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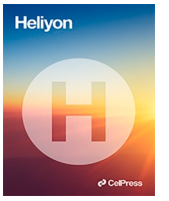

Review article

NAD^+: A key metabolic regulator with great therapeutic potential for myocardial infarction via Sirtuins family

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ABSTRACT

Myocardial infarction (MI) is one of the complex phenotypes of coronary artery disease, which results from the interaction of multiple genetic and environmental factors. Nicotinamide Adenine Dinucleotide (NAD^+) is an important cofactor regulating metabolic homeostasis and a rate-limiting substrate for sirtuin (SIRT) deacetylase. Numerous NAD^+ studies have shown that it can be used as an anti-MI treatment. However, there have been few systematic reviews of the overall role of NAD^+ in treating MI. MI, which has long been a global health problem, still lacks effective treatment till now, and the discovery of NAD^+ provides a new perspective on its adjuvant treatment. This review summarizes the role of NAD^+ signaling in SIRTs in alleviating MI.

1. Introduction

Despite current methods for treating Myocardial infarction (MI) being relatively mature, it remains an important public health problem worldwide and is still a major cause of high morbidity and mortality [1]. Timely revascularization after MI is the key to improving cardiac function level and preventing serious complications after MI, including percutaneous coronary intervention, thrombolytic therapy, and bypass surgery [2]. In addition, various substances and proteins have been reported to play a crucial role in cardiac repair/remodeling after MI, so drug intervention has aroused great interest [3]. It is necessary to find novel approaches for preventing MI by targeting the endogenous signaling pathways in cardiomyocytes. However, the mechanism of cardiac regulation has not been fully elucidated.

Many in vivo and in vitro studies have shown the importance of nicotinamide adenine dinucleotide (NAD^+)-dependent Sirtuins (SIRTs) in deacetylation activity in mediating cardiac damage following MI. Recently, as an important substance involved in energy metabolism in mitochondria, NAD^+ has attracted considerable attention through its assisting role in various biological processes, including anti-oxidative stress, cell cycle regulation, mitochondrial energetics, and so on [4,5]. Therefore, this review summarizes the role of NAD^+ signaling in SIRTs in alleviating MI.

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2. MI and associated mechanisms of NAD^+

2.1. Pathophysiology of MI

MI is the leading cause of mortality and morbidity in cardiovascular diseases [6]. MI is usually caused by plaque rupture resulting in sudden blood flow interruption through the epicardial coronary artery and subsequent occlusive thrombosis, resulting in cardiomyocyte death and impaired cardiac function due to myocardial hypoxia and energy depletion of cardiomyocytes.

During the period of MI, glycolysis become the major supplier of adenosine triphosphate (ATP), when glycogen stored in the heart begins to feed glycolysis. Recycling glycolysis-produced NADH through the mitochondria into cytosolic NAD^+ via the pathway of malate/aspartate shuttle to maintain glycolytic activity [7].

Some important structural remodeling occurs after MI, such as scarring at the infarct site. More importantly, vascular remodeling and interstitial fibrosis were also observed in the affected myocardium at non-infarct sites [8]. At the myocardial cell loss site, fibrous scarring plays a key role in maintaining structural integrity and restoring cardiac function, ultimately leading to impaired myocardial tissue. During MI, damage-associated molecular pattern (DAMP) proteins are also released from the myocardial muscle, triggering inflammatory fibrosis and cardiac remodeling [9].

2.2. NAD^+ metabolism in MI

In mammalian cells, NAD^+ is produced via two biosynthetic pathways: the kynurenine pathway using tryptophan as a substrate and the salvage pathway of regenerating NAD^+ from niacinamide. The main pathway is the salvage pathway, in which the rate-limiting step is catalyzed by niacinamide phosphoribosyl transferase [10].

Glycolytic and glucose oxidation metabolism as important metabolic pathways dependent on the redox ration of NAD/NADH, changes in its ration have been associated with various diseases, including MI [11]. The imbalance between oxygen delivery and the heart's ATP requirements leads to energy depletion and thus MI. MI results in a decrease in oxygen consumption to the heart and lower ATP and NAD^+ levels.

Major NAD^+ dependent enzymes, including SIRT1-7, poly adenosine diphosphate-ribose polymerase (PARPs), and cyclic ADP-ribose (cADPR, CD38/CD157), are energy sensors and transcriptional effectors, DNA repair and fat metabolism regulators, and second messengers in Ca^{2+} signal transduction [12–15]. Among them, SIRT3 defects have been shown to exacerbate cardiac dysfunction during post-ischemic recovery [16]. SIRT3 expression and activity were significantly decreased by ischemia-reperfusion [17]. The activity of all these enzymes is strictly controlled by the amount of NAD^+ in the cell.

3. Mechanism of NAD^+ in the anti-MI

3.1. Lysine acetylation regulation

The SIRT class of NAD^+-dependent lysine deacetylases has become a key mediator in cardiac protection. The SIRTs family, comprising seven proteins (SIRT1-SIRT7) that share the highly conserved NAD^+ binding catalytic domain has attracted great attention over the past few years. All families of SIRTs are NAD^+-dependent, but they vary in subcellular localization and substrate affinity.

SIRT1 has antithrombotic activity, preventing carotid thrombosis in mice by inhibiting endothelial tissue factors [18]. A study has shown that SIRT1 inhibits Forkhead transcription factor forkhead box O3a (FOXO3a) through deacetylation and subsequently down-regulates the transcription of Bcl-2 interacting mediator of cell death, thus preventing apoptosis and cellular oxidative stress responses [19,20]. SIRT1 regulates the downstream protein forkhead box O1 (FOXO1) through deacetylation, thereby controlling the expression of several proteins that respond to oxidative stress [21]. SIRT1 activation by exogenous NAD^+ supplementation can reduce the oxidative stress and inflammation of myocardial cells induced by hypoxia and enhance the viability of myocardial cells [22]. In addition, SIRT1 protects cardiomyocytes from ischemia/reperfusion (I/R) injury by regulating uncoupling protein 2 expression [23]. SIRT1 inhibitioneither pharmacologically or genetically prevents cardioprotection via ischaemic pre-conditioning (IPC) [24,25]. Conversely, SIRT1 activation either pharmacologically or genetically is sufficient to confer cardioprotection against acute MI [25–27].

SIRT2 is an important programmed necrosis regulator. NAD^+ deacetylates in a SIRT2-dependent manner in the context of I/R injury and shows that inhibitors of this deacetylase can prevent necrotizing injury [28]. SIRT2 can deacetylate nuclear factor erythroid2-related factor 2 (NRF2), which is closely related to the direct control of cellular iron homeostasis by stability [29]. FOXO3a is a transcriptional activator of the superoxide dismutase 2 (SOD2) gene, which encodes a powerful antioxidant MnSOD protein. SIRT2 has also been shown to deacetylate FOXO3a to resist oxidative stress [30].

SIRT3 mainly regulates global mitochondrial lysine acetylation to enhance antioxidant defense and maintain mitochondrial function, to maintain endothelial dysfunction in MI [31–33]. SIRT3 expression and activity are significantly reduced during MI [17]. SIRT3, through deacetylation, regulates the transcriptional activity of SOD2, which contributes to regulating mitochondrialcristae reactive oxygen species (mROS) homeostasis and autophagic cell death [34]. In addition, SIRT3-deficient mice are more susceptible to aortic coarctation-induced left ventricular hypertrophy through activation of mitochondrial permeability conversion pores [35]. NAD^+ depletion inhibits NAD^+-dependent SIRT3 activity, which can be rescued by supplementation with the NAD^+ precursor nicotinamide riboside [36].

SIRT4 functions primarily as an NAD^+-dependent ADP-ribosyltransferase [37]. Notably, SIRT4 acts opposite to SIRT3 and SIRT5 in regulating multiple metabolic pathways, including glutamine catabolism, fatty acid oxidation, and amino acid catabolism [38]. In a

study of angiotensin II (Ang II) -induced cardiac hypertrophy in mice, SIRT4 overexpression and knockdown were found to increase and decrease ROS in the heart and mitochondria. SIRT4 inhibits the binding of SOD2 to SIRT3, leading to increased acetylation and thus reduced SOD2 activity [39].

SIRT5-mediated dessuccinylation inhibits pyruvate dehydrogenase complex activity in the tricarboxylic acid (TCA) cycle, which is opposite to the function of SIRT3 [40]. SIRT5, which has limited deacetylase activity, also catalyzes the removal of succinyl groups from proteins [41]. Consistent with this, it has been shown that increased IRI in the hearts of SIRT5 deficient mice can be reversed by preventing succinate accumulation [42].

Studies have shown that SIRT6 is an activator of NRF2-dependent gene transcription. NRF2 pathway is the main target of SIRT6's antioxidant effect in MI and vascular endothelial dysfunction [43]. Deficiency of Sirt6 leads to cardiac hypertrophy and heart failure [44]. While promoting deacetylation is an attractive route to protect the heart, considerable effort is required to develop specific drugs to achieve this goal.

3.2. Calcium overload regulation

Dysfunction of Na^+/H^+ exchange, Na^+/Ca^{2+} exchange, and H^+/Ca^{2+} exchange are the key causes of intracellular calcium overload in MI, and the imbalance of intracellular calcium homeostasis aggravates ischemic injury of myocardial cells [45,46]. NAD^+ directly ameliorates passive stiffness and calcium-dependent active relaxation of cardiomyocytes by increasing deacetylation of myoglobin and sarcoplasmic reticulum caladenosine triphosphatase 2a, respectively [47].

Cluster of differentiation 38 (CD38) is a type II transmembrane protein with extracellular space-directed active sites that appears to produce anintracellular calcium signaling messenger [47]. CD38 defects protect the heart from I/R damage by activating SIRT1/-forkhead proteins (FOXOs)-mediated antioxidant stress pathways [48]. CD38 is the major catabolic enzyme of NAD^+. Since CD38 is an extracellular enzyme, interpreting these intracellular effects remains difficult. We boldly predict that NAD^+ may protect the myocardium from damage by regulating calcium homeostasis in cells.

3.3. DNA repair

MI causes oxidative DNA damage in the heart. There is now increasing evidence that NAD^+-dependent processes play an important role in genome maintenance and DNA repair mechanisms [49]. During MI, cardiomyocytes experience high oxidative stress levels, which leads to DNA strand breakage. This then triggers strong PARP activity, which hinders cell survival [50]. PARP and SIRT jointly act as substrates for NAD^+ and participate in the repair of DNA damage. The PARP-NAD^+-SIRT axis is also proposed to actively support DNA repair mechanisms [49,51].

SIRT3 can deacetylate PARP1, thereby blocking its catalytic activity [52]. PARP1 and SIRT6 can bind to each other, which is aggravated by DNA damage [53]. Besides cross-modification, there is evidence for transcriptional co-regulation, SIRT1 has been shown to negatively regulate the PARP1 promoter, while the SIRT1 promoter is regulated by PARP2 [54,55]. This adds an extra dimension to SIRT-ARTD crosstalk by co-modulating common pathways and goals for maintaining genome integrity [56].

4. Mechanism of NAD^+ in the cardiac remodeling/repair following MI

Although timely reperfusion therapy reduced acute mortality associated with MI, improved patient survival was accompanied by an increased chronic heart failure incidence, largely due to poor remodeling of the damaged left ventricle after the initial ischemic event [57]. As a result, despite surviving the initial MI, the quality of life of many patients deteriorates dramatically with heart failure onset, and current treatment options for this condition are few and do not address the fundamental problem of cardiomyocyte necrosis.

Acute ischemia can cause important changes in ventricular structure, that is, local changes in the infarct area and other parts. Myofibroblasts are fibroblast-like cells, which express α-smooth muscle actin microfilaments and enhance contraction ability, through signaling by macrophages-released transforming growth factor-β (TGF-β) [58]. Therapid proliferation and expression of type I and III fibrillar collagens by myofibroblasts are responsible for generating contractile scar tissue in the infarct site [59]. Currently, induction of cardiomyocyte proliferation is considered to be a promising method for heart regeneration after MI.

As mentioned above, NAD^+ can activate the SIRTs family, and SIRTs deficiency leads to various heart diseases. Protein p21 (p21) acetylation induces cardiomyocyte proliferation arrest while blocking p21 acetylation increases cardiomyocyte proliferation. P21 can be acetylated by SIRT1, which activates p21 ubiquitination by deacetylation [60]. SIRT1 is involved in the proliferation of cardiomyocytes induced by SIRT1 antisense long non-coding RNA (lncRNA) [61].

He et al. described the role of SIRT3 in cardiac remodeling after MI and proved that SIRT3 overexpression preserves cardiac function in MI mice [62]. Guo et al. reported another mechanism of the protective effect of SIRT3 on Ang II-induced cardiac fibrosis [63]. They have shown that $SIRT3^{-/-}$ mice inhibit myofibroblast transdifferentiation through the STAT3-nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2 pathway, thereby reducing myocardial fibrosis [63].

NAD^+ supplementation showed a specific anti-fibrosis ability in cardiomyocytes. SIRT6 activation by NAD^+ negatively regulates the differentiation of cardiac fibroblasts into myofibroblasts, and its depletion increases the proliferation of cardiac fibroblasts and extracellular matrix deposition and up-regulates the adhesion plaque-related genes and fibrosis-related genes through nuclear factor kappa-B (NF-κB) signal transduction [64,65]. NAD^+ activation of SIRT6 protects against cardiac hypertrophy after MI [66].

Cardiac systolic function was significantly reduced in cardiomyocyte-specific SIRT7-deficient mice. SIRT7 was shown to directly interact with GATA4 transcription factors and GATA4 knockdown reduced the worsening of cardiac hypertrophy in SIRT7 knockdown-

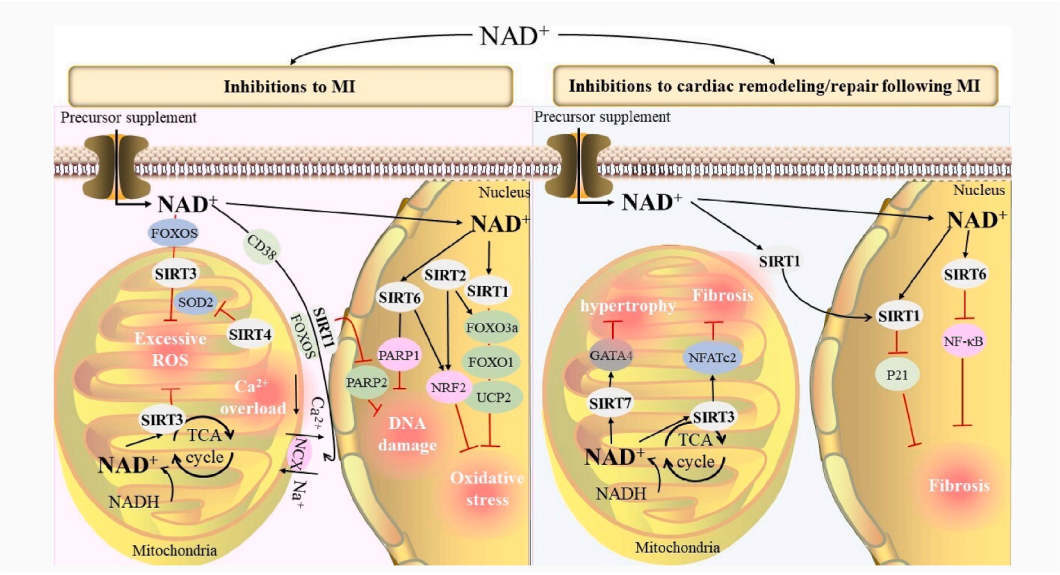

Fig. 1. Summary of the proposed pathways of cardiac metabolism covered in this review.

induced MI [67].

Here, we reviewed recent findings highlighting the role of NAD^+ metabolism during MI, and how NAD^+ plays a role in protecting the heartthrough the SIRT family. In addition, the obstacles in the field and the most recent advances, including the ongoing clinical studies of NAD^+ biosynthesis inhibitors, were also highlighted. Fig. 1 is a schematic diagram showing the relationship between NAD^+ and MI (Fig. 1).

5. Conclusion and prospect

NAD^+ depletion is one of the major pathogenesis of MI, and NAD^+ supplementation has shown therapeutic potential in restoring healthy metabolic and physiological functions. The pluripotency of this rich NAD^+ promotes its availability for therapeutic effects. In addition, NAD^+ acts as an auxiliary substrate in the deacylation of multiple interactions of cardiac cell nucleus transcriptional signals. These NAD^+-dependent signals are associated with or directly controlled by several aspects of metabolism, particularly in mitochondria. Numerousdata suggested that supplementing NAD^+ to enhance multiple cross-signaling between cells may be a viable treatment for alleviating MI. In addition, newer studies are needed to prove the close association between various cellular signals of NAD^+ and MI, which will help to improve the accuracy and effectiveness of MI-assisted therapy.

Credit authorship contribution statement

Xiaoqing Zhang and Zuowei Pei designed and directed the writing; Wei Yao drafted the aritle; All authors read and approved the final manuscript.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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