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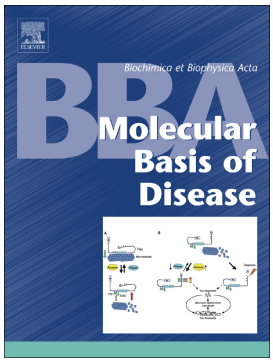

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NAD in Pathological Cardiac Remodeling: Metabolic Regulation and Beyond

Ignacio Norambuena-Soto[1,2], Yingfeng Deng[1], Charles Brenner[1], Sergio Lavandero[2,3,*], Zhao V. Wang[1*]

[1] Department of Diabetes and Cancer Metabolism, Beckman Research Institute of the City of Hope, Duarte, California 91010, USA.

[2] Advanced Center for Chronic Diseases (ACCDiS), Facultad Ciencias Químicas y Farmacéuticas & Facultad Medicina, Universidad de Chile, Santiago, Chile.

[3] Cardiology Division, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8573, USA.

For correspondence:

Sergio Lavandero, PhD, (slavander@uchile.cl)

Zhao V. Wang, PhD, (zhaowang@coh.org)

ABSTRACT

Nicotinamide adenine dinucleotide (NAD) coenzymes are carriers of high energy electrons in metabolism and also play critical roles in numerous signaling pathways. NAD metabolism is decreased in various cardiovascular diseases. Importantly, stimulation of NAD biosynthesis protects against heart disease under different pathological conditions. In this review, we describe pathways for both generation and catabolism of NAD coenzymes and the respective changes of these pathways in the heart under cardiac diseases, including pressure overload, myocardial infarction, cardiometabolic disease, cancer treatment cardiotoxicity, and heart failure. We next provide an update on the strategies and treatments to increase NAD levels, such as supplementation of NAD precursors, in the heart that prevent or reverse cardiomyopathy. We also introduce the approaches to manipulate NAD consumption enzymes to ameliorate cardiac disease. Finally, we discuss the mechanisms associated with improvements in cardiac function by NAD coenzymes, differentiating between mitochondria-dependent effects and those independent of mitochondrial metabolism.

KEYWORDS:

NAD; Heart failure; Cardiac remodeling; Nicotinamide riboside

INTRODUCTION

Nicotinamide adenine dinucleotide (NAD) coenzymes function primarily as carriers of high energy electrons in fuel oxidation, cellular bioenergetics, and biosynthetic processes as both generators and detoxifiers of reactive oxygen species (ROS). In addition, NAD^+, the oxidized, electron-accepting form, participates in DNA repair, post-translational modifications such as ADP-ribosylation and deacylation, and generation of calcium-mobilizing second messengers [1]. Cells have evolved multiple mechanisms to keep the level of NAD coenzymes in check via balancing biosynthesis and degradation. Among NAD biosynthetic pathways, the *de novo* or kynurenine pathway uses tryptophan as a primary source. In addition, the three salvageable precursor vitamins have unique entry points into NAD synthesis [2]. Nicotinic acid (NA) depends on enzymes of the so-termed Preiss-Handler pathway, which is tissue-specific. All known tissues express nicotinamide (NAM) phosphoribosyltransferase (NAMPT) and one or both nicotinamide riboside (NR) kinases [3] to generate NAD^+ [4] (**Figure 1**). The *de novo* kynurenine pathway and the Preiss Handler pathway produce nicotinic acid adenine dinucleotide (NAAD) as the final product for NAD synthesis, requiring glutamine-dependent NAD synthetase [5], whereas nicotinamide mononucleotide (NMN) produced from NAMPT or NR kinases is converted to NAD by nicotinamide mononucleotide adenylyl transferases (NMNAT).

The predominant anabolic pathway of NAD coenzymes is tissue dependent. For example, the liver actively uses the *de novo* biosynthetic pathway and releases NAM to circulation, whereas skeletal muscle primarily maintains NAD coenzyme levels via the NR kinase pathway [6]. As a result of glucose and fatty acid oxidation, cells generate NADH, the electron-carrying reduced form, and through the electron transport chain action cells can regenerate NAD^+. These two molecules, NAD^+ and NADH, can be phosphorylated by NAD kinases to generate $NADP^+$ and NADPH, respectively [7], which function primarily in biosynthetic pathways for nucleotides and lipids and also are required for the generation and detoxification of ROS.

The ubiquity of NAMPT expression can be explained by the observation that four different enzymes degrade NAD^+ to NAM plus ADP-ribose products. Poly (ADP-ribose) polymerases (PARPs) are a superfamily that includes DNA damage-inducible enzymes PARP1 and PARP2, forming polymers of ADP-ribose by cleavage of the glycosidic linkage between NAM and ADP-ribose [8]. Most members of the PARP superfamily are actually mono-ADPribosylating enzymes, which install ADP-ribose as a post-translational modification [9]. Significantly, five such enzymes are induced by the innate immune system in several cardiac relevant challenges including coronavirus infection [10]. Sirtuins are a family of NAD^+-dependent protein lysine deacylases with substrates in the nucleus, cytosol, and mitochondrial matrix [11]. Like members of the PARP family, the product of this reaction is also NAM. Uniquely, the other product is an acylated ADP-ribose [12]. CD38 is an enzyme with three membrane orientations, i.e., a type I membrane protein with its NAD active site oriented as an ecto-enzyme, a type II membrane protein with its NAD active site in the cytosol, and a type III membrane protein with its active site in the lumen of endolysosomes [13]. The type III form of CD38 converts $NADP^+$ plus NAAD to the powerful calcium mobilizing second messenger NAADP plus luminal NAD^+ [14]. In

addition, CD38 catalyzes the conversion of NAD^+ to cADP-ribose plus NAM [13], a reaction that also necessitates NAM salvage. Finally, sterile alpha and TIR motif containing 1 (SARM1) is an enzyme that is activated by accumulation of NMN in damaged neurons [15], which appears also to play a role in the heart [16]. Though unrelated in sequence to CD38, SARM1 also converts NAD^+ to ADP-ribose or cADP-ribose plus NAM [17].

There have been discussions regarding how NAD precursors are transported into cells. For example, the specific transporter of NAM has yet to be identified or NAM may only diffuse through cell membrane [18, 19]. The entry of NAM into cells was partially blocked by a pan-SLC inhibitor [20]. Therefore, there might be different ways of transport: through SLC transporter, by diffusion, or through other type of transporters or channels.

Regarding NR, it is well-accepted that NR is transported through the equilibrative nucleoside transporter (ENT). When ENT was blocked *in vitro*, the elevation of NAD^+ was prevented [21], and cell death ensued [22] under NR treatment.

As for NMN, Nikiforov et al. demonstrated that NMN needs to be first metabolized to NR to enter cells [22]. Along this line, Ratajczak et al. showed that in several tissues, NMN requires NRK1 to elevate intracellular NAD^+ levels [21]. However, in the liver, NMN still increases NAD^+ levels in the NRK1 knockout (KO) model, suggesting that NMN transport is more complex and does not depend only on its conversion to NR [21]. On the other hand, Grozio et al. showed that the Slc12a8 transporter is important for the transport of NMN in hepatocytes and the intestine [23]. However, this finding has caused controversies due to the methodology used to measure NMN [24, 25]. Therefore, more work remains to be done regarding the transport of NAD precursors.

NAD^+ level has been shown to vary in different diseases and pathological states, such as infection [10], heart failure [26], cancer [27], aging [28], and peripheral [29] and central neurodegeneration [30]. Changes in the NAD^+/NADH ratio may be caused by a decrease in NAD^+, impairment of oxygen availability, or other disturbances. In diseased hearts, NAD^+ biosynthesis decreases, and, at the same time, NAD^+ degradation pathways are elevated, causing a fall in the intracellular NAD^+ pool [31]. Strikingly, in many studies, loss of cardiac NAD coenzymes is accompanied by downregulation of salvage from NAM and upregulation of salvage from NR, which has been rationalized by the lower ATP cost of regenerating NAD coenzymes from NR than from tryptophan, NA, or NAM [26]. For example, in the transverse aortic constriction (TAC)-induced cardiac hypertrophy and heart failure model, after 2 [32], 4 [33], and 8 weeks [34], NAMPT expression is decreased both at the mRNA and protein levels. On the other hand, NRK2 levels are increased after TAC [35]. In ischemia and ischemia/reperfusion models, NAMPT expression is decreased [32], and NRK2 expression is increased in mice and humans [36]. Regarding the metabolic disease, it has been reported that mice fed with high fat diet or obese ZSF1 rats do not change the levels of NAMPT [37, 38]; on the other hand, Tur et al. showed that the activity of NAMPT is decreased in *db/db* mice, however, the protein levels of NAMPT were not examined [39]. Finally, in models of heart failure, NAMPT levels are decreased, and NRK2 levels are increased [26, 35, 40]. Interestingly, whether there is an endogenous source of NR remains unknown. Notably, as nucleotides, neither NAD^+ nor NMN are cell permeable. Both of these compounds have been used as supplements or

drug candidates to address cardiac and other conditions. However, NAD^+ and NMN require extracellular conversion to NR or NAM in order to augment cellular NAD coenzymes [21, 30].

In humans, contradicting results have been found related to heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). On one hand, Tong et al. showed that patients with either HFrEF or HFpEF have decreased NAMPT mRNA levels in right ventricle samples [41], and Diguet et al. found a decrease in NAMPT protein levels and an increase in NRK2 protein levels in left ventricle samples from patients with HFrEF [26]. On the other hand, Abdellatif et al. reported that, in left ventricle samples from patients with HFpEF, there are no changes in the levels of NAMPT protein [38]. Interestingly, Dou et al. showed that circulating levels of NAMPT are increased in patients with heart failure [42]. This finding has also been reported in the TAC-induced heart failure model in mice [34].

Studies related to NAD^+ consumption enzymes have demonstrated that PARP level and activity increase under doxorubicin cardiotoxicity [43, 44], heart failure due to mitochondrial genetic mutation [45], and myocardial infarction [46]. On the other hand, Boslett et al. showed that CD38 enzyme does not alter its expression after ischemia or ischemia/reperfusion [47].

All these differences in the expression of enzymes of the synthesis and consumption pathways are relevant to our understanding of treatment efficacy, either genetic or NAD precursors supplementation. Here, we describe the changes in NAD^+ level in various cardiac diseases. We then summarize strategies and treatments used to increase NAD^+ level in the heart for cardiomyopathy treatment. Finally, we discuss the molecular mechanisms of NAD^+-associated cardioprotection, focusing on both mitochondria-dependent and -independent actions.

Hypertensive heart disease

Cardiac hypertrophy is a main consequence of arterial hypertension. According to the latest epidemiological study, it is estimated that 20% of the world's population suffers from hypertension [48]. Different animal models have been generated to investigate hypertensive heart disease, including the spontaneously hypertensive rat (SHR) model, angiotensin II infusion, and TAC-induced pressure overload model [49]. Although it is well known that NAD^+ level decreases in hypertrophied hearts [26, 50], the consequences of this decline have yet to be fully elucidated (**Figure 2**).

One of the first studies demonstrating the relationship between treatment with exogenous NAD^+ or its precursors and cardiac response was conducted by Cox et al., which showed that NAM treatment prevented pathological cardiac hypertrophy and ameliorated oxidative stress in the heart in a volume overload rat model [51] (**Table 1**). Along the same line, Lee et al. found that NMN supplementation diminished cardiac hypertrophy and improved subsequent heart failure caused by TAC [52].

The sirtuin literature is complex and has been shown multiple effects in different tissues [53]. It also has been influenced by assumptions that these NAD^+-dependent protein

lysine deacylases are conserved in animals as longevity genes [11]. While this does not preclude important roles for sirtuins in the heart, caution needs to be exercised in examining sirtuin claims. Some studies have attributed the effect of decreased NAD^+ in the heart to the reduction of sirtuin activity. Pillai et al. showed that administration of NAD^+ decreased angiotensin II-induced hypertrophy through SIRT3, not SIRT1 [50]. A later study by Ma et al. reported that NR supplementation reduced TAC-induced hypertrophy and restored SIRT3 activity [54]. However, only correlation not causality was revealed in these studies. Nevertheless, SIRT3 has been shown to play a protective role against cardiac hypertrophy and cardiomyopathy [55-57]. In a model of SIRT3 deletion, there was elevated cardiac hypertrophy and mortality 4 weeks after TAC [55]. In a different study, SIRT3 deletion led to cardiac hypertrophy and decreased fatty acid oxidation at baseline, causing triglyceride accumulation, metabolic switch, and fibrosis in response to TAC [56]. Similarly, Koentges et al. showed metabolic changes at baseline with an increased NADH content in the heart under SIRT3 deficiency at early times (8 weeks old), but at 24 weeks old, the heart recovered mitochondrial function in SIRT3 deletion mice [57]. However, SIRT3 knockout mouse hearts showed an increase in mitochondrial permeability transition pore (mPTP) opening in 16-month old mice [55]. Interestingly, Lee et al. demonstrated that NMN supplementation prevented mPTP opening induced by TAC [52].

Therefore, SIRT3 may be essential to maintain cardiac metabolism and function at baseline in both young and old mice. Under stress such as TAC, SIRT3 exerts a cardioprotective role. However, thus far no evidence proves that reversion or prevention of hypertrophy by NAD precursors work through SIRT3. It is also unclear how the heart may compensate for SIRT3 deficiency in maintaining its metabolic function in middle-aged mice [57]. Moreover, SIRT3 is not the only sirtuin in mitochondria. It is possible that in hypertrophic hearts, SIRT5 may compensate for SIRT3 loss, whereas SIRT4 has been shown to have pro-hypertrophic effects [58, 59].

Like the literature on SIRT3, the literature on SIRT5 is conflicting. In some studies, SIRT5 was shown to be protective in the heart against cardiac hypertrophy and heart failure. Sadhukhan et al. were the first to report that SIRT5 ablation induced pathological remodeling in the heart, showing that SIRT5 knockout mice had cardiac dysfunction and hypertrophy [60]. Consistently, Hershberger et al. found that SIRT5 deletion mice were more sensitive to TAC-induced pathological remodeling with more severe cardiac dysfunction and lower survival rate [61]. At the mitochondrial level, the NAD^+/NADH ratio was decreased [61]. Interestingly, this group showed that SIRT5 ablation in the postnatal period did not augment TAC sensitivity [62]. Therefore, SIRT5 may be necessary for heart development, making SIRT5-deficient hearts more sensitive to TAC if deleted early in life. However, Sadhukhan et al. refuted this proposition, as they showed that, two days after birth, SIRT5 knockout mice did not show appreciable alterations in the heart [60]. Finally, Guo et al. generated a transgenic mouse model overexpressing SIRT5 and showed that SIRT5 prevented the development of heart failure, fibrosis, and inflammation [63]. In contrast, Zhang et al. found that SIRT5 knockout mice developed less left ventricular hypertrophy and higher ejection fraction under pressure overload, giving a deleterious role to SIRT5 [64]. This effect was attributed to decreased ATP and increased AMP levels, leading to AMPK activation and increased NADH level in mitochondria [64].

The nonmitochondrial sirtuins have also been examined for cardiac functions. For example, Tang et al. showed that SIRT2 was cardioprotective in aging models or angiotensin II infusion because SIRT2 KO mice had worse cardiac function, and overexpression of cardiac specific SIRT2 prevented cardiac hypertrophy and fibrosis [65]. Along the same line, Sarikhani M. et al. showed that SIRT2 deletion worsened cardiac function in a hypertrophy model through NFAT activation [66]. Wu et al. discovered that NMN administration prevented isoproterenol-induced hypertrophy and cardiac dysfunction and restored the expression and activity of SIRT1, which was decreased in the isoproterenol hypertrophy model [67]. However, this study is short of a cause-effect experiment to determine whether NAD coenzyme repletion protects the heart through SIRT1 or is an epiphenomenon of improvement in the heart.

Two groups reported that TAC caused a decrease in SIRT6 expression, and when SIRT6 was overexpressed, TAC-induced cardiomyocyte death and dysfunction were prevented [68, 69]. Moreover, either whole-body or cardiomyocyte-specific SIRT6 deletion induced cardiac hypertrophy [68]. However, in another hypertrophy model, this time by abdominal aortic constriction, an increase in SIRT6 expression was observed. Interestingly, a decrease in its activity was correlated with a reduction in NAD^+ level [70]. In addition, hypertrophy induced by angiotensin II *in vitro* also increased the expression of SIRT6. Finally, as in the *in vivo* model of hypertrophy by TAC, overexpression of SIRT6 prevented hypertrophy *in vitro* by angiotensin II [70]. Pretreatment with NAD^+ maintained SIRT6 activity in the presence of angiotensin II [70]. Nevertheless, more work is required to reconcile opposing reports of SIRT6 expression changes in the heart in response to TAC.

Lastly, Vakhrusheva et al. generated the SIRT7 KO mouse model and showed that SIRT7 deletion mice developed cardiac hypertrophy [71]. In the same vein, Yamamura et al. conducted TAC in cardiomyocyte-specific SIRT7 KO mice, showing that these mice developed more severe cardiac hypertrophy and heart failure than control mice. In support of a functional role in protecting cardiac hypertrophy, NMN prevented phenylephrine-induced hypertrophy only if SIRT7 was present [72].

Collectively, sirtuins have an important role in cardiac hypertrophy, but it remains to be elucidated whether the protective effects of NAD^+ precursors are related to sirtuins. Along this line, it is unclear whether NAD^+ improves general metabolism or functions as a specific substrate and whether this translates into an increase in energetics. In addition, changes in nuclear sirtuins may lead to epigenetic changes related to hypertrophy, oxidative stress, or even mitochondrial dynamics. Therefore, both mitochondrial and non-mitochondrial mechanisms need to be clarified.

Ischemic heart disease

Ample studies have shown that NAD^+ level and specifically the NAD^+/NADH ratio are essential in preventing cardiac damage in ischemia, either myocardial infarction (MI) or ischemia/reperfusion (I/R) [47, 73] (**Figure 2**). At both *in vitro* with hypoxia/reperfusion and *in vivo* with MI or I/R, NAD^+ level in cardiac cells and tissue decreases, so that seeking to restore its level by direct administration of NAD^+ or its precursors has become a promising treatment strategy [74-76]. Nevertheless, little is known about the molecular

mechanism by which the administration of NAD^+ or its precursors exerts their protective effects against MI or I/R.

An example of the protection exerted directly by NAD^+ was shown by Zhang et al. in a rat model [77] (**Table 1**). NAD^+ when administered intravenously before ischemia decreased infarct size and cell death markers in a dose-dependent manner. At the same time, an increase in SOD2 protein and enzymatic activity was observed [77], suggesting that the protection may be due to the activation of antioxidant enzymes. Moreover, Zhai et al. showed that intravenous NAD^+ administration before reperfusion in a swine model decreased the plasma level of cardiac damage markers. In addition, NAD^+ reduces cardiomyocyte death by necrosis and inflammation in the heart [76]. However, either study demonstrated the molecular mechanism of protection by NAD^+. Liu et al. reported that intraperitoneal NAD^+ administration protected against I/R, promoting an increase in GSH (glutathione), which would explain the decrease in MDA (malondialdehyde) level after I/R [78]. These findings suggest that NAD^+ administration may act through both mitochondrial and non-mitochondrial mechanisms since it increases the antioxidant capacity of the heart, reducing reperfusion-induced oxidative stress, and decreasing cardiomyocyte death. However, further studies are needed to demonstrate a cause-effect relationship other than the aforementioned descriptive associations.

On the other hand, administration of NAD^+ precursors, such as NMN, NAM, and NR, has also been tested, and all have shown positive effects on the protection against I/R. Yamamoto et al. found that acute administration of NMN decreased infarct size in mouse hearts against I/R, and this effect may be mediated by SIRT1 since the protection was lost in SIRT1 deletion mice [73]. The importance of SIRT1 had already been demonstrated previously by the same group, in which infarct size was larger in SIRT1 deletion mice after I/R and, on the contrary, overexpression of SIRT1 decreased infarction [79]. Although it seems that SIRT1 mediates some action of NMN, SIRT1 KO alone exacerbated reperfusion injury. It therefore remains to be addressed if the diminishing of NMN protection is due to the absence of SIRT1 or underlying cardiomyopathy by SIRT1 deletion.

Furthermore, NMN administration has a chronic protective effect in the heart. Hosseini et al. showed that a 30-day treatment of NMN decreased infarct size in old mice after I/R [80]. At the mechanistic level, NMN administration prevented the decline in mitochondrial potential and decreased ROS while increasing the enzymatic activity of SOD and GPx [80]. Although there is no effector protein identified, it is inferred that the protective effect may be through the preservation of mitochondrial function and antioxidant mechanisms. Similarly, Jafari-Azad et al. demonstrated that administration of NMN in aged rats increased NAD^+ level and decreased infarct size after I/R [81]. Thus, NMN may act through two different mechanisms: maintaining mitochondrial homeostasis and activating antioxidant enzymes.

Interestingly, Li et al. recently described that NMN administration did not always protect the heart as it may depends on the basal cardiac NAD^+ level [75]. They showed that NAD^+ level was variable. Treatment with NMN did not protect against cardiac I/R at night or during dark hours in mice since NAD^+ level was high. On the other hand, pretreatment with NMN during daylight hours when there was low NAD^+ level was protective [75]. One

explanation for this circadian variation in NAD^+ level is the difference in NAMPT expression, with a higher level at night [75]. This is consistent with the findings by Hsu et al. that transgenic mice overexpressing NAMPT increased NAD^+ level, reduced cell death, and decreased infarct size [32]. Moreover, Tur et al. used P7C3, which has been termed as a NAMPT activator, to increase NAD^+ level and found smaller infarct size after I/R or MI [39]. However, either work falls short of a key experiment testing the hypothesis that the cardioprotective effect is mediated by SIRT1.

Furthermore, Sukhodub et al. demonstrated that mice fed with NAM-rich diet decreased infarct size after I/R in an *ex vivo* Langendorff model [82]. NAM prevented cardiomyocyte death under hypoxia by reducing mitochondrial ROS and increasing SOD and catalase expression [83]. Oral delivery strategies have recently been evaluated to augment NAD^+ precursor bioavailability. Nie et al. showed that NR by oral administration decreased infarct size in mice after I/R [84]. This emphasizes the importance of the NAD^+ salvage pathway in protecting against cardiac ischemia damage. Ahmad et al. showed that NRK2 protein level increased after MI, probably as a compensatory effect to the decrease of other NAD^+ synthesis enzymes [36]. Furthermore, NRK2 deletion mice were shown to be more susceptible to post-infarction mortality than wild-type mice, manifesting more severe cardiac hypertrophy and accelerated heart failure [36]. On the contrary, NRK2 overexpression protected cardiomyocytes from *in vitro* hypoxia/reperfusion [36]. However, it remains to be answered whether the effects stem from the lack of NRK2 or a decrease in NAD^+ in the heart.

Porter et al. demonstrated that H9c2 myoblast cells were more susceptible to death if SIRT3 was downregulated, involving mitochondrial dysfunction, reduced oxygen consumption, and decreased complex 1 activity [85]. SIRT3 heterozygous deletion hearts had larger infarct size post-I/R and more acetylated proteins, like an aged mouse heart [85]. However, SIRT3 KO mice were not tested. On the other hand, Li et al. showed that SIRT6 was decreased by aging and I/R. A proposed SIRT6 activator, MDL800, reduced cell death and infarct size following I/R which may be mediated by FoxO1 activation [86]. Although none of these studies had used NAD^+ precursors to test whether these proteins are essential for NAD^+ effect, it is suggested that the cardioprotective effect by NAD^+ may be through both mitochondria-dependent and -independent mechanisms.

Another approach to increase NAD^+ level is to suppress its degradation, and the enzyme most targeted in this strategy is CD38. Guan et al. used CD38 deletion mice which, although NAD^+ level was not measured, showed a similar level of protection against I/R as intraperitoneal NAD^+ administration [74]. In addition to increased NAD^+ level, lower ROS generation and increased SOD2 and catalase expression were also observed in CD38 knockdown H9c2 cells [74]. Although FoxO1 and FoxO3 protein levels were increased, it is inconclusive that these transcriptional factors are responsible for the protection afforded by the decrease in NAD^+ degradation [74]. On the other hand, Boslett et al. showed that genetic deletion of CD38 did not cause basal change in NAD^+ level, but under I/R, the NAD^+ decrease was lower than that of wild-type mice. In addition, there was a higher GSH level, and this could also be a protection mechanism against I/R [47]. The same group tested a CD38 inhibitor, which showed protection against I/R, but again without modifying NAD^+ level. Instead, an increase in $NADP^+$ level was observed [87], suggesting that the protection by NAD^+ may be due to greater availability and conversion

to $NADP^+$. As noted above, NADPH provides electrons for glutathione reactivation, thereby offering a clearly testable mechanism for resistance to ROS.

Additional questions are raised regarding cardioprotection of NAD^+ against I/R – whether it is due to its direct action on mitochondrial function or through its non-mitochondrial activity, such as its conversion to $NADP^+$ and antioxidant enzyme activation. Cumulative evidence so far demonstrated that both mitochondria-dependent and -independent mechanisms contribute to NAD^+ protection, which may be different under various disease conditions.

Metabolic disease-associated heart dysfunction

A number of different animal models mimic characteristics of metabolic disease such as insulin resistance, obesity, and diabetes. Treatment with STZ (streptozotocin) disrupts pancreatic beta cells and causes insulin-dependent diabetes. Instead, high fat or high fructose diet or genetic modifications, such as *db/db* mice lacking functional leptin receptor, have been used to induce chronic obesity and diabetes [88, 89]. A decrease in cardiac NAD^+ level has been observed in these models, also altering the NAD^+/NADH ratio [37, 90, 91] (**Figure 3**). Despite these findings, little has been focused on the effect of NAD^+ or its precursor administration on cardiac performance and the underlying mechanisms.

The benefits of restoring NAD^+ level in metabolic disease have been investigated through two approaches: administering NAD^+ precursor NR and overexpressing NAD^+ biosynthesis enzyme NAMPT (**Table 1**). Hu et al. demonstrated that NR administration restored NAD^+ level in the heart in *db/db* mice [90]. Further, NR treatment reversed fibrosis and partially improved cardiac dysfunction in these mice [90]. This work also revealed that NR protected the heart through both mitochondrial and non-mitochondrial mechanisms by preserving mitochondrial function and activation of SIRT1. NR induced Mfn2 expression through co-regulators PPARα and PGC-1α, which are downstream targets of SIRT1 [90]. This action prevented mitochondrial fission and oxidative stress induced in the *db/db* model. Nevertheless, the change of SIRT1 is only correlative, and further tests are needed to assess the cause-effect relationship between SIRT1 activation and protection under NR administration.

In addition, De Castro et al. demonstrated that, in a rat model of high fat diet feeding, NR decreased NADPH oxidase activity without altering antioxidant enzymes, suggesting that NR reduces oxidative stress in the heart [92]. However, NR treatment did not affect cardiac function [92]. One of the problems of this study is that high fat diet was administered for a short time, and no cardiac damage was evidenced. Therefore, it is unknown whether NR treatment has cardioprotective effects in the model of cardiac damage by high fat diet feeding. It is also necessary to investigate whether other NAD^+ precursors have similar effects to strengthen the findings on cardioprotection by restoring NAD^+ content.

On the other hand, Oka et al. showed that mice fed on high fat diet for three months induced NAMPT level and decreased NAD^+/NADH and NADPH/$NADP^+$ ratios, as well as diastolic dysfunction [37]. Overexpression of NAMPT prevented diastolic dysfunction and

increased NAD^+ level, but the NAD^+/NADH ratio was kept low because NADH level was also elevated [37]. However, at the same time, NADPH level was increased, preventing the decrease in the NADPH/$NADP^+$ ratio [37]. NAMPT overexpression improved high fat diet-induced oxidative stress via NADK, the enzyme responsible for the conversion of NAD^+ to $NADP^+$, suggesting that NADPH elevation may be a mechanism of protection [37]. Consistently, NAMPT deficient mice had more significant diastolic dysfunction and oxidative stress than wild-type mice after being fed on high fat diet [37]. In contrast, Chiao et al. showed that mice overexpressing NAMPT increased NAD^+/NADH ratio, improved cardiac myopathy, and decreased SOD2 acetylation in a model of STZ-induced diabetes [91]. In this case, there was no change of NADPH oxidase, suggesting that the mechanism may not be oxidative damage and that the SOD2 pathway may be relevant. However, NADPH level in the heart was not evaluated [91]. These studies employed different pathological models, which may explain why the protection mechanism differs. Nevertheless, restoration of antioxidant capacity in the heart may be a key mechanism against cardiomyopathy in metabolic disease.

As in other cardiovascular diseases, sirtuins have mixed results because some studies lacked controls and used controversial activators. In diabetes and obesity, there are reports of decreased expression of SIRT1, SIRT3, and SIRT6 [93-95]. In support of a potential role for SIRT3 in diabetic cardioprotection, Li et al. described that SIRT3 overexpression in *db/db* mice decreased acetylated proteins, ROS production, and cardiac fibrosis and improved contractile function [96]. In addition, SIRT3 deletion mice developed more significant cardiac dysfunction than wild-type mice in an STZ model of diabetes [97].

SIRT6 has also been shown to be cardioprotective in metabolic disease. Kanwal et al. showed that in high fat diet fed or *db/db* mice, SIRT6 was decreased, and SIRT6 overexpression ameliorated cardiac hypertrophy and fibrosis, improved insulin sensitivity, and prevented mitochondrial fission and dysfunction in the heart [95]. Recently, Huang et al. reported that a SIRT6-specific inhibitor, OSS-128167, exacerbated damage in mouse hearts in an STZ model of diabetes [98]. Diabetic mice decreased SIRT6, and SIRT6 inhibitor increased cardiomyocyte death, fibrosis, and oxidative damage due to elevated MDA and inflammation in the heart [98].

Current studies evaluating sirtuins' role in cardioprotection did not conduct the test of administration of NAD^+ or its precursors. These reports only proved that sirtuins play a role in cardiometabolic disease, but the relevance to NAD^+ is elusive. In addition, NAD^+ precursors have only been demonstrated to exert non-mitochondrial actions, but little has been studied concerning mitochondrial mechanism. Therefore, it remains to be clarified whether NAD^+ and its precursors act only through non-mitochondrial antioxidant pathways or also through improving metabolism by increasing mitochondrial function in cardiometabolic disease.

Cardio-oncology

Recently, there has been much research on cardio-oncology, emphasizing the cardiotoxic effect of cancer treatment. Most cardiotoxicity studies have focused on anthracycline

therapy, but other chemotherapeutic drugs have also been shown to cause cardiac damage [99]. For example, fluoropyrimidines have been linked to a risk of up to 20% cardiotoxicity [100]. The associated cardiac myopathies are arrhythmias, angina, and MI [101]. Taxanes, such as paclitaxel, present an incidence of 5 to 20% of arrhythmias or decreased ejection fraction [102, 103]. Treatment with anthracyclines, such as doxorubicin, causes cumulative, dose-dependent cardiomyopathy [104]. There are differences in the incidence of cardiomyopathy by anthracycline, varying from 5 to 48% in increasing doses from 400 to 700 mg/m^2 [105, 106]. In addition to the accumulated dose, comorbidities affect the cardiac damage induced by anthracyclines, which may cause cardiotoxicity with doses lower than those described [107].

In search of the mechanisms by which doxorubicin causes cardiac damage, studies have focused on both mitochondria-dependent and -independent alterations. NAD^+ level is affected in either mechanism, and NAD^+ precursors have been used to improve or prevent cardiotoxicity (**Figure 3**). Recently, Awad et al. showed that long-term treatment with doxorubicin led to mitochondrial fragmentation, causing mitochondrial dysfunction with decreased ATP level and calcium overload [108] (**Table 1**). Although NAD^+ level was not measured, pretreatment with NAM prevented doxorubicin-induced damage to the heart and mitochondrial dysfunction [108]. Li et al. showed that NMN ameliorated doxorubicin cardiotoxicity in p53 deletion mice, demonstrating that p53 is not required for the protective action [109]. At the same time, NMN increased the mRNA levels of electron transport chain complexes, improving oxygen consumption and ATP production [109]. Lastly, Zheng et al. described that NR improved cardiac function dose-dependently and decreased cell death, ROS production, and MDA level in cardiomyocytes [110]. The underlying mechanisms may involve the improvement of autophagic flux [110]. Taken together, all these three studies demonstrated that NAD^+ precursors prevent doxorubicin cardiotoxicity. However, it remains unclear whether the cardioprotective effects are mitochondria-dependent.

A study by Zheng et al. showed that SIRT1 is important for NR cardioprotection [110]. Along this line, Kuno et al. observed that SIRT1 deletion in the heart aggravated the cardiotoxicity induced by doxorubicin [111]. Several studies have also shown that overexpression of SIRT1 [112] decreased or prevented cardiomyocyte damage as well as cardiac dysfunction. In addition, Wu et al. demonstrated that SIRT6 protected against doxorubicin cardiotoxicity since heterozygous deletion mice for SIRT6 suffered more significant death, fibrosis, and cardiac atrophy after doxorubicin treatment. In contrast, SIRT6 overexpression decreased doxorubicin-induced death in cardiomyocytes [113].

Cheung et al. demonstrated that doxorubicin decreased SIRT3 and SOD2, and SIRT3 overexpression reduced mitochondrial ROS in H9c2 cells [114]. Later, Tomczyk et al. found that overexpressing SIRT3 in the heart improved cardiac function and decreased fibrosis and cardiomyocyte death following doxorubicin treatment [115]. At the same time, SIRT3 prevented SOD2 depletion and oxidative stress induced by doxorubicin [115]. However, in both studies, NAD^+ precursors have not been used to confirm the involvement of NAD^+-mitochondrial mechanism in SIRT3 cardioprotection.

Given the importance of NAD^+ for mitochondrial function, it is necessary to continue investigating the mechanism involved in doxorubicin cardiomyopathy and how NAD^+

participates in the early stage to prevent cardiotoxicity or the late stage for potential treatment.

Heart failure (HFrEF and HFpEF)

All the cardiac diseases described above lead to heart failure, either with HFrEF or HFpEF. Hypertension or ischemia commonly causes HFrEF, and those associated with aging, obesity, and diabetes are related to HFpEF. In both cases, it has been reported that cardiac NAD^+ content is decreased, and there is an imbalance in the NAD^+/NADH ratio (**Figure 4**).

Lee et al. in a TAC-induced HFrEF model using Ndufs4 KO mice and Zhan et al. in a TAC-induced HFrEF model using KLF4 KO mice demonstrated that NMN administration increased NAD^+ content, elevating the NAD^+/NADH ratio, and improved cardiac function [52, 116] (**Table 1**). NR is another NAD^+ precursor that positively affects cardiac function in heart failure models. Diguet et al. showed that NR administration improved contractile function in two models of HFrEF, one in SRF deletion mice and the other one by TAC [26]. Similarly, NR treatment was shown to improve contractile function, decrease cardiac remodeling markers, and increase mouse survival in a model of HFrEF by Laminin mutation [40]. However, in a model of HFrEF due to mitochondrial DNA damage, where there is cardiac hypertrophy and survival issue (less than eight weeks), NR administration from week 6 did not affect cardiac function or markers of hypertrophy [45]. In these studies, the same dose of NR was used (400 mg/kg/day), so the failure to obtain cardioprotective results from NR in the Lauritzen et al. study may be due to the late start of treatment when cardiac failure is already advanced. This proposition may also suggest that NR administration is useless in the late stage of HF. Interestingly, in two of these studies, NAM was also administered, and in both, NAM did not affect NAD^+ level or cardiac function [26, 40]. It is important to point out that NAMPT expression level was dramatically decreased in heart failure [26, 40, 116, 117], which may explain why NAM is not an effective candidate to increase NAD^+ level in heart failure. In addition, NR administration has also been found to improve cardiac function in HFpEF models [41, 118]. Abdellatif et al. demonstrated that NAM treatment in a mouse model of HFpEF improved cardiac function [38]. The difference compared to HFrEF is that, in this model of HFpEF, NAMPT was not decreased. Collectively, these findings suggest that not all NAD^+ precursors are equal in improving every type of heart failure. Significantly, NR has been shown to be effective when the NMRK2 gene was induced [26], suggesting that a damage-induced gene expression program may be a key diagnostic for likely NR efficacy.

The mechanisms proposed to explain the improvement in cardiac function are linked to mitochondrial function and enzymes that use NAD^+. It is well known that acetylated proteins are increased in heart failure [41, 52, 116-119]. In the mitochondrial matrix, a wide variety of metabolic stresses cause protein lysine hyperacetylation via mass action [120]. Administration of NAD^+ precursors, either NMN or NR, decreases the level of acetylated proteins [52, 116, 118], such as cyclophilin D to inhibit the opening of the mPTP [52, 116] as well as TCA-associated proteins [118]. Martin et al. showed that NMN administration improved energy utilization and fatty acids and glucose oxidation,

depending on the mitochondrial sirtuin, SIRT3 [117]. Along the same line, Tong et al. found that SIRT3 had an essential role in the development of HFpEF since SIRT3 deletion mice displayed worse cardiac function in a model of HFpEF [41]. Another sirtuin that has shown cardioprotective potential in heart failure is the nuclear type SIRT6. SIRT6 protein level was decreased in both HFrEF and HFpEF models [69, 121]. On the other hand, overexpression of SIRT6 in the heart [69] or endothelium [121] improved cardiac function. The proposed mechanism involves an improvement in fatty acid oxidation [121, 122]. In HFrEF, another mitochondrial sirtuin, SIRT5, has been shown declined, but the protection by NAD^+ or its precursors in this model has not been evaluated [123]. Finally, SIRT1 in heart failure models has shown contradictory results. There is evidence that SIRT1 was decreased [124], not changed [40], or increased [125] in its protein level. Van le et al. showed that in HFrEF, there was an increase in SIRT1, and SIRT1 deletion mice had better cardiac function [125]. Thus, the role of SIRT1 in heart failure remains to be clarified.

Although there is evidence that sirtuins are relevant for the progression of heart failure, further studies are needed to confirm whether NAD^+ precursors act through sirtuins. On the other hand, cumulative findings showed that the increase of NAD^+ levels through precursors, such as NR or NMN, improves mitochondrial function and energy production through more efficient metabolic processes, such as glucose and fatty acid oxidation. It remains to be elucidated whether the protective mechanism depends on epigenetic changes or is due to an increase in the enzymatic activity of TCA and/or electron transport chain related to mitochondria.

Application to the clinic: From bench to bedside

Despite the large number of studies that have demonstrated that administering NAD^+ precursors is cardioprotective against various cardiac diseases, the findings have yet been translated into clinic. Niacin (nicotinic acid) is available in several different formulations. Niacin has been used to control plasma cholesterol level and reduce phosphorous absorption. Daily intake of 1,000 mg or higher in humans is considered safe and efficacious in managing dyslipidemia [126]. NAM has been extensively studied as a skin cancer chemo-preventative agent and has well established human safety [127]. Following up on the first in human safety data on NR [128], there was a 3-dose NR safety study over 8 weeks that showed excellent availability and tolerability [129]. Human safety has been well replicated by others [130-132]. Regarding the effect of NR, it has been observed that NR improved peripheral blood mononuclear cell mitochondrial function and decreased inflammatory parameters [131]. These effects in peripheral blood mononuclear cells were reinforced by Wang et al., showing a significant correlation among high level of NAD^+, increased mitochondrial respiration, and low expression of proinflammatory cytokines [132]. Subsequently, Dollerup et al. and Elhassan et al. demonstrated that NR administration did not modify mitochondrial function in skeletal muscle in diabetes [133, 134]. Finally, Martens et al. reported that NR administration decreased blood pressure in patients with blood pressure above normal [135]. However, Remie et al. showed that in obese patients, no changes in cardiometabolic parameters, blood pressure, or ejection fraction were observed by NR treatment [136]. Therefore, the

effect of NR on cardiovascular disease remains to be fully elucidated. A first approximation to this is the study by Abdellatif et al., where a prospective study of 20 years showed that people who had diets rich in NAD^+ precursors had a lower risk of death, mainly due to a low number of deaths from cardiovascular causes [38]. A 30-patient study (NCT03423342) recently evaluated cardiac function by echocardiography in HFrEF patients following NR administration for 12 weeks. In this trial, Wang et al. demonstrated that administration of NR was safe, but cardiovascular parameters were not changed [132]. To date, two clinical trials will test the effect of NAD^+ precursor administration in cardiovascular disease. The NACAM study (NCT04750616) will evaluate the administration of NAM in patients requiring cardiac surgery. Although its main objective is renal damage, plasma troponin T, which approximates cardiac damage following surgery, will be determined. On the other hand, the NRII study (NCT04528004) will evaluate mitochondrial function in cardiac tissue of patients with heart failure after NR administration for two weeks. These are the first clinical studies to assess cardiac function following NAD^+ precursor administration, which could lay the groundwork for future clinical application of NAD^+ in cardiovascular disease.

CONCLUSIONS AND FUTURE PERSPECTIVES

In hypertrophic, ischemic, and cardiometabolic diseases, NAD^+ precursor administration has shown positive results by both mitochondrial and non-mitochondrial mechanisms, unlike in the case of cancer treatment cardiotoxicity and heart failure where the cardioprotective effects by NAD^+ precursors are only related to the improvement of mitochondrial dysfunction. Whereas sirtuin-dependent actions have been widely examined, the potential for NAD coenzyme-dependent bioenergetics, ADP-ribosylation, calcium signaling, and SARM1 functions remain underexplored. Taken together, NAD^+ precursors may be a promising therapy to stimulate the activity of multiple effectors simultaneously, i.e., cytosolic, mitochondrial, and nuclear, for programmatic protection in cardiovascular disease.

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CONFLICTS OF INTERESTS

Charles Brenner is chief scientific advisor of ChromaDex and Juvenis and a co-founder of Alphina Therapeutics and owns stock or options in these companies.

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Table 1: Effects of NAD^+ and NAD^+ precursors in cardiac disease.

Disease	Model	Alteration in NAD metabolism	NAD^+ precursor	Findings	*In vivo* Intervention	Protection mechanism	Ref.
Hypertension	Volume overload (arteriovenous fistula)	Increased NADH oxidase activity	NAM	Prevents hypertrophy	None	Prevents oxidative stress	[51]
	Pressure overload (TAC)	Not studied	NMN	Prevents hypertrophy	None	Prevents acetylated mitochondrial proteins, improving mitochondrial function	[52]
	Isoproterenol	Not studied	NAD^+	Prevents hypertrophy and fibrosis	SIRT3-KO	SIRT3-dependent	[50]
	Pressure overload (TAC)	Not studied	NR	Prevents hypertrophy and inflammation	None	Prevents oxidative stress	[54]
	Isoproterenol	Not studied	NMN	Prevents hypertrophy and fibrosis	None	Prevents oxidative stress	[67]
	Pressure overload (TAC)	Not studied	NMN	Prevents hypertrophy and fibrosis	SIRT7-KO	SIRT7-dependent	[72]
Myocardial infarction	*In vivo* Ischemia / Reperfusion	Not studied	NAD^+ (before ischemia)	Reduces myocardial infarct size	None	Reduces oxidative stress and cell death	[77]
	In vivo Ischemia / Reperfusion	Not studied	NAD^+ (before reperfusion)	Reduces myocardial infarct size and fibrosis	None	Reduces inflammation and cell death	[76]
	Ex vivo Ischemia / Reperfusion	Not studied	NAD^+ (before ischemia)	Reduces LDH release	None	Reduces oxidative stress	[78]
	In vivo Ischemia / Reperfusion	Not studied	NMN (before ischemia or before reperfusion)	Reduces myocardial infarct size	SIRT1-KO	SIRT1-dependent	[73]
	Ex vivo Ischemia / Reperfusion	Not studied	NMN (before ischemia)	Reduces myocardial infarct size	None	Reduces oxidative stress	[80]
	Ex vivo Ischemia / Reperfusion	Not studied	NMN (before ischemia)	Reduces myocardial infarct size	None	None	[81]
	In vivo Ischemia / Reperfusion	Not studied	NMN (before ischemia)	Reduces myocardial infarct size	None	None	[75]
	In vivo Ischemia / Reperfusion	Decreased NAMPT expression	NAMPT overexpression	Reduces myocardial infarct size	None	None	[32]
	Ex vivo Ischemia / Reperfusion and *In vivo* Myocardial infarction	Decreased NAMPT activity	P7C3, NAMPT activator. (Before ischemia and/or before reperfusion)	Reduces myocardial infarct size	None	None	[39]
	Ex vivo Ischemia / Reperfusion	Not studied	NAM-rich diet	Reduces myocardial infarct size	Potassium channel antagonist	Sarcolemmal Potassium channel-dependent	[82]
	In vivo Ischemia / Reperfusion	Not studied	NR (before ischemia)	Reduces myocardial infarct size	None	None	[84]

Metabolic disease	*db/db*	Not studied	NR	Improves cardiac systolic function and decreases fibrosis	None	Reduces oxidative stress and increases mitochondrial fusion	[90]
	HFD	NAMPT and NADK expression independent	NAMPT overexpression	Improves diastolic function	NADK inhibitor	Prevents oxidative stress	[37]
	STZ	Not studied	NAMPT overexpression	Increases cardiac function	None	None	[91]
Cancer treatment cardiotoxicity	Doxorubicin	Not studied	NAM	Prevents arrhythmia and cell death	None	Prevents mitochondrial fission, calcium overload and inflammation	[108]
	Doxorubicin	Not studied	NMN	Prevents systolic dysfunction	None	Increases mitochondrial function	[109]
	Doxorubicin	Not studied	NR	Prevents systolic dysfunction	Chloroquine	Improves autophagic flux	[110]
Heart failure with reduced ejection fraction (HFrEF)	TAC in Ndufs4 KO	Not studied	NMN	Prevents cardiac hypertrophy and dysfunction	None	Decreases acetylated protein and improves calcium handling	[52]
	TAC in KLF4 KO	Decreased NAMPT expression	NMN	Prevents cardiac dysfunction	None	Decreases acetylated protein, ROS, and cell death	[116]
	SRF KO	Decreased NAMPT expression and increased NMRK2 expression	NR	Prevents cardiac dysfunction	None	None	[26]
	Lamin A/C mutation	Decreased NAMPT, NMNAT1, and NMNAT3 expression and increased NMRK2 expression	NR	Prevents cardiac dysfunction	None	None	[40]
Heart failure with preserved ejection fraction (HFpEF)	Aged + HFD + DOCP	Not studied	NR	Reverses diastolic dysfunction and fibrosis	None	Decreases acetylated protein related to mitochondrial metabolism	[118]
	HFD + L-NAME	Decreased NAMPT expression and NMNAT1-2-3 expression independent	NR	Reverses diastolic dysfunction	None	Improves oxygen consumption	[41]
	HFD + L-NAME	Decreased NAMPT expression and NMNAT1-2-3	P7C3, NAMPT activator.	Reverses diastolic dysfunction	None	Improves oxygen consumption	[41]

		expression independent					
	ZSF1 obese mice/ Aging/ Dahl-salt mice	NAMPT expression independent	NAM	Prevents diastolic dysfunction	None	Decreases body weight and improves mitochondrial metabolisms	[38]

Abbreviations: DOCP: desoxycorticosterone pivalate; HFD: high fat diet; KLF4: Krüppel-like factor 4; LDH: lactate dehydrogenase; NAD: nicotinamide adenine dinucleotide; NADK: NAD kinase; NAM: nicotinamide; NAMPT: nicotinamide phosphoribosyltransferase; NMN: nicotinamide mononucleotide; NR: nicotinamide riboside; SIRT: sirtuin; SRF: serum response factor; STZ: streptozotocin; TAC: transverse aortic constriction; KO: knockout.

FIGURE LEGENDS

Figure 1. Overview of the biosynthetic and catabolic pathways of NAD^+.

There are three major pathways for NAD^+ (nicotinamide adenine dinucleotide) biosynthesis. The *de novo* pathway uses tryptophan as substrate, which is transformed into NAMN (nicotinate mononucleotide) through various enzymes. Then, NMNAT (nicotinamide mononucleotide adenylyl transferase) transforms NAMN to NAAD (nicotinic acid adenine dinucleotide). Finally, NADSYN (NAD synthase) generates NAD^+. On the other hand, the Preiss-Handler pathway uses NA (nicotinic acid) as substrate, which through NAPRT (nicotinic acid phosphoribosyltransferase), is transformed into NAMN, and then follows the same pathway mentioned above. Lastly, the third pathway is the salvage pathway which uses two different substrates: NR (nicotinamide riboside), which is phosphorylated by NRKs (NR kinases) to form NMN (nicotinamide mononucleotide); NAM (nicotinamide), which is transformed to NMN by NAMPT (nicotinamide phosphoribosyltransferase) and then to NAD^+ by NMNAT. On the other hand, there are four main NAD^+ consumption enzymes. PARP (poly(ADP-ribose) polymerase) uses NAD^+ to induce posttranslational modification of substrates (PARylation). Sirtuins use NAD^+ as a co-factor to deacetylate substrates. CD38 (cyclic ADP-ribose synthase) uses NAD^+ and produces NAM, ADPR (ADP-ribose), and cADPR (cyclic ADPR). Finally, SARM1 (sterile alpha and Toll/interleukin-1 receptor motif-containing 1) cleaves NAD^+ to generate NAM and cADPR.

Figure 2. Overview of the role of NAD metabolism in hypertrophic and ischemic hearts.

NAD^+, NAM, NMN, and NR are protective against hypertrophy and ischemia/reperfusion. However, no evidence has been shown regarding the protective mechanism. The most studied targets have been oxidative stress, protein acetylation, and sirtuins.

Figure 3. Overview of the role of NAD metabolism in cardiometabolic and cancer treatment cardiotoxicity.

NR and NAMPT are protective against cardiometabolic disease. On the other hand, NAM, NMN, and NR protect against doxorubicin cardiotoxicity. In both diseases, the protective mechanism remains elusive. Nevertheless, two factors may participate in cardioprotection: the increase in the NAD^+/NADH ratio reducing oxidative stress and sirtuin activation.

Figure 4. Overview of the role of NAD metabolism in heart failure.

NMN and NR are protective against heart failure, i.e., HFrEF and HFpEF, through augmenting glucose and fatty acid metabolism. On the other hand, NAM protects against heart failure in a NAMPT-dependent manner.

Highlights

- NAD coenzymes are decreased in the heart under various cardiovascular diseases
- Elevation of the availability of NAD coenzymes improves cardiac function and ameliorates cardiomyopathy
- Molecular mechanisms of NAD cardioprotection may involve mitochondria-dependent and -independent actions