesis into NMN within the body through salvage pathways (Amjad et al., 2021). For example, NR is phosphorylated by nicotinamide riboside kinase (NRK) to form NMN, while NAM is catalyzed by nicotinamide phosphoribosyltransferase (NAMPT) to transform into NMN (Imai, 2011). Subsequently, NMN synthesized in the cytoplasm enters mitochondria or nuclei, where it is catalyzed by nicotinamide mononucleotide adenylyl transferases 1–3 (NMNAT1–3) to convert into NAD^+ (Revollo et al., 2007; Kane and Sinclair, 2018). NAD^+ can be synthesized via both a de novo pathway from tryptophan and a salvage pathway from endogenous/exogenous intermediates, with the latter being predominant in maintaining in vivo NAD^+ levels.

Inside the body, NAD^+-consuming enzymes, such as sirtuins, poly(adenosine diphosphate (ADP)-ribose) polymerase (PARP), and cluster of differentiation 38 (CD38), degrade NAD^+ into NAM, establishing a cycle of NMN biosynthesis and degradation (Bai et al., 2011a, 2011b; Shen et al., 2021). Sirtuins are a class of NAD^+-dependent deacetylases, encompassing SIRT1–SIRT7, which play crucial roles in various metabolic pathways and cellular signaling processes. They regulate cellular functions through protein deacetylation and phosphorylation, significantly influencing the extension of lifespan and promoting the delay of age-related diseases (Zhang et al., 2020). PARP is a type of NAD^+-dependent DNA repair enzyme with a DNA damage-sensing function, which is activated upon recognizing structural damage to DNA fragments and consumes NAD^+ during DNA repair to convert it into NAM.

CD38 is a protein found in immune cells that consumes NAD^+ and possesses intracellular signal transduction activity (Camacho-Pereira et al., 2016). It catalyzes the synthesis of NAM, ADP-ribosyl (ADPR) cyclase, and cyclic ADPR (cADPR) using NAD^+ as a substrate. In turn, cADPR promotes Ca^{2+} release and cell apoptosis, while ADPR cyclase regulates various cellular functions through Ca^{2+} mobilization. These processes are closely related to immune function and inflammatory responses in the organism (Piedra-Quintero et al., 2020). The NAM resulting from NAD^+ consumption subsequently re-enters the salvage pathway and thus the NAD^+ synthesis cycle (Fig. 1).

Recent research has unveiled that sterile alpha and Toll/interleukin-1 receptor (TIR) motif-containing protein 1 (SARM1), as the central regulatory factor associated with axonal pathological degeneration in neurodegenerative diseases, possesses NAD^+ degradation activity. This is promoted via its TIR domain, whereas it is inhibited by another armadillo (ARM) domain upon binding to NAD^+, an interaction that prevents axonal degeneration. However, the destruction

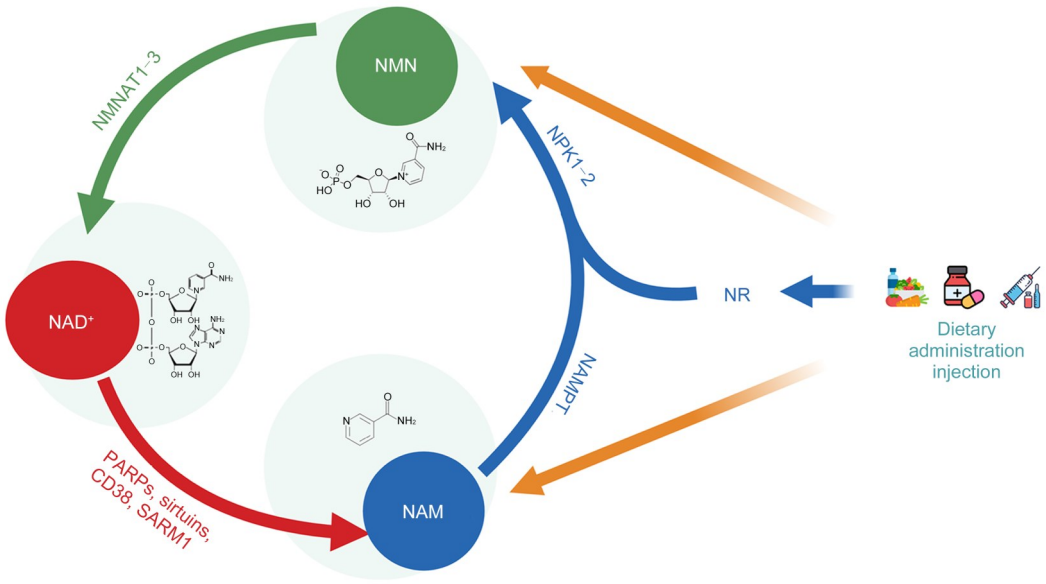

Fig. 1 Biosynthesis and depletion processes of nicotinamide mononucleotide (NMN). CD38: cluster of differentiation 38; NAD$^+$: nicotinamide adenine dinucleotide; NAM: nicotinamide; NAMPT: nicotinamide phosphoribosyltransferase; NMNAT: nicotinamide mononucleotide adenylyl transferase; NR: nicotinamide riboside; NRK: nicotinamide riboside kinase; PARP: poly(adenosine diphosphate (ADP)-ribose) polymerase; SARM1: sterile alpha and Toll/interleukin-1 receptor (TIR) motif-containing protein 1.

of the NAD$^+$-binding site ARM or the disruption of the ARM–TIR interaction results in the persistent activation of SARM1, leading to axonal degeneration. This discovery not only reveals the specific role of SARM1 in the process of NAD$^+$ consumption but also suggests potential therapeutic targets for the treatment of neurodegenerative diseases (di Stefano et al., 2015; Jiang et al., 2020).

3 Anti-aging mechanisms of NMN

3.1 Roles of NMN in cellular energy metabolism

Comprehensive studies have revealed numerous connections between aging and energy metabolism. Endogenous NAD$^+$ levels decline with age, impacting various physiological processes, such as energy metabolism, DNA repair, and cellular signal transduction. NMN, a precursor of NAD$^+$, can elevate the intracellular NAD$^+$/NADH ratio through supplementation. This enhancement of NAD$^+$ levels leads to improved mitochondrial functionality, increased fatty acid oxidation, and heightened mitochondrial respiratory chain activity. Mitochondrial functionality here is primarily considered from the aspect of cell dependency level, encompassing mitochondrial quality control and cellular energy supply (Monzel et al., 2023). Furthermore, NAD$^+$ modulates multiple metabolic pathways, such as those involving glucose, fatty acids, and amino acids, contributing to the maintenance of normal energy metabolism, the reduction of intracellular reactive oxygen species (ROS) levels, and the mitigation of inflammatory responses, jointly decelerating the aging process.

The incidence of metabolic disorders, such as insulin resistance and liver metabolic abnormalities related to glucose metabolism, escalates with age (Palmer and Jensen, 2022). In type 2 diabetes, an abnormal NAD$^+$/NADH ratio is observed due to substrate overoxidation. NAMPT, the rate-limiting enzyme in mammalian NAD$^+$ biosynthesis, influences NAD$^+$ biogenesis in response to a high-fat diet and aging, which is related to the pathogenesis of type 2 diabetes. NMN, a product of the NAMPT reaction and a crucial intermediary of NAD$^+$, can ameliorate impaired glucose tolerance and hepatic insulin sensitivity by restoring the NAD$^+$ levels reduced by diet and age. Moreover, NMN can regulate the expression of SIRT1 target transcription factors, including c-Myc, nuclear factor-κB (NF-κB), peroxisome proliferator-activated receptor γ (PPARγ), and p53, leading to the restoration of gene expression related to oxidative stress, inflammatory responses, and circadian rhythms. The beneficial effects

of NMN treatment on primary hepatocytes have been further confirmed by the use of a SIRT1-specific inhibitor, indicating that SIRT1 is among the biomolecules mediating the role of NMN in improving metabolic functions. As an activator of sirtuin proteins, NMN enhances the activity of SIRT1 and other members of the sirtuin family (SIRT2–SIRT7), demonstrating significant beneficial effects. The above research findings offer novel therapeutic avenues for diabetes and elderly type 2 diabetes patients with defects in NAD^+ synthesis regulated by NAMPT (Yoshino et al., 2011). Mills et al. (2016) confirmed the potential of NMN to improve insulin sensitivity and plasma lipid spectra and enhance energy metabolism while inhibiting age-related weight gain. Consistent with the observed phenotypes, NMN was found to reduce the expression of aging-related genes in key metabolic organs, such as skeletal muscle, white adipose tissue, and the liver. The administration of NMN significantly reduced age-induced changes in the expression of these genes (Mills et al., 2016).

Notably, NMN supplementation is effective not only in animal models but also in humans. A randomized controlled trial spanning ten weeks in postmenopausal women demonstrated that NMN supplementation could improve muscle insulin sensitivity, insulin signaling, and muscle remodeling in overweight or obese pre-diabetic postmenopausal women. Although NMN supplementation did not alter the concentration of NAD^+ in the muscle, it increased the content of NMN metabolic products, namely, *N*-methyl-2-pyridone-5-carboxamide and *N*-methyl-4-pyridone-5-carboxamide. In this manner, NMN supplementation enhances the turnover of NAD^+ in the muscle, improving muscle insulin sensitivity without raising NAD^+ levels. Meanwhile, the effects on insulin sensitivity in the liver and adipose tissues were less pronounced, with NMN selectively influencing muscle insulin sensitivity. The primary mechanism of action may involve the modulation of key components of glucose uptake and muscle-remodeling signaling pathways, such as the elevation of phosphorylation levels of protein kinase B (AKT) serine-473 (Ser473) and threonine-308 (Thr308), as well as mammalian target of rapamycin (mTOR) serine-2448 (Ser2448) (Yoshino et al., 2021). In addition, NMN supplementation increased the number of myocytes in skeletal muscle and enhanced the platelet-derived growth factor (PDGF) signaling pathway. Nonetheless, further research is needed to precisely elucidate the impact of NMN on metabolic processes. The above study provides fresh insights into diabetes treatment, while more comprehensive studies and trials involving diverse populations are required to validate its efficacy and safety (Frederick et al., 2016; Fletcher et al., 2017). NMN treatment has shown extremely positive results in patients with polycystic ovary syndrome, which is characterized by similar endocrine features. The metabolic dysfunctions of these patients, such as obesity and insulin resistance, were almost entirely normalized, further validating the role of NMN in improving energy metabolism (Aflatounian et al., 2022).

Senescent cells exhibit mitochondrial dysfunction, including abnormalities in mitochondrial morphology and structure, reduced intracellular adenosine triphosphate (ATP) content, and elevated ROS levels (Fang et al., 2014, 2016). A key measure of mitochondrial activity is the number of mitochondrial DNA copies that progressively declines with age. Therefore, the regulation of mitochondrial DNA copy numbers is instrumental in mitigating mitochondrial dysfunction. Research has indicated that NMN ameliorates mitochondrial functionality by boosting nucleotide levels, as evidenced by both cellular and animal studies. NMN operates via two discrete metabolic pathways. One involves enhancing the synthesis of ubiquinone in high-energy-demand tissues such as the heart and the liver, thereby activating the de novo synthesis of pyrimidine nucleotides. The other pathway involves the stimulation of gene expression related to NMN hydrolase, like CD157, expediting the hydrolysis of NMN to ribose-5-phosphate (R5P), which enhances nucleotide synthesis. By accelerating nucleotide synthesis, mitochondrial DNA replication is promoted, leading to an increase in the number of mitochondrial DNA copies and thus fortifying mitochondrial function (Nomiyama et al., 2022).

Chronic heart failure is closely linked to mitochondrial dysfunction, primarily caused by cumulative damage from high-level reactive oxygen metabolism (Sanada et al., 2011). Despite extensive antioxidant therapies, the results have been suboptimal, necessitating novel approaches to address mitochondrial dysfunction. Studies have shown that reducing NAD^+ levels in murine models hinders mitochondrial metabolism in cardiac cells, leading to heart failure in experimental

animals (Walker and Tian, 2018; Zhou et al., 2020; Abdellatif et al., 2021; Tong et al., 2021; Walker et al., 2023). However, short-term supplementation with the NAD^+ precursor NMN could enhance cardiac cell metabolism and improve cardiac function (Zhang et al., 2017). NMN treatment has also demonstrated similar efficacy in a mouse model of myocardial fibrosis, reducing cardiac ejection fraction and aggravating myocardial fibrosis by upregulating cardiac cell SIRT6 protein expression (Yu et al., 2020).

As women age, their oocytes develop structural and functional mitochondrial abnormalities, resulting in decreased reproductive capability. NMN supplementation could enhance the quality of aged mouse oocytes and augment ovulation by restoring NAD^+ levels. Studies have revealed that NMN treatment restores ATP and SIRT1 protein levels, reduces abnormal mitochondrial distribution, and rectifies gene expression related to mitochondrial dysfunction in aged oocytes (Bertoldo et al., 2020; Huang et al., 2022; Jiang et al., 2023; Li et al., 2023; Meng et al., 2024; Singh et al., 2024). This suggests that the beneficial effects of NMN on aged oocytes are mediated through mitochondrial function (Miao et al., 2020). SIRT3, a crucial mitochondrial protein, regulates oxidative stress and mitochondrial function. Recent research has demonstrated that NMN supplementation can reverse cellular senescence and alleviate mitochondrial dysfunction in mesenchymal stem cells (MSCs) by modulating the NAD^+/SIRT3 pathway (Wang et al., 2022). In addition, NMN reduces oxidative stress in aged mouse liver cells and the expression of nuclear factor erythroid 2-related factor 2 (*Nrf2*) and its downstream genes (Luo et al., 2022). However, in SIRT3-deficient mice, the effect of NMN was attenuated, further substantiating the pivotal role of SIRT3 in the ability of NMN to enhance mitochondrial function and regulate oxidative stress levels.

3.2 Roles of NMN in immunoregulation and cell apoptosis

As age increases, the immunoreactivity of the human body weakens, particularly regarding natural killer (NK) cells, which are essential for cancer resistance and viral infection. The NAD^+ metabolic pathway plays a crucial role in the immune system, and NMN may enhance immune function and alleviate the process of immunosenescence by regulating immune cell metabolism. The immune system identifies and combats pathogens and foreign bodies invading the body, releasing inflammatory mediators to initiate an inflammatory response. However, excessive inflammatory responses can lead to tissue damage and diseases, including autoimmune and chronic inflammatory conditions. However, NMN intervention can alleviate the inflammatory response by regulating the function of immune cells.

Macrophage-mediated systemic inflammatory responses can damage various tissues and organs and are a major cause of death from sepsis and multiple organ dysfunction syndrome. Research has shown that oral or intraperitoneal injection of NMN can enhance the immunotoxicity and function of mouse NK cells (Takeda and Okumura, 2021). Inflammation leads to the accumulation of CD38 in tissues. With age, inflammation induced by senescent cells causes the accumulation of $CD38^+$ immune cells, resulting in decreased NAD^+ levels and affecting immune function. Components of the senescence-associated secretory phenotype (SASP) secreted by senescent cells may induce the accumulation of $CD38^+$ immune cells, leading to a decline in NAD^+ levels. The ectoenzyme activity of CD38 may be involved in regulating the availability of NMN to regulate cellular NAD^+ levels.

During aging, the cellular NAD^+ biosynthesis pathway is becoming suppressed, whereas external supplementation with NMN can enhance NAD^+ levels and improve immune function (Chini et al., 2020). NMN can reprogram the phenotype of macrophages, reducing the proportion of pro-inflammatory M1 phenotype macrophage activation and enhancing the expression of anti-inflammatory M2 phenotype-specific markers (Cros et al., 2022). Consistent with a study on NMN treatment for silicosis, NMN modulates macrophage homeostasis, concurrently reducing the activation ratios of $CD4^+$ and $CD8^+$ T cells, thus alleviating inflammatory damage in the process of silicosis (Wang et al., 2023). Moreover, NMN can regulate stem cell differentiation and self-renewal, thereby enhancing the immune response and preventing cellular aging and tissue degeneration. Overall, NMN can regulate NAD^+ levels in various immune cells, impacting their development, differentiation, and other aspects, subsequently improving the immune function.

Cell apoptosis is a critical and inevitable element of the aging process, and the anti-aging effects of NMN

are associated with the regulation of cell apoptosis. Previous research has demonstrated that NMN treatment can reduce oocyte apoptosis and increase the number of oocytes, indicating its important role in regulating cell apoptosis (Miao et al., 2020). The role of NMN mainly involves enhancing PARP activity and SIRT1-mediated histone modifications to maintain chromosomal structure and stability, as PARP activity and SIRT1 expression are closely related to cell apoptosis. The regulation of cell apoptosis by NMN can also help to mitigate the toxic side effects of chemotherapy. For instance, during the treatment of late-stage hepatocellular carcinoma with the drug sorafenib, the overexpression of SIRT1 and the restoration of NAD^+ levels through NMN could reduce cell apoptosis. Sorafenib induces cell apoptosis by affecting the NAD^+/SIRT1/adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) axis (Garten et al., 2019). In clinical practice, the dose-dependent toxic side effects of many anti-cancer drugs severely limit their application. To this end, the protective effect of NMN could be a potential strategy to prevent these side effects. For example, the chemotherapy drug cisplatin can induce cognitive impairment in the nervous system, while doxorubicin treatment can cause cardiac toxicity and the loss of certain physiological functions. However, combined treatment with NMN and chemotherapy drugs with toxic side effects can reduce the undesirable side effects without affecting the anti-tumor effects. The primary mechanism is that NMN inhibits the expression of genes related to cell apoptosis and DNA damage, protecting related tissues and organs from the effects of chemotherapy drugs (Yoo et al., 2021; Margier et al., 2023).

Research has also shown that NAMPT expression significantly decreases during myocardial ischemia, reperfusion, and pressure overload. Preventing the downregulation of NAMPT can reduce the death of myocardial cells in case of myocardial injury (Hsu et al., 2009). Ultraviolet (UV) radiation and metabolic toxins cause DNA damage that can block transcription and lead to cell apoptosis. For instance, high sugar-induced corneal epithelial cell damage is a key pathological process in diabetes-related eye diseases. In vitro experiments have shown that NMN treatment reduces the apoptosis of corneal epithelial cells, increases cell vitality, enhances cell migration, and restores the tight connections of cells (Pu et al., 2022). In another study, NMN could reduce the death of outer cells in the acute phase of retinal detachment and inhibit the pathological proliferation of glial cells in the late stage of retinal detachment (Chen et al., 2020). Exposure to ultraviolet B (UVB) radiation can cause corneal edema and cell apoptosis in mice; however, NMN treatment has been proven to be highly effective in preventing such damage. This beneficial effect of NMN has been verified in human corneal epithelial cells. Regarding the relevant mechanism, the activation of AKT signaling pathway and the reduction of B-cell lymphoma-2 (BCL-2)-associated X protein (BAX)/BCL-2 ratio are involved in this biological process (Zhao et al., 2020). Therefore, NMN has significant potential in the treatment of diabetes-related eye complications and other eye damage-related diseases induced by various factors. The roles of NMN in immune function and cell apoptosis are closely linked to its involvement in regulating energy metabolism and signaling pathways, while further research is necessary to explore these intricate relationships.

3.3 Roles of NMN in DNA damage repair

NAD^+, as the biosynthetic product of NMN, plays a crucial role in regulating DNA repair enzymes, thereby modulating genomic stability and maintaining DNA integrity, which in turn reduces the frequency of random mutations and decelerates the aging process. Accumulated DNA damage impairs cellular functions, leading to accelerated cellular senescence and apoptosis. Members of the PARP family are essential in NAD^+-mediated DNA damage repair, with PARP-3 primarily involved in repairing double-strand DNA breaks and PARP-1 and PARP-2 activated in the base excision repair triggered by single-strand DNA breaks (de Vos et al., 2012). Upon cellular DNA damage, activated PARP consumes significant amounts of NAD^+ in the repair process, leading to a deficit in NAD^+ supply, which negatively affects cellular metabolism and survival. Furthermore, through the accumulation of ROS, decreased NAD^+ levels cause damage to mitochondrial DNA and nuclear DNA (Cohen, 2020). Several protein molecules participate in NAD^+-dependent DNA repair, including those in the PARP and sirtuin families, exhibiting mutual interdependency and regulation and working in concert during the DNA repair process. When NAD^+ is depleted, SIRT1 is activated, directly mediating cellular apoptosis (Fang et al., 2014).

Sirtuins play a pivotal role in regulating aging-related epigenetic modifications. They achieve gene silencing and DNA repair regulation through the deacetylation of specific lysine residues of histones, facilitating the formation of a more repressed chromatin structure related to lifespan extension (Wątroba et al., 2017). One study found that NMN supplementation bolstered DNA repair in ataxia telangiectasia neurons. Beyond a previously discovered mechanism involving NAD^+-dependent SIRT1 participating in DNA repair through deacetylation and activation of relevant repair proteins in the double-strand DNA break repair process (Chalkiadaki and Guarente, 2015), it was also found that NMN supplementation can enhance neuronal DNA repair via the DNA-dependent protein kinase (DNA-PK) catalytic subunit (DNA-PKcs) regulatory pathway. Other NAD^+-dependent sirtuins such as SIRT6 and SIRT7 may also contribute to DNA repair by elevating NAD^+ levels (Fang et al., 2016). Moreover, increasing NAD^+ levels could reduce neuronal DNA damage levels in Alzheimer's disease mouse models, providing evidence for the protective effect of NMN supplementation on neurons (Hou et al., 2018). Miao et al. (2020) attempted to reverse aged oocyte function with NMN treatment and also found that NMN supplementation could restore the spindle/chromosome structure and kinetochore-microtubule attachment, maintaining the euploidy and maturation of aged oocytes.

UV radiation-induced DNA damage significantly elevates the risk of cellular mutations and tumor occurrences, contributing to aging and certain degenerative diseases. Recent research has highlighted the pivotal roles of NAD^+ in UV radiation-induced DNA damage. Animal experiments have shown that NAM protects mice from carcinogenesis induced by UV radiation. In cell culture experiments, NAM supplementation has been found to enhance the repair capacity of primary human melanocytes for UV-induced DNA damage (Thompson et al., 2014). Furthermore, immortalized human keratinocyte (HaCaT) cells treated with NAM demonstrated an increase in both the overall nucleotide excision repair rate and the number of irradiated melanocytes undergoing DNA repair (Surjana et al., 2013). Besides, a randomized controlled trial demonstrated that oral NAM significantly reduces actinic keratosis precancerous lesions and potentially lowers the incidence rate of non-melanoma skin cancer (Surjana et al., 2012). The above studies provide valuable insights into the potential application of NMN in melanoma prevention and the exploration of melanocyte response mechanisms to DNA damage.

In summary, NAD^+ plays several fundamental roles in the DNA repair process. Firstly, it acts as a critical auxiliary factor in the DNA repair pathway, interacting with various DNA repair enzymes to facilitate DNA repair. Secondly, it participates in cellular stress responses as a signaling molecule, regulating a host of gene expression and cellular metabolic processes. Thirdly, following DNA damage, cells release stress signals that modulate a range of cellular physiological processes, including DNA repair and apoptosis, with NAD^+ playing a crucial regulatory role. Finally, NAD^+ functions as an antioxidant, safeguarding cellular DNA from free radical damage. Therefore, NMN supplementation in vitro provides an effective approach to alleviate various forms of cellular DNA damage.

4 Conclusions and future perspectives

Research on the anti-aging mechanisms of NMN is continuously expanding, revealing its crucial roles in energy metabolism, mitochondrial function, immune function, cell apoptosis, and DNA repair (Fig. 2). Additionally, NMN influences certain aging-related signaling pathways, including AMPK (Zhou et al., 2021), mTOR (Zhao et al., 2023), and phosphoinositide 3-kinase (PI3K)/AKT (Verma et al., 2023), which are responsible for regulating cell metabolism, autophagy, and cell proliferation. By modulating these pathways, NMN exhibits anti-aging effects (Fig. 3). Moreover, NMN has been found to mitigate skin-aging pigmentation issues. By downregulating the cyclic adenosine monophosphate (cAMP)/Wnt signaling pathway, NMN treatment reduces melanin production in senescent melanocytes, as supported by studies using human skin models (Brito et al., 2022). In summary, the anti-aging mechanism of action of NMN is complex and involves multiple molecular pathways and biological processes. It is necessary to further explore this mechanism and evaluate clinical application prospects for treating and preventing aging-related diseases.

Despite the numerous studies confirming the anti-aging role of NMN in recent years, existing research

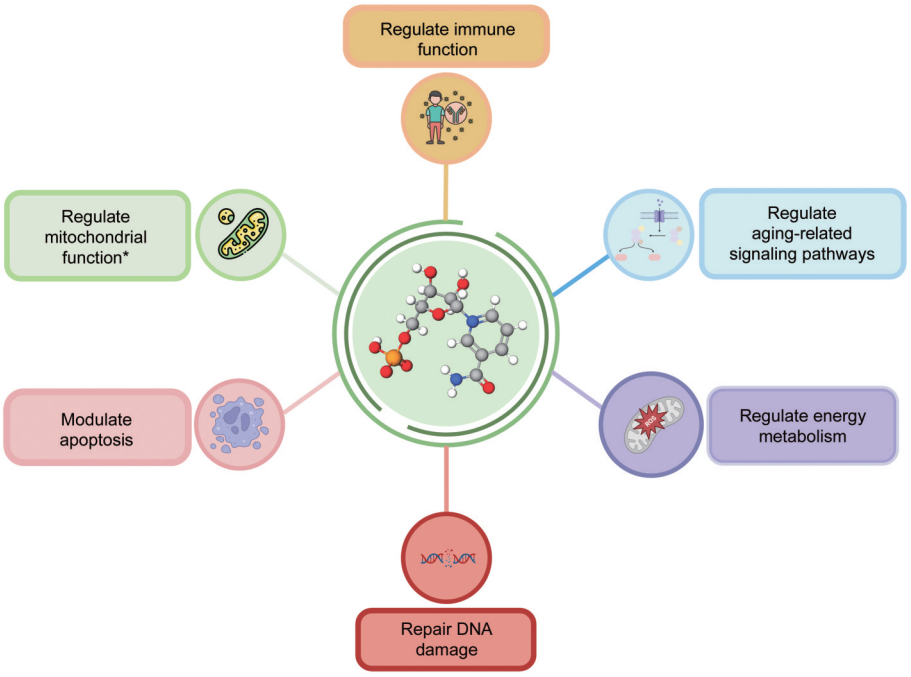

Fig. 2 Anti-aging mechanism of nicotinamide mononucleotide (NMN). *Mitochondrial function mainly refers to cell dependence, like the mitochondrial quality control and cell energy supply.

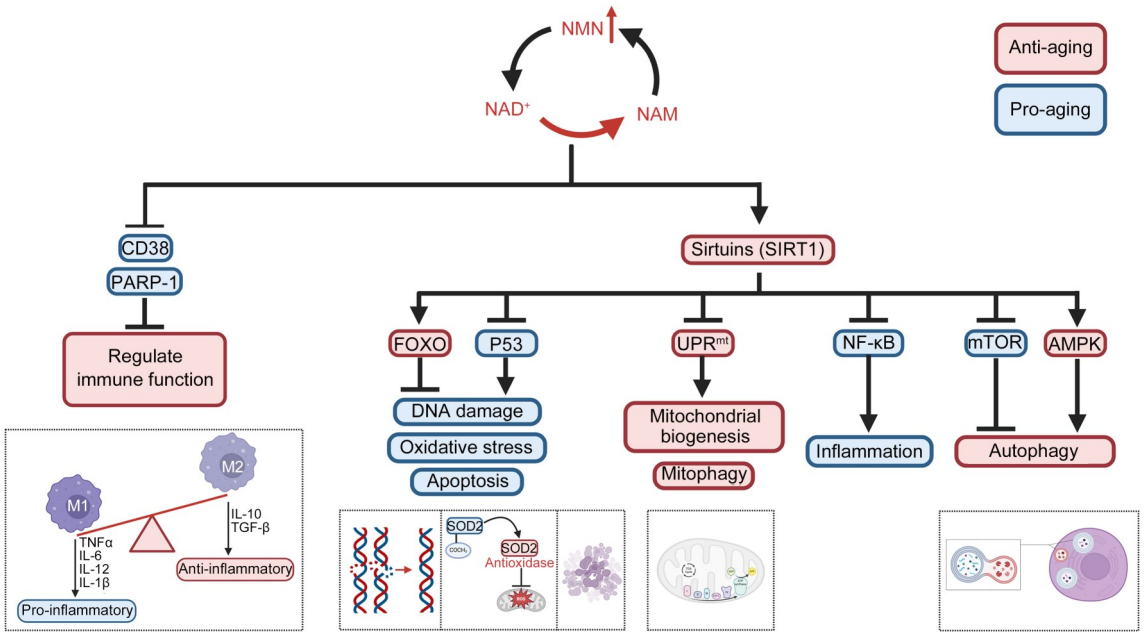

Fig. 3 Signal pathway of the anti-aging effect of nicotinamide mononucleotide (NMN). NMN facilitates the synthesis of nicotinamide adenine dinucleotide (NAD^+), resulting in reduced levels of NAD^+-consuming enzymes, such as cluster of differentiation 38 (CD38) and poly(adenosine diphosphate (ADP)-ribose) polymerase-1 (PARP-1), thereby modulating immune function and reprogramming macrophage phenotypes towards increased activation of the anti-inflammatory M2 phenotype. As the primary consumers of NAD^+, the activation of sirtuins due to elevated levels of NAD^+ orchestrates the regulation of critical metabolic processes, stress responses, and the biology of aging via the activation or inhibition of downstream signaling pathways, ultimately exerting an anti-aging effect. AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; FOXO: forkhead box protein O; IL: interleukin; mTOR: mammalian target of rapamycin; NAM: nicotinamide; NF-κB: nuclear factor-κB; TGF-β: transforming growth factor-β; TNFα: tumor necrosis factor α; SOD2: superoxide dismutase 2; UPR^{mt}: mitochondrial unfolded protein response.

still has limitations. Firstly, most studies have been conducted with a small sample size and using animal models, and have not been verified in human trials. Secondly, the optimal dosage for NAD^+ anti-aging has not been gauged. While NMN efficacy has been found to be dose-dependent (Mills et al., 2016), the dose of 100, 250, or 500 mg had no significant adverse effects on healthy adult males (Irie et al., 2020). Nevertheless, NMN treatment in immune cells may promote NAMPT expression, potentially exacerbating the inflammatory state in arthritis. Therefore, when using NAMPT/NAD^+ signaling modulators to treat arthritis, potential adverse effects must be considered (Wang et al., 2021). To maximize the efficacy of NMN, determining its optimal dosage is crucial, as different target organs and effector molecules may require different levels and modes of action (Table 1). Further investigations into the optimal dosage and targeting mechanisms of NMN are crucial to explore its therapeutic effects more comprehensively. Moreover, studies using dual-labeled isotope NMN have revealed that orally administered NMN can be rapidly absorbed and efficiently transported into the bloodstream, converting into NAD^+ in major metabolic tissues like the liver and skeletal muscle. However, this effect is transient: within 15 min of NMN supplementation, the body's NMN and NAD^+ levels quickly rise and then return to their original levels. Thus, maintaining a steady increase in systemic NMN levels and sustaining high levels for its continued functionality present a significant challenge for NMN treatment (Mills et al., 2016). Current NMN applications involve several technical challenges, such as improving the conversion rate of NMN and maximizing NAD^+ levels while ensuring stability, which necessitates further investigations.

Table 1 Effects of nicotinamide mononucleotide (NMN) in different doses and different target organs

Administration	Duration	Subjects	Disease	Organ	Key finding	Reference
IP	10 d	Mouse	High-fat diet-induced type 2 diabetes, aging-induced type 2 diabetes	Liver, WAT, SM	Enhanced insulin sensitivity	Yoshino et al., 2011
PO	12 months	Mouse (naturally aging)		Liver, WAT, SM	Mitigated physiological decline	Mills et al., 2016
PO	10 weeks	Human (female)	Overweight or obese postmenopausal pre-diabetes	SM, liver, AT	Increased muscle insulin sensitivity	Yoshino et al., 2021
PO	8 weeks	Mouse	Polycystic ovary syndrome	Muscle, liver, ovaries	Normalized energy metabolism	Aflatounian et al., 2022
IP	5 d	Mouse	Cardiac-specific Kruppel-like factor 4 (KLF4) deficience	Heart	Improved heart function	Zhang et al., 2017
IP	4 weeks	Mouse	Cardiac fibrosis	Heart	Improved heart function	Yu et al., 2020
IP	10 d	Mouse (maternally aging)		Ovaries	Better fertilization	Miao et al., 2020
In vitro	24 h	Cell (replicative aging MSCs)		MSCs	Alleviated cell aging	Wang et al., 2022
IP	4 weeks	Mouse (naturally aging)		Liver	Reduced levels of oxidative stress	Luo et al., 2022
IP	3 d, 4 d	Mouse	Sepsis, peritonitis	Heart, lungs	Improved survival	Cros et al., 2022
PO	7 d, 28 d	Mouse	Silicosis	Lungs	Alleviated lung damage	Wang et al., 2023

To be continued

Table 1 (continued)

Administration	Duration	Subjects	Disease	Organ	Key finding	Reference
In vitro	24 h	Cell	Hepatocellular carcinoma	HCCs	Prevented cell apoptosis	Garten et al., 2019
PO	20 d (5-d injection and 5-d pause; four cycles in total)	Mouse	Chemotherapy-induced cognitive impairment	BT	Prevented cognitive dysfunctions	Yoo et al., 2021
IP (acute experiment), PO (chronic experiment)	5 d (acute experiment), 60 d (chronic experiment)	Mouse	Doxo-induced cardiotoxicity and physical dysfunction	Heart, SM	Prevented damage	Margier et al., 2023
In vitro	48 h	Cell	Diabetes mellitus (DM)-related corneal epithelial dysfunction	HCECs	Increased survival	Pu et al., 2022
PO	7 d	Mouse	Retinal detachment	Eyes	Protected retinal photoreceptors	Chen et al., 2020
PO	25 d	Rat	Adjuvant-induced arthritis (AIA)	Both hind paws, spleen	Worsened severity of AIA	Wang et al., 2021
In vitro	20 d	Cell (aging melanocytes)		Melanocytes	Reduced melanin production	Brito et al., 2022

IP: intraperitoneal; PO: peros; In vitro: in vitro cell culture; WAT: white adipose tissue; SM: skeletal muscle; AT: adipose tissue; MSCs: mesenchymal stem cells; HCCs: hepatocellular carcinoma cells; BT: brain tissue; HCECs: human corneal epithelial cells.

Author contributions

Hongjun KANG conceptualized this manuscript. Min WANG and Lianrong ZHU wrote the original draft and achieved the visualization. Min WANG, Yuan CAO, Yun LI, Lu WANG, and Yuyan LIU were all involved in the investigation. Zihui DENG was responsible for the project management. All authors contributed to the article and approved the final version.

Compliance with ethics guidelines

Min WANG, Yuan CAO, Yun LI, Lu WANG, Yuyan LIU, Zihui DENG, Lianrong ZHU, and Hongjun KANG declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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