Overview to Pyridine Nucleotides Review Series

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Abstract

Pyridine nucleotides are abundant soluble coenzymes and they undergo reversible oxidation and reduction in several biological electron-transfer reactions. They are comprised of two mononucleotides, adenosine monophosphate and nicotinamide mononucleotide, and are present as oxidized and reduced nicotinamide adenine dinucleotides in their unphosphorylated (NAD^+ and NADH) and phosphorylated ($NADP^+$ and NADPH) forms. In the past, pyridine nucleotides were considered to be primarily electron-shuttling agents involved in supporting the activity of enzymes that catalyze oxidation-reduction reactions. However, it has recently been demonstrated that pyridine nucleotides and the balance between the oxidized and reduced forms play a wide variety of pivotal roles in cellular functions as important interfaces, beyond their coenzymatic activity. These include maintenance of redox status, cell survival and death, ion channel regulation, and cell signaling under normal and pathological conditions. Furthermore, targeting pyridine nucleotides could potentially provide therapeutically useful avenues for treating cardiovascular diseases. This review series will highlight the functional significance of pyridine nucleotides and underscore their physiological role in cardiovascular function and their clinical relevance to cardiovascular medicine.

Keywords

pyridine nucleotides; NAD(H); NADP(H); metabolism; redox; cardiovascular disease

Pyridine nucleotides are small molecules comprised of two mononucleotides, adenosine monophosphate (AMP) and nicotinamide mononucleotide (NMN). They consist of oxidized and reduced nicotinamide adenine dinucleotides in their unphosphorylated (NAD^+ or NADH) and phosphorylated ($NADP^+$ or NADPH) forms. Arthur Harden first discovered the existence of a high molecular weight ferment (enzyme) and a low molecular weight co-ferment (coenzyme), while Hans von Euler-Chelpin isolated the coenzyme and later described the character of NAD^+ as being comprised of two mononucleotides, namely, AMP and NMN. These investigators won a Nobel Prize in 1929 for their investigations into the fermentation of sugar and fermentative enzymes. Subsequently, Otto Warburg, another Nobel laureate, provided evidence for the functional significance of NAD^+, which serves to transfer hydrogen, and discovered another coenzyme, $NADP^+$ [1]. Since then, it has become increasingly clear that these small molecules, termed pyridine nucleotides, are involved in a wide variety of cellular functions, including energy production, metabolism, reduction-

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None

oxidation (redox) reactions, cell survival and death, transcriptional regulation, and protein modification. Furthermore, interest in the field of pyridine nucleotides has been dramatically stimulated in the past decade by the discoveries that 1) the sirtuin family proteins, the key regulators of energy metabolism and lifespan, utilize NAD^+ as a co-factor[2, 3], 2) nicotinamide phosphoribosyltransferase (Nampt), an enzyme of the salvage pathway, is a key enzyme for NAD^+ synthesis[4, 5] 3) NADPH provides electrons to both oxidases and reductases, thereby stimulating oxidative and reductive stress[6], and 4) pyridine nucleotides regulate ion channels[7, 8] (Figure).

Generally, pyridine nucleotides have been shown to serve 1) as coenzymes for various dehydrogenase enzymes to regulate cellular metabolism, 2) as electron carriers to synthesize adenosine triphosphate (ATP) in mitochondria via the electron transport chain (ETC) and oxidative phosphorylation, 3) as electron donors for glutathione (GSH), thioredoxin (Trx), and NADPH oxidases (Noxs) to regulate the redox status, 4) as donors of adenosine diphosphate (ADP)-ribose moieties in ADP-ribosylation reactions, 5) as substrates for NAD^+-dependent enzymes, such as mono-ADP-ribose transferases (MARTs), poly(ADP-ribose) polymerases (PARPs), cyclic ADP-ribose synthases (cADPs) and sirtuins, and 6) as redox regulators that modify ion channel function. As one can speculate from these findings, pyridine nucleotides play an important role in regulating a wide variety of functions in the heart and other cardiovascular tissues. Therefore, understanding the role of pyridine nucleotides has become increasingly important in the field of cardiovascular medicine. We therefore put forward a review series to summarize our current knowledge of the cardiovascular function of pyridine nucleotides. The goal of this editorial is to provide brief highlights on the cardiovascular role of pyridine nucleotides under both physiological and pathological conditions as discussed in individual review articles of this series.

Biosynthesis of pyridine nucleotides

How are pyridine nucleotides generated in cardiomyocytes? First of all, NAD^+ and NADH are interchangeable through oxidation/reduction reactions, as are $NADP^+$ and NADPH. Since NAD^+ can be converted to $NADP^+$ by NAD kinase (NADK), describing how NAD^+ is synthesized would be most informative. The biosynthesis of NAD^+ occurs through two major pathways: a *de novo* pathway and a salvage pathway[9, 10] (Figure). The *de novo* pathway (the Preiss-Handler pathway) begins with tryptophan to generate quinolinic acid (QA). QA is converted to nicotinic acid mononucleotide (NaMN) by quinolate phosphoribosyltransferase (QAPRT). NaMN is then adenylylated by nicotinic acid mononucleotide adenylyltransferase (NaMNAT) to produce nicotinic acid adenine dinucleotide (NaAD), which is subsequently amidated to NAD^+ by NAD synthase (NaDS).

On the other hand, the salvage pathway regenerates NAD^+ from nicotinic acid (Na), nicotinamide (Nam), or nicotinamide riboside (NR) present in the metabolites of NAD^+ or dietary sources. Na is converted to NaMN through Na phosphoribosyltransferase (NaPRT). Nam is converted to NMN by Nampt, and NMN is subsequently adenylylated by Nam/Na mononucleotide adenylyl transferase (Nmnat) to form NAD^+. NR is used to generate NMN by NR kinase (NRK). Among the components of the salvage pathway, Nam is the major precursor of the NAD^+ synthesizing pathways in mammals, and Nampt is the rate-limiting enzyme[4]. Thus, Nam and Nampt are the most important components of the NAD^+ synthesizing pathways in mammalian cells. Importantly, in the heart, the expression of Nampt is regulated by stress[11]. Furthermore, the levels of Nampt and NAD^+ display circadian oscillations that are regulated by the core clock machinery in mice[12, 13]. While the expression of Nampt is regulated by the circadian transcription factor CLOCK, Nampt in turn negatively regulates the core circadian clock machinery CLOCK/BMAL1 through NAD^+/Sirt1. How NAD^+ levels are regulated through changes in Nampt expression in

response to stress and how this mechanism is influenced by the clock genes remain to be elucidated. Na and Nam are collectively called niacin or vitamin B3. Vitamins taken up through diet can be precursors of pyridine nucleotide biosynthesis through the salvage pathway. Nevertheless, it remains to be elucidated whether supplementation of vitamins or precursors of NAD^+ can maintain or improve NAD^+ levels during stress, thereby influencing the energy metabolism and other cellular functions[14].

Cellular metabolism

Pyridine nucleotides play an important role in regulating energy metabolism. The heart requires a high level of energy, in the form of ATP, nutrients, lipids, carbohydrates, and amino acids, to continue its pumping and maintain a constant protein turnover. The predominant energy source in the adult heart is fatty acids, used for fatty acid β-oxidation that produces NADH, the reduced form of flavin adenine dinucleotide ($FADH_2$), and acetyl-CoA. However, in the failing heart, the energy source shifts from fatty acids to carbohydrates, for glycolysis[15, 16]. The expression of the enzymes involved in fatty acid β-oxidation is regulated at the level of transcription by nuclear receptor transcription factors, such as peroxisome proliferator-activated receptor (PPAR) and PPARγ co-activator 1 α (PGC-1α)[17]. In the failing myocardium, fatty acid β-oxidation is downregulated, which is accompanied by an increase in glucose uptake and glycolysis. During glycolysis, the tricarboxylic acid (TCA) cycle, and fatty acid β-oxidation, NAD^+ is utilized as a coenzyme to produce NADH. During ATP synthesis through the mitochondrial ETC and oxidative phosphorylation, NADH is utilized as a hydride donor to generate a proton motive force across the inner mitochondrial membrane. NADPH is produced in the pentose phosphate pathway, and is re-oxidized as a coenzyme of aldose reductase in the polyol pathway. While aldose reductase utilizes NADPH to reduce the reactive products of lipid peroxidation under normal conditions[18], excessive activation of the polyol pathway in diabetes reduces the amount of NADPH, which, in turn, induces oxidative stress. NADPH is also utilized as a coenzyme for *de novo* fatty acid synthesis and in the biosynthesis of cholesterol. Because NAD^+/NADH and $NADP^+$/NADPH play a central role in energy production and metabolism as electron carriers and coenzymes, an imbalance in the ratios of the oxidized and reduced forms affects the energy level and cellular metabolism in the heart. Under normal conditions, NADH and acetyl-CoA, which are the products of fatty acid β-oxidation, inhibit carbohydrate oxidation through phosphorylation/inhibition of pyruvate dehydrogenase (PDH). Thus, carbohydrate oxidation is regulated by PDH activity, and the ratios of NADH/NAD^+ and acetyl-CoA/free CoA play a central role in regulating PDH activity[15]. The regulation of cellular metabolism by pyridine nucleotides, the metabolic changes during ischemia, ischemic preconditioning, ischemia and reperfusion, pulmonary artery hypertension, and heart failure, and the effect of the changes in enzymatic activities upon cardiac function will be reviewed by Gary Lopaschuk and his colleagues.

Oxidative and reductive stress

The reduced forms of pyridine nucleotides, NADH and NADPH, not only serve as electron donors to produce ATP (mainly by NADH), but also regulate the cellular redox status (mainly by NADPH) through Noxs, GSH and Trx. Electrons provided by NADPH/NADH are transferred to either molecular oxygen to produce O_2^- by Nox, or to GSH or Trx whose cysteine residues have been oxidized in the oxidative environment. Uncoupled NO synthase can also produce O_2^- using electrons obtained from NADPH.

The function of Noxs is unique in that these enzymes purposefully produce reactive oxygen species (ROS), which damage proteins and DNA, causing apoptotic cell death and mitochondrial permeability transition pore (mPTP) opening, ATP depletion and necrotic cell

death[6]. Nox2 and Nox4 are the major Noxs in the heart. Nox4 is primarily expressed on intracellular membranes, including mitochondrial membranes in cardiomyocytes, while Nox2 is preferentially expressed on the plasma membrane[19, 20]. The expression of Nox2/4 is upregulated during cardiac hypertrophy and heart failure. However, the role of Noxs in hypertrophy is not clear. Whereas systemic deletion of Nox4 exacerbates load-induced hypertrophy in mice[21], cardiac-specific deletion of Nox4 inhibits it[20]. Until recently, it was believed that Noxs are unlikely to be expressed in mitochondria. However, both ROS production in mitochondria and cardiomyocyte apoptosis in response to pressure overload are ameliorated in Nox4 cardiac-specific knockout mice. Given this, together with the presence of a mitochondrial localization signal in Nox4, it is likely that Nox4 is expressed in mitochondria. The fact that Nox4 consumes pyridine nucleotides for O_2^- production raises an intriguing possibility that Nox4 and the ETC may compete with one another for pyridine nucleotides. It should be noted that whether Nox4 preferentially uses NADH or NADPH as a substrate has been debated. Overexpression of Nox4 in cardiomyocytes *in vitro* and *in vivo* induces cardiomyocyte apoptosis rather than hypertrophy, suggesting that Nox4 stimulates cardiomyocyte apoptosis through ROS production and mitochondrial dysfunction[19]. On the other hand, Nox4 can also act as a sensor to generate O_2^- as a signaling molecule in the presence of hypoxia, suggesting that Nox4 also possesses an important physiological function[6]. Further investigations are required to understand these pathological and physiological roles of Nox in greater detail.

In contrast to Nox, GSH and Trx reduce ROS and oxidized proteins, thereby protecting against oxidative stress[22, 23]. GSH-dependent antioxidant systems, composed of GSH-dependent peroxidase (Gpx) and glutaredoxin (Grx), have been shown to protect cells against H_2O_2. Although the intracellular concentration of Trx1 is not as high as that of GSH (sub-μM vs mM range)[24], Trx1 is able to reduce key proteins through direct/indirect protein-protein interactions, thereby exerting a significant influence on a wide variety of cellular functions[23, 25–27]. Trx1 is upregulated in response to ischemia/reperfusion (I/R), and overexpression of Trx1 is cardioprotective against I/R by 1) reducing ROS and oxidized proteins, 2) modulating signaling proteins and transcription factors, 3) upregulating mitochondrial proteins, 4) inhibiting expression of proinflammatory cytokines, and 5) preventing the oxidative stress-induced downregulation of the K^+v4 channel through modification of the ion channel[26].

The cellular source of electrons for reducing thiols is NADPH, which is produced primarily through glucose-6-phosphate dehydrogenase (G6PD), a cytosolic enzyme in the pentose phosphate pathway. The way in which G6PD couples to Nox, GSH and Trx1 is not well understood. For example, stimulation of G6PD appears to enhance O_2^- production through Nox in failing hearts[28]. It can also induce hyper-production of GSH and "reductive stress", which can, in turn, lead to cardiac dysfunction[29]. It is unclear why Nox and antioxidants are not equally affected under these conditions. It is possible that the activity of Nox, GSH and Trx1 might be regulated locally and their functions compartmentalized. When one considers the function of these molecules, it is important to elucidate how they regulate posttranslational oxidative modification of specific targets. For example, Trx1 prevents pathological hypertrophy through reduction of class II histone deacetylases (HDACs)[30, 31]. The regulation of Nox, GSH and Trx1 by pyridine nucleotides will be summarized by Jun Sadoshima and his colleagues.

NADH not only acts as an electron donor in the mitochondrial ETC to produce an electrochemical gradient for ATP synthesis but it also serves as a source of electrons by itself or after conversion into NADPH in mitochondria. $NADP^+$ is synthesized from NAD^+ by NADK, while NADPH is converted from NADH by three major enzymes in the matrix of mitochondria: NAD(P) transhydrogenase, the $NADP^+$-dependent isocitrate

dehydrogenase (IDH-NADP$^+$) and malic enzyme[32]. The IDH-NADP$^+$ and malic enzyme are dependent upon TCA cycle intermediates. Thus, respiration and the activity of mitochondrial antioxidants are linked at the level of NADH. Therefore, the state of oxidative phosphorylation affects the activity of nearly all antioxidants. The proper balances in the NADH/NAD$^+$ and NADPH/NADP$^+$ ratios are also essential for the regulation of the metabolism and redox state in the heart. The role of pyridine nucleotides in the energy metabolism and their interaction with the antioxidant pathways will be reviewed by Brian O'Rourke.

NAD$^+$-dependent enzymes and their functions

Pyridine nucleotides also act as substrates for NAD$^+$-dependent enzymes, such as PARPs and sirtuins. Both proteins induce posttranslational modifications of target proteins, thereby regulating key cellular functions such as DNA repair and transcription. However, excessive activation of the NAD$^+$-dependent enzymes causes depletion of NAD$^+$, thereby secondarily disturbing other NAD$^+$-dependent functions in cells. PARPs polymerize ADP-ribose derived from NAD$^+$ onto target proteins in the nucleus. Although the primary function of PARPs is to regulate single-strand DNA break repair through poly-ADP ribosylation, they also affect cell death through consumption of NAD[25, 33, 34] and stimulation of AIF-induced cell death, termed parthanatos[35]. PARP-1 is hyperactivated in response to cardiac stress, including I/R, pressure overload, and ROS. Inhibition of PARP-1 protects the heart from I/R injury and pressure overload through multiple mechanisms, including inhibition of the depletion of NAD$^+$ and ATP, inhibition of mitochondrial-to-nuclear translocation of AIF, and inhibition of mitochondrial complex I dysfunction.[36, 37] Hyperactivation of PARP-1 depletes nuclear NAD$^+$, thereby inhibiting transcription of sirtuin-dependent genes, such as mitochondrial genes, and stimulating proapoptotic genes, such as p53. Although the catalytic activity of PARP-1, namely, the stimulation of poly-ADP ribosylation of target proteins, also appears to stimulate myocardial injury, the direct involvement of enzymatic targets of PARP-1 in myocardial injury remains to be shown. While excessive activation of PARP-1 causes depletion of ATP, PARP-1 can be cleaved by caspase-3, which serves as a negative feedback mechanism to prevent further activation of PARP-1.

Sirtuins are mammalian homologues of the silent information regulator (Sir) proteins in yeast. The Sir 1–4 proteins were initially discovered as gene silencers of the silent mating loci and telomerases. Sirtuins are evolutionarily conserved from bacteria to humans, and they comprise 7 isoforms, sirtuins 1–7, that serve as NAD$^+$-dependent deacetylases (Sirt1–3 and 5–7) and as an ADP-ribosyltransferase (Sirt4). Their cellular localizations are different; Sirt1, 6 and 7 are predominantly localized in the nucleus, although Sirt1 is also located in the cytosol in some situations, Sirt2 is preferentially localized in the cytosol, and Sirt3–5 are predominantly localized in the mitochondrial matrix.

Sirtuins are involved in transcriptional regulation, glucose and fatty acid metabolism, apoptosis, energy metabolism, and DNA repair[2]. Sirt1, the most characterized isoform in the sirtuin family, deacetylates transcription factors, such as PPARγ, PPARα, PGC-1α, and the forkhead box subgroup O (FoxO) family, to induce insulin secretion, gluconeogenesis and fatty acid β-oxidation. Importantly, Sirt1 is activated by energy stress and in turn activates metabolic adaptation. For example, Sirt1 works in parallel with AMP-dependent kinase (AMPK)-mediated phosphorylation to activate PGC-1α during caloric restriction and exercise. Interestingly, a cross-talk exists between Sirt1 and AMPK where AMPK stimulates Sirt1 with or without upregulation of Nampt, whereas Sirt1 stimulates AMPK though deacetylation of LKB1, an upstream regulator (reviewed in [38]). Sirt1 also controls apoptosis and inflammation through deacetylation of p53 and NF-kB, respectively[39].

In the heart, mild to modest upregulation of Sirt1 prevents aging-induced cardiomyopathy[40]. However, the issue of whether endogenous Sirt1 controls aging in the heart requires further investigation. Just as other molecular mechanisms extending lifespan often confer stress resistance to the organism, Sirt1 protects the heart from I/R by inducing preconditioning effects or directly inhibiting cell death during ischemia and reperfusion[41, 42]. The deacetylation of FoxOs plays an important role in mediating the Sirt1 protective effect. The Sirt1-FoxO axis also protects the heart from nutrient starvation and prolonged ischemia through activation of autophagy[43]. Importantly, however, upregulation of Sirt1 during pressure overload facilitates downregulation of genes involved in the energy metabolism and cardiac contraction by suppressing transcription through the estrogen-related receptor element (ERRE), where upregulation of Sirt1 and PPARα competitively excludes binding of estrogen-related receptor α (ERRα) to the ERRE[44]. Thus, the effect of Sirt1 upon the heart is stimulus-dependent.

Sirt3 knockout mice developed cardiac hypertrophy and interstitial fibrosis at 8 weeks of age and showed more severe cardiac hypertrophy in response to angiotensin II and pressure overload than control mice. The overexpression of Sirt3 protected the heart against hypertrophic stimuli by upregulating MnSOD and catalase via FoxO3a[45]. However, whether endogenous Sirt3 regulates hypertrophy through its nuclear targets remains to be elucidated. Alternatively, Sirt3 may inhibit cardiac hypertrophy by deacetylating mitochondrial targets, such as cyclophilin D[46]. In fact, the function of many mitochondrial genes is regulated by acetylation of lysine residues. Sirt3 deacetylates proteins involved in the metabolism of the mitochondrial matrix, including acetyl-CoA synthase 2. Recently, general control of amino acid synthesis–like 1 (GCN5L1) has been identified as the protein acetyltransferase in mitochondria[47]. How the balance of protein acetylation in mitochondrial proteins is regulated appears to be a hot topic in the field.

Polyphenol compounds, including resveratrol, and small-molecule compounds mimicking the function of resveratrol have been shown to extend the lifespan of mice fed a high fat diet. The major premise is that these compounds mimic the effect of dietary restriction, currently the most established intervention to prevent age-related diseases and extend lifespan in many species, from yeast to primates, by stimulating the action of sirtuins. However, whether Sirt1 has a major effect upon lifespan extension in lower organisms and whether resveratrol and other small-molecule compounds mediate lifespan extension through Sirt1 in mammals have been debated extensively[48]. Regardless of the underlying mechanism, if caloric restriction mimetics prevent both aging and stress-induced myocardial injury, they will become promising candidates for cardiovascular therapy. Maha Abdellatif will review recent progress in the study of sirtuins.

Pyridine nucleotide ion channel interaction

The state of redox couples of pyridine nucleotides, namely, NADH/NAD$^+$ and NADPH/NADP$^+$, also plays an important role in regulating ion channel activities. For example, the β-subunits of the voltage- gated (Kv) channels bind to pyridine nucleotides, and intracellular changes in the redox ratio of these nucleotides affect the inactivation or activation characteristics of these channels[7]. Other K channels, such as the KATP channels and the KNa channels, have also been shown to respond to changes in intercellular levels of pyridine nucleotides[49, 50], although the physiological significance of these regulatory mechanisms has not been fully assessed. An intriguing study also shows that the cystic fibrosis transmembrane conductance regulator (CFTR) channels (Cl$^-$ channels) are regulated by the pyridine nucleotide redox potential[51, 52]. This suggests that CFTR has the ability to sense the energy and redox status of the cell through pyridine nucleotides. In addition to direct binding to channel protein or associated subunits, pyridine nucleotides also regulate the

activity/conductance of ion channels through ROS- or protein kinase-dependent posttranslational modifications. In the heart, the elevated intracellular NADH results in a rapid reduction in the cardiac Na^+ current (I_{na}) through downregulation of sodium channels ($Na_v1.5$), which is associated with ventricular tachycardia[8]. Since the NADH/NAD$^+$ ratio may increase during I/R, this enhances mitochondrial ROS, thereby predisposing the heart to fatal arrhythmia through decreases in Na^+ conductance [53]. An increase in the cytosolic NADH/NAD$^+$ ratio also inhibits cardiac sarcoplasmic reticulum Ca^{2+} release channels in cardiomyocytes[54]. It should be noted that an accurate assessment of the NADH/NAD$^+$ ratio in subcellular compartments with standard metabolomic methods is challenging. Further investigation is necessary to clarify how the redox status of NADH/NAD$^+$ is regulated in pathophysiological conditions in the heart. Oxidative stress increases ryanodine receptor calcium leakage[55], and scavenging of ROS with antioxidants has been reported to decrease the incidence of arrhythmias[56]. Thus, the regulation of pyridine nucleotides and consequent changes in the redox status in cells play an important role in regulating several ion channels. This regulatory axis could link changes in cell energetics to excitability, allowing the cell to mount an integrated response to altered states of metabolism or redox potential. Perturbation in this mode of regulation may be associated with fatal arrhythmia and the progression of heart failure. Regulation of ion channels by pyridine nucleotides will be reviewed by Aruni Bhatnagar and his colleagues.

Summary

We here described that pyridine nucleotides act as electron carriers, enzyme substrates, and redox regulators. They have been recognized as important regulators of energy production, metabolism, redox reactions, survival/death, and ion channels under normal and pathological conditions. The deregulation of pyridine nucleotides is intimately involved in the pathogenesis of heart failure, I/R injury, arrhythmia, and age-associated abnormality in the heart. Importantly, both the metabolic status of cells and the redox status of the subcellular compartment regulated by pyridine nucleotides secondarily affect the function of mitochondria and ion channels. Changes in the activity of sirtuins and PARPs in the nucleus affect expression of genes through transcriptional as well as epigenetic mechanisms. Furthermore, cellular mechanisms regulated by pyridine nucleotides appear to be linked to one another, since they are widely used as co-substrates in many enzymatic processes. For example, NAD$^+$ may be used not only by sirtuins and PARP but also by the glycolysis/TCA cycles. NADH may be competitively used by the ETC and mitochondrial Nox, and also by GSH/Trx2 after it is converted to NADPH in mitochondria. Nox, GSH and Trx might compete for electrons provided by NADPH. More investigations are required to clarify the interactions among multiple cellular functions through competition for pyridine nucleotides. In order to elucidate how changes in the level of pyridine nucleotides affect the function of cardiomyocytes, systematic approaches globally assessing the effects of pyridine nucleotides are needed. We hope that this review series serves as a convenient introduction to the understanding of the complex functions of pyridine nucleotides in cardiovascular tissues under both physiological and pathological conditions.

Acknowledgments

List of Abbreviations

AIF	apoptosis inducible factor
AMPK	AMP-dependent protein kinase
cADP	cyclic ADP-ribose synthase
CFTR	cystic fibrosis transmembrane conductance regulator
ERRα	estrogen-related receptor α
ERRE	estrogen-related receptor element
ETC	electron transport chain
FDH2	flavin adenine dinucleotide
FoxO	forkhead box subgroup O
G6PD	glucose-6-phosphate dehydrogenase
GCN5L1	general control of amino acid synthesis–like 1
Gpx	GSH-dependent peroxidase
Grx	glutaredoxin
GSH	glutathione
HDAC	histone deacetylases
I/R	ischemia/reperfusion
IDH	the $NADP^+$-dependent isocitrate dehydrogenase
MART	mono-ADP-ribose transferases
mPTP	mitochondrial permeability transition pore
NaAD	nicotinic acid adenine dinucleotide
NAD+	oxidized nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide
NADK	NAD kinase
Na	nicotinic acid
NaDS	NAD synthase
Nam	nicotinamide
NaMN	nicotinic acid mononucleotide
NaMNAT	nicotinic acid mononucleotide adenylyltransferase
Nampt	nicotinamide phosphoribosyltransferase
NaPRT	Na phosphoribosyltransferase
NMN	nicotinamide mononucleotide
Nmnat	Nam/Na mononucleotide adenylyl transferase
Nox	NADPH oxidases
NR	nicotinamide riboside
NRK	NR kinase

PARP	poly(ADP-ribose) polymerase
PDH	pyruvate dehydrogenase
PGC-1α	PPARγ co-activator 1α
PPAR	peroxisome proliferator-activated receptor
QA	quinolinic acid
QART	quinolate phosphoribosyltransferase
ROS	reactive oxygen species
Sir	silent information regulator
TCA	tricarboxylic acid

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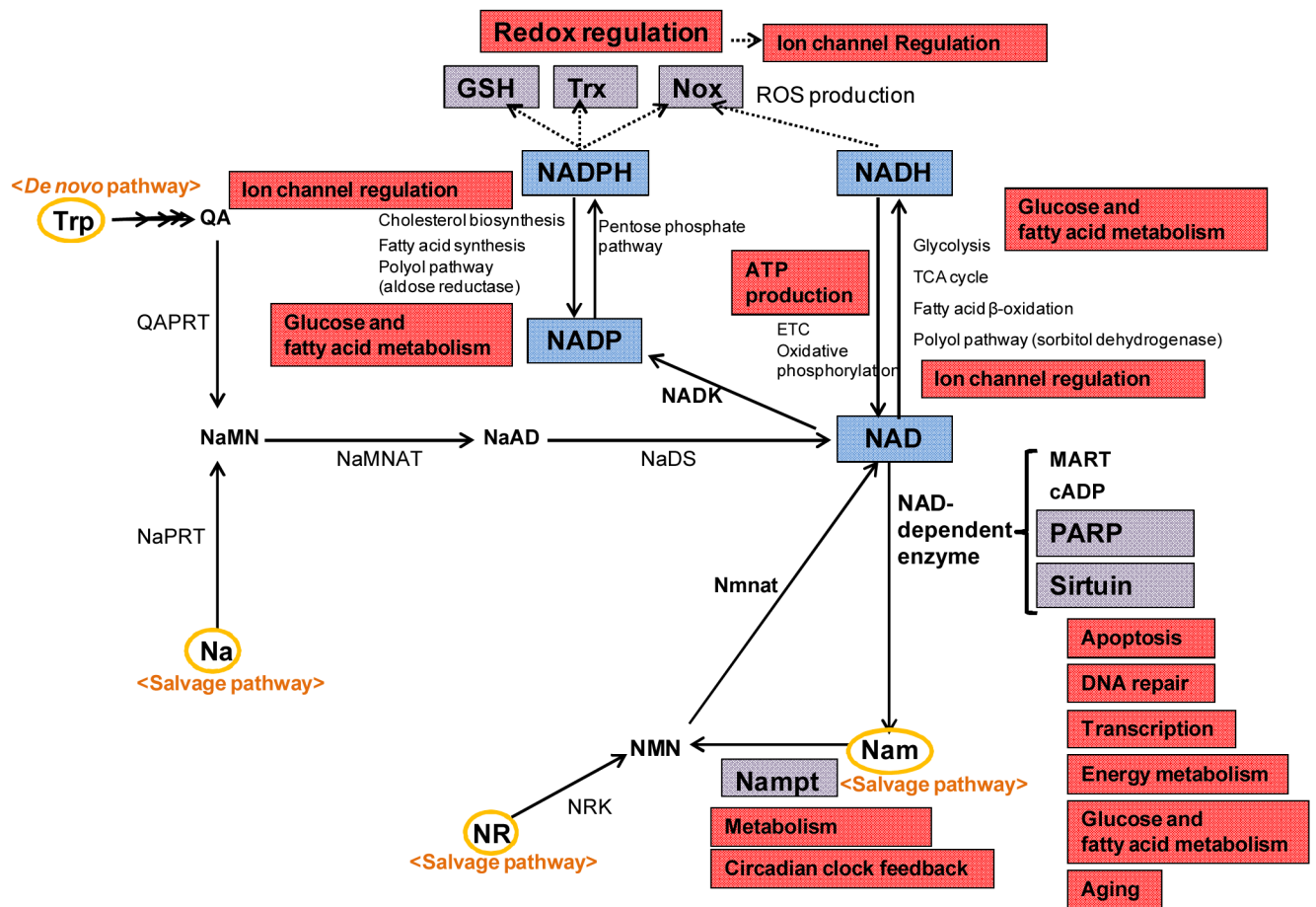
Figure. Schematic of pyridine nucleotides biosynthesis and their functions
Pyridine nucleotides are involved in a wide variety of cellular functions, including energy production, metabolism, redox reactions, survival/death, and ion channels under normal and pathological conditions. Trp, tryptophan; Na, nicotinic acid; QA, quinolinic acid; NaMN, nicotinic acid mononucleotide; Nam, nicotinamide; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; Nampt, nicotinamide phosphoribosyltransferase; Nmnat, Nam/Na mononucleotide adenylyl transferase; NADK, NAD kinase; NaPRT, Na phosphoribosyltransferase; QAPRT, quinolate phosphoribosyltransferase; NaMNAT, nicotinic acid mononucleotide adenylyltransferase; NaAD, nicotinic acid adenine dinucleotide; NaDS, NAD synthase; Trx, thioredoxin; Nox, NADPH oxidase; GSH, glutathione; Redox, reduction-oxidation; ROS, reactive oxygen species; PARP, poly(ADP-ribose) polymerases; MART, mono-ADP-ribose transferase; cADP, cyclic ADP-ribose synthase; ETC, electron transport chain.