Send Orders for Reprints to reprints@benthamscience.ae

Current Medicinal Chemistry, 2021, *28, Page 1-11* 1

333ARTICLE TYPE : review

NAD precursors, mitochondria targeting compounds and ADP-ribosylation inhibitors in treatment of inflammatory diseases and cancer

Palmiro Poltronieri[a*], Valeria Mezzolla[b], Ammad Ahmad Farooqi[c], Maria Di Girolamo[d]

[a]*Institute of Sciences of Food Productions, National Research Council of Italy, via Monteroni km 7, 73100 Lecce, Italy.*

[b]*Division of Nephrology, Dialysis and Transplantation, Department of Emergency and Organ Transplantation, Aldo Moro University of Bari, Bari, Italy*

[c]*Department of Molecular Oncology, Institute of Biomedical and Genetic Engineering (IBGE), Islamabad 44000, Pakistan*

[d]*Sol & Pharma s.r.l. Biotechnology Research, 66030 Mozzagrogna, Italy.*

ARTICLE HISTORY

Received: 01.19.2020

Revised: 13.11.2020

Accepted:

DOI:

Abstract: Mitochondrial dysfunction and oxidative stress are prominent features of a plethora of human disorders. Dysregulation of mitochondrial functions represents a common pathogenic mechanism of diseases such as neurodegenerative disorders and cancer. The maintenance of the Nicotinamide adenine dinucleotide (NAD^+) pool, and a positive NAD^+/NADH ratio, are essential for mitochondrial and cell functions. The synthesis and degradation of NAD^+ and transport of its key intermediates among cell compartments play an important role to maintain optimal NAD levels, for regulation of NAD^+-utilizing enzymes, such as sirtuins (Sirt), poly-ADP-ribose polymerases, and CD38/157 enzymes, either intracellularly as well as extracellularly. In this review, we present and discuss the links between NAD^+, NAD^+-consuming enzymes, mitochondria functions, and diseases. Attempts to treat various diseases with supplementation of NAD^+ cycling intermediates and inhibitors of sirtuins and ADP-ribosyl transferases may highlight a possible therapeutic approach for therapy of cancer and neurodegenerative diseases.

Keywords: ADP-ribosyl transferases; sirtuins; NAD cycling; nicotinamide; nicotinamide riboside; nicotinamide mononucleotide; compartmentalization

1. INTRODUCTION

Mitochondria are intracellular organelles performing essential functions for energy production [1]. They produce ATP in the Krebs cycle, oxidative phosphorylation and fatty acid oxidation. These reactions point out to mitochondria as the principal source of reactive oxygen species (ROS) within the cell; thus, it comes natural to believe that dys-regulation of mitochondrial functions is a pathogenic mechanism shared by many human diseases [2-4]. The maintenance of the nicotinamide adenine dinucleotide (NAD^+) pool as well as a positive NAD^+/NADH ratio are essential for well-functioning mitochondria [5]. Indeed, NAD^+ participates in many redox reactions and plays essential roles in the control of mitochondrial biology, metabolism, energy production, mitophagy, activation of apoptotic programs and in regulation of intracellular signals [6].

*Address correspondence to this author at the Institute of Sciences of Food Productions, National Research Council of Italy, via Monteroni km 7, 73100 Lecce, Italy; Tel/Fax: +39-0832-422609, +39-0832-422620; E-mail: palmiro.poltronieri@ispa.cnr.it

NAD^+ metabolism and mitochondrial well-being are therapeutic targets for ageing and neurodegeneration-related diseases. NAD^+-consuming reactions are carried on by poly-ADP-ribose polymerases (PARPs) and mono-ADP-ribose transferases, in addition to NAD-dependent histone deacetylases (sirtuins) and CD38/NAD glycohydrolase [6]. In addition, NAD^+ degradation, cycling and re-synthesis need to be considered within various compartments of the cell and in the framework of relocalization between compartments [7, 8]. Various different NAD^+ pools are present in cells, i.e. mitochondrial, cytosolic and nuclear pools [9]. Depletion of NAD^+ in mitochondria has been indicated as the cause of ageing and of several human diseases [10]. Reactions based on NAD^+ dependent enzymes are influenced by compounds such as nicotinamide (Nam), a competitive inhibitor. In cells, the uncontrolled activity of NAD^+ degrading enzymes such as PARP1/2 or CD38 may cause cell death in a cell-specific pathway, i.e. apoptosis, necrosis and parthanatos [11]. A compartment-specific NAD^+ pool may decrease at such a level that the rapid

0929-8673/19 $58.00+.00

increase of nicotinamide may inhibit either ADP-ribosyl transferases including MARylating sirtuins, and NAD-dependent protein deacetylases. Increased NAD^+ degradation and impairment of NAD^+ synthesis cause a decline in NAD^+ levels in mitochondria, especially when levels of NAD^+ synthesis enzymes are decreased [12]. Mitochondria play a critical role in cell viability, since energy depletion and reduction of oxygen metabolism induce cell death pathways in cells, including neurons and neuroglia [16]. Therefore, in this review the roles of NAD levels, involvement of enzymes consuming NAD^+, and those required to restore NAD^+ levels are discussed. Finally, prospects for the use of inhibitors and NAD^+ intermediates are introduced in treatment of various diseases, either in slowdown of neurodegenerative disease progress or to stop cancer growth.

2.1.NAD^+ cycling

Cellular NAD^+ concentrations change during aging, and modulation of NAD^+ availability may extend lifespan [12], and its consumption is linked to oxidative stress [13]. *De novo* synthesis of NAD in cells, called the kynurenine pathway, originates from tryptophan. NAD precursor kynurenine has been used in some trials to study the replenishment of NAD pools under stress conditions [14]. Nicotinamide (NAM), the product of enzymes that use NAD as cofactor/substrate, is the starting substrate in the NAD^+ salvage pathway [15], predominant in maintaining NAD^+ levels in many cells. One pathway involves nicotinic acid phosphoribosyltransferase domain containing 1 (NAPRT1) starting from nicotinic acid (NA) (niacin, a form of vitamin B3). NA is supplied by diet and metabolized by NAPRT1 to nicotinic acid mononucleotide (NAMN) that is transformed in NAD in the Preiss-Handler pathway. A second pathway involves nicotinamide phosphoribosyltransferase (NAMPT), that produces nicotinamide mononucleotide (NMN) from nicotinamide (NAM) to which 5-phospho-α-D-ribosyl 1-pyrophosphate (PRPP) donates the ribose group, reaction that consumes ATP. In neurons, NAMPT orchestrates the NAD+ salvage pathway, and resides in the mitochondrial matrix [16]. The body circadian clock is ensured by transcription-translation feedback loop in which transcription factor pairs CLOCK/BMAL1 and NPAS2:BMAL1 activate expression of *Cryptochrome* (*Cry1* and *2*) and *Period* (*Per1*, *2*, and *3*), with CRY and PER proteins causing repression of CLOCK/BMAL1. DNA binding activity of these heterodimers is regulated by NAD redox state. The core clock proteins induce circadian rhythmic transcription of *NAMPT* in the heart and in other organs. NAMPT-mediated NAD+ biosynthesis participates to maintain the circadian clock [17, 18], with Sirtuin 1 modulating the activity of the clock complex through deacetylation of PER, BMAL1 and histone H3 at *NAMPT* cis-acting site, which suppresses *NAMPT* transcription [19, 20]. The transcription factor KLF15 integrates inputs from the core clock and from metabolic signals to promote *NAMPT* transcription through binding to *NAMPT* enhancer. NAMPT, NAD^+ and Sirt1 have been indicated as "time regulation" enzymes determining the biological age of organisms, while their decay may contribute to senescence [21]. Nicotinamide phosphoribosyltransferase (NAMPT) acts via enzymatic activity to synthesize nicotinamide mononucleotide (NMN), precursor of NAD^+ [22]. NAMPT expression decreased during the treatment of APP/PS1 mice with its inhibitor, FK866, and was rescued by supplementation with NAD^+ [23]. NMN is a substrate for nicotinamide mononucleotide adenylyl transferases (NMNATs), also known as NAD synthase. In eukaryotic cells, there are three isoforms of Nicotinamide mononucleotide adenylyltransferase (NMNAT1, 2 and 3). NMNAT1 is localized in nuclei, NMNAT2 in the cytosol, and NMNAT3 in mitochondria. NAD^+ is produced in each compartment by the resident NMNAT [24]. NMNAT3 is not essential to maintain NAD^+ levels in mitochondria, thus other NMNATs may have a major role [25]. In humans, the gene *nmnat3* codes for two mRNAs, *NMNAT3v1* and *FKSG76*, through alternative splicing: NMNAT3v1 protein is cytosolic and inactive, whereas FKSG76, localized to mitochondria, cleaves NAD^+ in the reverse reaction, more favorable than NAD^+ synthesis [25]. NMN production with NAD^+ degradation has also been reported for NMNAT2 [26]. The extracellular NAD^+ sustains mitochondrial NAD pool in an ATP-independent manner, while metabolic precursors NAM, NMN, nicotinamide riboside (NR) and nicotinic acid (NA) were not effective when added to the medium; cytosolic NAD^+, not requiring ATP driven pumps but only the mitochondrial NAD/NADH shuttle, sustained mitochondrial NAD^+ pool even in presence of oligomycin, inhibiting ATP formation. Nicotinamide riboside (NR) is an additional salvage pathway element and NAD^+ precursor. NR is converted to NMN by nicotinamide ribose kinases, NRK1 and NRK2, and then NMN is converted to NAD^+ by NMNATs, which utilize either NMN or nicotinic acid mononucleotide (NaMN) [27]. NR can give rise to NAM by purine nucleoside phosphorylase (NP), and after NAM modification to NMN, NMNAT converts NMN to NAD^+ [28]. NR can enter cells through the Nrt1 transporter, thus NR can be supplemented with diet or drugs. NR does not produce side effects or flushing [28]. Also the NR reduced form, NRH, can be supplemented as NAD^+ precursor, being NRH more stable than NR in plasma, and can be converted to NAD^+ through the NMNH intermediate, with adenosine kinase (ADK) acting as a NRH kinase [28]. NAMPT can metabolize specific inhibitors (FK866, KPT-9274, CHS-828 and GMX1778) into phosphoribosyl derivatives that inhibit NAMPT and block NAD^+

synthesis. For instance, compounds bearing the 3-pyridinyl ring bound to urea or to an amide group are recognized as substrates and bind the NAMPT active site where they are linked with phosphoribosylpyrophosphate (PRPP). In this reaction, FK866 efficiently suppressed NAD^+ production and reduced NAD^+ levels, leading to loss of ATP as potential anticancer drugs [29]. Following this study, a research was performed to verify whether NAMPT can metabolize Vacor, a rodenticide, and transform it into Vacor adenine dinucleotide (VAD), a mimetic of NAD. VAD produced inhibition of NMNAT2 and NMNAT3, but not of NMNAT1 [30]. Results showed the coordinated requirement of NAMPT and NMNAT2 in NAD^+ synthesis, and their inhibition led to derangement of the NAD^+ pool. The study showed that VAD can be used as an antimetabolite with anticancer potential, especially in cancers overexpressing NAMPT. Similarities, either structural as well as functional, are present in human NAMPT and NAPRT, that uses nicotinic acid (NA) to produce nicotinic acid mononucleotide (NaMN) [31]. Using FK866 to inhibit NAMPT, A375 cells were treated with nicotinamide, nicotinic acid, nicotinamide riboside, kynurenine and quinolinic acid, as precursors of NAD^+, showing that each substrate has organelle-specific ability to rescue from NAMPT block [31]. The authors showed that cytosolic NAD^+ content decreased, mitochondrial NAD^+ did not change, so that NAMPT was not affected in mitochondrial compartment, whereas nicotinamide riboside kinase (NRK) was found active in nuclei and in mitochondria, and NAPRT was predominant in the cytosol and mitochondria [30]. NAMPT and NAPRT can be secreted extracellularly (eNAMPT, eNAPRT) as cytokines and Damage associated Molecular Patterns (DAMPs): eNaMPT is known as pre-B cell colony-enhancing factor or visfatin [32, 33], acting through the activation of Toll-like receptor 4 (TLR4) [34]. This enzyme is involved in human inflammation, obesity, diabetes, and has been indicated as a target for anticancer and immunotherapy strategy [35], and eNAPRT is a biomarker of sepsis and septic shock [36].

Ectonucleotidases form two groups based on substrate specificity: one group includes enzymes that metabolize extracellular NAD^+, such as CD38, CD157, and CD203; in the second group are enzymes that degrade ATP, such as CD39 (ENTPDases) and CD73 [37-39].

Adenine nucleotides (AdNs) have an important role in immunity and inflammation [40]. Intracellular AdNs originating from ATP or NAD are signaling molecules in immune cells, such as T lymphocytes, macrophages, microglia and astrocytes. The ectoenzyme ecto-5′-nucleotidase/cluster of differentiation 73 (CD73), expressed on multiple cells, is active on NAD and adenosine monophosphate (AMP), catalyzes the conversion of purine 5’-mononucleotides to nucleosides, such as adenosine, and dephosphorylates NMN to produce NR [41]. NAD glycohydrolase/Cluster of differentiation 38 (CD38), catalyzes the synthesis of cyclic ADP-ribose (cADPR) and cADPR hydrolysis, leading to NAD^+depletion [42], a state that can be rescued by the increase of NMNAT activity. CD38 has been implicated in the regulation of intracellular NAD^+ levels. CD38 may insert into intracellular membranes or in plasma membrane as an ectoenzyme, and degrades NAD^+ as well as NMN and NADP, generating the second messengers cyclic ADP ribose (cADPR), ADP ribose (ADPR), and nicotinic acid adenine dinucleotide phosphate (NAADP). CD38 facilitated autophagy for its role in autophagic fusion with lysosomes [43]. Various cell compartments are involved in CD38 activity: in CD38 knockout mouse, no NADase activity was detected in the plasma membrane, sarcoplasmic reticulum, mitochondria and nuclei [44]. Sterile alpha and TIR motif containing 1 (SARM1) is an ADP-ribosyl cyclase 1/cyclic ADP ribose hydrolase, similar to CD38. SARM1 is required for the activation of an injury-induced axon degeneration, and facilitates mitophagy in depolarized mitochondria; thus, SARM1 has been involved in neuroprotection and in neuronal death [43]. To protect from NAD^+ consumption by SARM1 activity, cytosolic NMNAT1 was overexpressed, producing a beneficial effect that could be related also to a chaperone function [45]. CD38 inhibitor 78c was administered to slow down the age-related NAD^+ decline: a therapy with 78c improved physiological parameters, such as glucose homeostasis, cardiac function, muscle architecture, and exercise capacity. The mechanisms of these anti-aging effects are still to be identified [46]. A schematic view of NAD^+ homeostasis, NAD^+ salvage pathway, role of NAD^+ precursors and of compartmentalization of enzymes involved, is presented in Figure 1. ADPR released by CD38 is an agonist of the non-selective cation and Ca^{2+} permeable channel Transient Receptor Potential of Melastatin subfamily 2 (TRPM2), activated by ADPR binding to its Nudix homology domain [47], regulating functions such as cytokine production, insulin release, oxidative stress and cell death. ADPR-2'-phosphate (ADPRP) is also a potent agonist [48]. TRPM2 activation produces Ca^{2+} influx, and provides positive feedback for channel activation, leading to necrosis and cell death. NMNAT-2 and CD38 sequentially lead to the production of 2'-deoxy-ADPR, an endogenous TRPM2 activator [40].

2.2. Parylation/Marylation reactions and players

Poly-ADP-ribose polymerases (PARPs), mono-ADP-ribose transferases (ARTs) and sirtuins use NAD^+ to modify proteins, in post-translational modifications (PTMs), namely, PARylation and MARylation [49]. Seventeen ARTs of the diphtheria toxin group, (ARTD1 to ARTD17), two cholera toxin group ARTC enzymes (hARTC1, hARTC5), and a subgroup of sirtuins are

enzyme writers that add mono-ADP-ribose (MAR) to proteins, while a minority of them (PARP1-2, PARP5a and 5b/ARTD1-2, ARTD5-6) can produce poly-ADP-ribose (PAR) polymers, an activity that is linked to catalytic triad H-Y-E in their active site. MARylation occurs on arginine, while PARylation targets various amino acids, glutamate and aspartate being the first one to be studied, and also lysine, tyrosine and serine, the last one mediated by the interaction of PARP1/2 with histone parylation factor 1 (HPF1) [50]. ADP-ribosylation on serines in histones may lead to the exclusion of acetylation on the same residue by histone acetylases (HATs), with consequence on epigenetic signaling.

MAR/PAR structures, recognized by MAR/PAR readers, regulate protein-protein interactions. The main domains present in reader proteins are the Macrodomain, the PAR Binding Zinc finger domain (PBZ), the PAR binding domain (PBD), the WWE (tryptophan/glutamate) domain, the Oligonucleotide binding (OB) motif, the PilT N-terminal (PIN) domain (in PIN and Exo1 nucleases), the RNA recognition Motif (RRM), the serine arginine repeats and lysine arginine repeats (SR/KR), among others, recognizing and binding MAR and PAR structures, and enabling the formation of protein complexes important in cell signaling [51].

Finally, PTMs require enzymes able to remove the modifications, named erasers. Macrodomain proteins may be either MAR readers, as well as erasers with hydrolase activity [51]. ADP ribose hydrolases (ARHs) and poly ADP-ribose glycohydrolase (PARG) cleave ADP-ribose/ADP-ribose bonds and ADP-ribose-protein bonds. Terminal ADP-ribose protein glycohydrolase (TARG) and ectonucleotide pyrophosphatase/ phosphodiesterase 1 (ENPP1) remove the last ADP-ribose group, transforming it into phosphoribose bound to the proteins [52].

Enzymes maintaining PAR homeostasis include nucleoside diphosphates linked to some moiety X (NUDX, NUDT) hydrolases that cleave ADP-ribose to produce adenosine monophosphate (AMP) and ribose-5-phosphate (R5P) [47]. Some Nudix proteins have pyrophosphatase activity using as substrates ADP-ribose and NAD^+, with PAR hydrolysis producing adenine and adenosine nucleotides.

2.3. Human ARTD1-3 relevance in diseases.

In presence of damaged DNA, such as single or double strand breaks, activated PARP1 and 2 (ARTD1, ARTD2) catalyze the transfer of ADP-ribose units from NAD^+ to proteins, forming long and branched ADP-ribose polymers (PAR). [50]. A NAD^+ binding pocket in Deleted in breast cancer 1 (DBC1) regulates DBC1/PARP1 interaction, so that DBC1 may block DNA repair [10]. When NAD^+ concentrations decline, DBC1 is tightly bound to PARP1, producing accumulation of damaged DNA, and NAD^+ supplementation relieves the inhibition: the binding of NAD^+ to the Nudix (NHD) domain of DBC1 prevents it from inhibiting PARP1 [53]. The excessive activation of PARP1 and 2 by DNA damage was proposed to cause NAD^+ depletion and finally cell death, a process involving one of the forms of apoptosis, parthanatos [11]. Neuronal cell death has been associated with neurodegenerative disease progression.

The accumulation of Amyloid-ß (Aß) peptide in the brain is one of the causative agents in Alzheimer's disease. The aggregation of amyloid fibers is linked to the generation of free radicals that cause mitochondrial failure as well as DNA damage. PARP1 activation contributes to the functional energy decline, lowering oxygen consumption, membrane potential, NAD^+ levels, resulting in cellular bioenergetic deficit in AD animal models [54]. Inactivation of Alcohol dehydrogenase 1 (ADH1) has been shown in PARP1-dependent PARylation of ADH1, in Parkinson disease in mouse primary neurons in which α-synuclein fibrils activate PARP1, and in neurodegeneration in *D. melanogaster* [55]. PARP1 activated by DNA breaks affects glycolysis and causes energy depletion [56]. PARylated PARP1 binds to and inhibits hexokinase 1 (HK1), which interacts through its PAR-binding domain [57], and the interaction inhibits glycolysis without interference with NAD^+ or NAM competition.

PARP1 activity is regulated by acetylation on K498 and K524. Sirtuin 1 and Sirt3 deacetylate PARP1, decreasing PARP1 activity, and this regulation may be exploited to protect against cardiac hypertrophy [58].

PARP hyperactivation has been indicated as causative for cell death and in neurodegenerative diseases: the mechanism initiates with protein aggregates activating PARP1, leading to energy depletion, drop in intracellular NAD^+, leading to cell death. Some findings show that PARylation affects liquid-liquid phase separation and aggregation of Aß oligomers [59]. Excessive PARP1 activity contributes to the pathogenesis of stroke, myocardial infarction, neurodegeneration, and various diseases involving excessive inflammation states. Thus, PARP1 inhibition and drug control of the inflammatory state can improve these diseases [60]. PARP1 inhibitors may reduce cell necrosis in stroke and infarction of myocardium, can down-regulate multiple pathways of inflammation and tissue injury, in circulatory shock, diabetic complications and colitis [61, 62].

Synthetic lethality is a condition in which an inhibitor targets a gene product that compensates a pathway defective for a mutated gene, as in the case of DNA repair complexes. PARP inhibitors are used as therapeutics in certain cancers, such as in homologous recombination (HR)-defective cancers, and homologous recombination defective (HRD) cancers. In cancers mutated in *BRCA1BRCA2*, *ATM*, *ATR*, *FANC* and *PALB2*, a treatment with poly-ADP-ribose polymerase inhibitors (PARPi) has been successfully applied in phase III trials. Olaparib, rucaparib, niraparib, veliparib (ABT-888), and

talazoparib block DNA repair, trap PARP proteins on DNA, and block PARP catalytic activity, interfering with replication and leading to cell death [63]. Also, some cancers defective in PTEN as prostate cancers can be sensitive to PARP inhibitors, due to downregulation of Rad51. Since lysine methylase SMYD3, often overexpressed in tumors, regulates BRCA1/2 and DNA Repair, inhibiting SMYD3 with BCI-121 promotes cancer inhibition by PARPi such as olaparib [64]. Olaparib, as well as similar inhibitors, may induce cancer resistance in patients due to extrusion by multidrug resistance proteins and ATP-binding cassette pumps. PARP1 inhibitor AZD2281 was more effective when co-administered with the P-glycoprotein inhibitor tariquidar [65, 66]. Non-NAD-like PARP1 inhibitors, binding to sites different from the NAD binding site, have been studied for prostate cancer treatment [67]. XAV939 is a potent inhibitor of PARP1 in cells and a promiscuous tankyrase inhibitor, differently from IWR1 and AZ-6102, selective for tankyrase [68]. PJ34 and UPF1069 are broad PARP/tankyrase inhibitors: PJ34 inserts a flexible region into a hydrophobic pocket in several ADP-ribosyltransferases. PARP1 inhibition by PJ34 improved the function of endothelial progenitor cells (EPCs) during stress-induced premature aging [69], stabilized NAD^+ levels and increased Sirtuin 1 activity [70]. Although PJ34 induces death in cancer cells, in association with other cytostatic drugs, PJ34 stimulated mitochondrial fusion and hyperpolarization and protected mitochondria [71]. PARP-1 has a role in regulating the intracellular trafficking of key cellular proteins such as nuclear factor-kappa B (NF-κB), is a transcription coactivator of NK-kB complex, and plays a role in cellular trafficking during inflammation. PARP3 is considered a MARylating enzyme, for the absence of DNA binding and automodification domains: PARP3 may interact with PARP1 in DNA repair. While PARP1 homodimers can autoPARylate in the nucleus and possibly in mitochondria, PARP1-PARP3 heterodimers are active in the nucleus. PARP3 has been involved in cellular response to DNA damage and mitotic progression; it has been shown to modify the mitotic spindle components NuMa1 and the tankyrase ARTD5/PARP5a, the DNA repair proteins Ku80 and ARTD1/PARP1, and the histone H2B.PARP3 is also present in the cytoplasm, similarly to PARP2. PARP3 interacts with and ADP-ribosylates the glycogen synthase kinase GSK3β: GSK3β is a positive regulator in ubiquitination and degradation of Rictor, that is a drug target in PTEN deficient tumors [72-74]. Several chemical structures have been developed and studied for higher specificity toward certain PARP enzymes, so that various approaches can be exploited to treat particular disease states. For instance, ABT-888 showed high specificity toward PARP2 [72]. Certain chemical structures were shown to target PARPs and tankyrases [68], or only tankyrases, such as XAV939 and G007-LK[73], while conjugates of ADP and morpholino nucleosides target PARP1/2/3 with high specificity [74]. To this aim, a highly active and selective ribose-functionalized NAD^+ was identified and used *in vitro* [75].

Small-molecule inhibitors targeting MARylating PARPs (containing the H-Y-Θ catalytic triad) have been studied, such as OUL35 inhibiting PARP10 [76-79]. Several PARP14 inhibitors have been studied, showing low selectivity over H-Y-E PARPs [80-83]. A quinazolin-4(3H)-one scaffold with propynyl in R1 and pyrimidine in R2 substitutions, ITK7, showed high specificity toward PARP11/ARTD11 [80], with activity toward nuclear pore complex proteins, inducing PAR to dissociate from nuclear envelope. Tankyrases (TKs), interact with E3 ubiquitin ligase RNF146/Iduna, that modifies axin to target it to the proteasome. In this pathway TKs antagonize β-catenin degradation: inhibitors specific for TKs were shown effective in Wnt-driven cancers [83]. Due to the presence of many different ADP-ribosyl transferase enzymes with PARP domain in humans (ARTD1-ARTD17, ARTC1, ARTC5)[84], it is important to use selective inhibitors to target a particular enzyme or phenotype, in order to overcome drawbacks due to undesired side effects. While for PARP1 there are many target proteins, as shown in proteomic data [85], for other ARTD and ARTC group enzymes few proteins are known to be MARylated, and MARylation inhibition can be detected promptly [86]. PARP13/ARTD13 known as Zinc-finger Antiviral Protein (ZAP) is inactive, and has antiviral action, with involvement in stress granule assembly. PARP7, PARP10 and PARP12 also play a role in suppressing viral replication [49]. ARTC1 modifies Grp78/BiP in ER, and modifies T-cell coreceptors and hemopexin [87]. Among macrodomain-containing PARP in group 6, PARP14/ARTD8 MARylates HDAC2 and HDAC3 [88]. ARTD8 inhibitors may be applied in lymphoma and myeloma, and in therapeutic approach in asthma [89]. PARP16/ARTD15 MARylates karyopherin-1-beta [90], and has a role in ER stress and Unfolded Protein Response [91]. ARTD10 targets and modifies GSK3β and NEMO (NF-kB subunit, IKK-γ), and plays a role in neurodegenerative disorders [92]. Thus several PARPs converge on NF-kB dependent transcription and pro-inflammatory pathway, and PARP1 activates STAT-1 and STAT-6 dependent transcription.

Since PARylation and MARylation may be affected at the same time by non-specific inhibitors, and each enzyme may have a specific role in certain diseases [93], pharmacological teams are developing high-throughput drug discovery screens to find and individuate inhibitors of mono-ADP-ribosylation reactions using high-throughput screens [94]. To this aim, 4-benzyloxybenzimide derivatives have been developed, specifically inhibiting PARP10 in the nanomolar range [78]. Finally, N-(2(-9H-carbazol-1-yl)phenyl)acetamide

(GeA-69) was identified as a novel allosteric PARP14 inhibitor acting on macrodomain 2 (MD2) [95]. A scheme describing therapeutic potential of various ART inhibitors is shown in Table 1.

2.4. Sirtuins

Sirtuins (Sirt) are histone and non-histone NAD-dependent protein deacetylases (HDAC) of type III. NAD^+ is hydrolyzed, forming NAM and ADP-ribose, that receives the acetyl group to form 2'-O-acetyl-ADP-ribose [96]. Silent information regulator/sirtuin 1 (Sirt1) is cytoplasmic, and is involved in calorie/glucose restriction and life extension [97], through the activation of mitochondrial Unfolded protein response (UPR_{mt}). Sirt1 targets are histones, p53, RB1, E2F1, Forkhead box protein O1 and 3 (FOXO1, FOXO3, and Forkhead in rhabdomyosarcoma- FKHR) transcription factors, and peroxisome proliferator activated receptor gamma (PPARγ) coactivator 1 alpha (PGC-1α) [98]. Activation of AMP-activated protein Kinase (AMPK) induces the phosphorylation of Sirt1 and PGC-1α, increases NAD^+ availability by upregulating the synthesis pathway.

Increased NAD^+ degradation or impairment of NAD^+ synthesis causes a decline in NAD^+ levels in mitochondria. Agents inducing oxidative stress, producing reactive oxygen species (ROS), over time induce damage and failure of mitochondria, one of the causative factors of Alzheimer's disease (AD) [99-101].

Sirt1 affects cell metabolism, promotes oxidative catabolism to sustain energy and induces mitochondrial biogenesis. PGC-1α protects cells against oxidative stress, relieves mitochondrial dysfunction, and is linked to Alzheimer's disease (AD) [102]. Sirt1 suppressed amyloid-β production [103], protected against alpha-synuclein aggregation, and activated molecular chaperones. Sirt1 protected against neurodegeneration in animal models for Alzheimer's disease and amyotrophic lateral sclerosis [104], and protected from mutant huntingtin by activating the mammalian Target of Rapamycin (mTOR) complex (TORC1) and CREB transcriptional pathway [105].

Sirt3, Sirt4 and Sirt5 reside in mitochondria and are involved during mitochondrial dysfunctions. Sirt3 regulates the unfolded protein response (UPR_{mt}) pathway and mitophagy [106], in association to other sirtuins.

Sirt1 upregulates autophagy/mitophagy through various activities. Sirt1 deacetylates the autophagy proteins ATG5, ATG7, and MAP1LC3/LC3, and the nuclear proteins LC3 at K49 and K51, enabling the nucleocytoplasmic transport and interaction with ATG7; and increases BECN1, RAB7, LC3, ATG12, and BNIP3 expression by deacetylating FOXO1 and FOXO3 [61]. In the attempt to pursue health improvement, resveratrol and stilbenes have been used to improve Sirt1 and AMPK activity, leading to inhibition of the mTOR and NF-κB pathways [108], inducing mitochondrial biogenesis. Sirt1 and mTOR converge on S6 kinase 1 (S6K1) with opposite effects, since acetylation impedes S6K1 phosphorylation by mTOR, essential to maintain intestinal stem cells for prolonged lifespan [109], while AMPK activates mTOR, such as during calorie restriction. Resveratrol, sirtuin-activating compounds (STACs) and rapamycin are compounds that can block mTOR and downstream NF-kB signaling, and induce UPR_{mt} and mitochondrial biogenesis, extending fitness and lifespan. Energy boosters are chemical structures sustaining mitochondrial function [110]. Rapamycin, as well as resveratrol, nicotinamide riboside, nicotinamide and PARP inhibitors, can couple longevity to increased respiration [111].

Also supplementation of NAD^+ intermediates such NMN increased cell signaling, which led to mTOR inhibition and up-regulation of mitophagy, a process that is also Sirt6 and Sirt7 dependent [47]. NAD^+ replenishment induced Sirt3-PGAM5-FUNDC1-dependent mitophagy, but also activated a Sirt2/Sirt4/Sirt5/PARP dependent inhibition of mitophagy, thus the balance between the induction and inhibition signals regulates overall mitophagy levels.

In presence of DNA damage and low NAD^+ levels in mitochondria, Sirt3, as well as Sirt4, can have an anti-apoptotic role [5]. Sirt3 was shown to have an important role in cardiovascular diseases and extended ageing in humans [112]. Co-immunoprecipitation data showed Sirt3 interaction with PARP1, and overexpressed Sirt3 decreased PARP1 acetylation levels [61]. Sirt3 protects cells from hypoxia through PGC-1α and superoxide dismutase (MnSOD)-dependent pathways [113]. Treatment of the knocked-out *SIRT3* cells with Sirt3 recombinant protein, prior to oxygen/glucose deprivation (OGD), restored cell viability and reduced cell damage, measured as released lactate dehydrogenase (LDH), and increased ATP levels in mitochondria [113-115]. Cells expressing oligomeric α-synuclein within the cytosolic and mitochondrial-enriched fractions showed low Sirt3 levels [115].

The application of an AMPK agonist, 5-aminoimidazole -4-carboxamide-1-β-d-ribofuranoside (AICAR) led to higher Sirt3 levels, restored mitochondrial function, and decreased α-synuclein oligomers [10]. Sirt3 induces the FOXO3a translocation from the cytosol to the nucleus [116]. Sirt3 promotes UPR_{mt} [117], and by deacetylating GDH promotes amino acid metabolism [114].

Sir4, Sirt6 and Sirt7 possess ADP-ribosyl transferase activity. Sirt4 ADP-ribosylates glutamate dehydrogenase (GDH) and inhibits the conversion of glutamate to α-ketoglutarate (α-KG) [119], decreasing glutamine uptake, relevant for cancer cell growth, and interfering with epithelial to mesenchymal transition (EMT) in gastric cancer. α-KG upregulates H3/H4 histone acetylases, and is required for α-KG dependent N6-methyladenine demethylase ALKBH5, and epigenetic RNA modification

enzyme: other intermediates of the Krebs cycle also have similar influence on epigenetic enzymes [120]. Sirt4 also hydrolyzes lipoamide cofactors from the dihydrolipoamide acetyltransferase (DLAT), the E2 subunit of the mammalian pyruvate dehydrogenase complex (PDH), a mechanism of switch regulating cellular metabolism.

Sirt6 and Sirt7 are localized in the nuclei. Overexpression of Sirt6 is found in skin cancer and in non-small cell lung carcinoma (NSCLC) with poor prognostic value, but in other types of cancers it is considered a tumor suppressor. Sirt6 regulates by deacetylation NAMPT activity, and restores NAD(P)(H) pools in cancer cells [121]. A role of Sirt6 in Alzheimer's disease has been hypothesized. Sirt6 has been related to DNA repair, genome integrity, telomere maintenance, energy metabolism, inflammatory states, and various processes regulating lifespan. Sirt6 is found depleted in AD patients. Sirt6 decreases in level during ageing. Sirt6 has a role in stabilization and phosphorylation of tau protein [122]. Sirt6 has been involved in genome integrity, DNA repair, energy metabolism and inflammation, and is found decreased during ageing and cell senescence. Sirt6 was found to auto–ADP-ribosylate [123]. Sirt6 ADP-ribosylates PARP1, enhancing its DNA repair activity [124]. Sirt6 ADP-ribosylates epigenetic enzymes such as lysine demethylase KDM2A [125], chromatin-silencing factors such as nuclear corepressor protein KAP1 [126], regulating KAP1 interaction with HP1α and LINE1 retrotransposon silencing [127]. Sirt6 ADP-ribosylates BAF170, activating the transcription of a subset of Nrf2 target genes [128], and this may sustain Nrf2-dependent boost of mitochondrial function. Lamin A binds Sirt6 and promotes histone deacetylation, and Sirt6-mediated functions upon DNA damage [129]. Sirt6 ADP-ribosylating activity induced p53- and p73- dependent cell death in cancer cells [130]. Sirt6, in particular the catalytically active form, associates in a phosphorylation-dependent mode with Ras-GTPase activator G3BP1, transcription factors NKRF, BCLAF1 and THRAP3, the telomerase regulator YLPM1, and the RNA polymerase complex factors XRN2 and COIL [131].

Sirt7 has auto-modifying ADPRT activity, leading to change in Sirt7 distribution on chromatin [132]. Sirt7 auto-modification occurs on several sites, as proteomic studies identified eight MARylated peptides. In the ELHGN catalytic motif, shared by sirtuins, H187 is a conserved residue involved in acetylated substrate recognition as well as deacetylation activity. H187 is oriented toward the NAD^+-binding pocket and the main catalytic site, as the flanking residues E185 and N189. On the contrary, in Sirt6 and Sirt7 these flanking residues are faced in the opposite direction, toward the surface of the cavity, with the interaction of both residues through their side chains to form a loop. These residues are important for their role in the ADP-ribosylation reaction. E185 is the catalytic residue that initiates the reaction, whereas N189 acts as the first acceptor of the ADP-ribosyl moiety [132]. Sirt7 plays a key role in mitochondrial function, and in the liver, it regulates autophagy and the physiological response to calorie restriction [132]. Sirt7 has been involved in non-homologous end joining (NHEJ) DNA repair [133, 134].

Sirt7 is enriched in nucleoli: auto-MARylation affects Sirt7 relocalization to genomic loci. The epigenetic pathway involving ADP-ribosyl-Sirt7 recognition by the ADP-ribose binding macrodomain of histone H2A1.1 (mH2A1) under glucose starvation induces auto-modified Sirt7 to enrich mH2A1 in loci associated with metabolic genes, changing chromatin-binding dynamics during glucose starvation [132]. Antagonism has been observed between Sirt7 and H_3K_{27}me3 marks, competing for mH2A enrichment upon metabolic stress. Although most sirtuin inhibitors have been developed to target deacetylase activity, others can block the NAD^+ binding site, such as selisistat, with a carboxamide moiety that mimics the amide group of the endogenous pan-sirtuin inhibitor [112]. The SIRT2-selective inhibitor AGK2 could reduce α-synuclein-induced cytotoxicity in a *Drosophila* model of Parkinson's disease: three SIRT2 inhibitors (AGK2, AK1 and AK7), were neuroprotective in Huntington's disease animal models, with toxic accumulation of protein aggregates [135]. New compounds, such as diketopiperazine-containing 2-anilinobenzamides, simultaneously target the "selectivity pocket" substrate-binding siteand the NAD^+-binding site [136]. A scheme describing the potential therapeutic use of sirtuin inhibitors is shown in Table 2. The links between PARPs and sirtuins are presented in figure 2on PARP1/Sirt1 and Sirt3/PARP1 interconnections and figure 3, indicating PARP1 and SIRT1 upstream regulator and downstream effectors, showing interactions between sirtuins, activity of various ARTDs and their positive and negative feedbacks.

3.1Role of NAD^+metabolic products in regulation of cell function

1-methylnicotinamide (MNAM) produced from nicotinamide by nicotinamide-N-methyltransferase (Nnmt) links sirtuins to lifespan extension [137]. Aberrant expression levels of *NNMT*, whose excessive activity consumes S-adenosyl methionine (SAM), have been implicated in cancer, metabolic, and neurodegenerative diseases [138]. SAM is required for methylation of lysines in histones, therefore Nnmt enzymatic activity regulates epigenetic modifications. Sirt1 levels are stabilized by MNAM through regulation of ubiquitination. Higher levels of Sirt1 lead to a decrease in protein acetylation levels. In hepatocytes, this leads to decreased levels of triglycerides and cholesterol, in endothelial cells to decrease prostacyclin PGI2, and to

nitric oxide synthesis. Altered NNMT expression levels have cell-specific effects, ranging from proliferation of cancer cells, to changes in metabolic rate in adipocytes, to altered metabolism of lipids and cholesterol in hepatocytes [139].MNAM serves as a substrate for a newly identified aldehyde oxidase, GAD-3, in *C. elegans*, and generates hydrogen peroxide, acting as a mitohormetic ROS signal. MNAM oxidized by AOX produces pyridones that are excreted through the urine [139]. MNAM addition to SH-SY5Y neuroblastoma cell line was not linked to mitochondrial complex I activity, since ROS production did not change, but rescued cells from toxicity of 1-methyl-4-phenylpyridinium (MPP^+) and rotenone, inhibitors of complex I, and also increased the level of ATP. Furthermore, the addition of MNAM protects from lipotoxicity in renal tubular kidney cells [139].

In individuals affected by chronic obstructive pulmonary disease (COPD), *NNMT* is over-expressed in the lungs and skeletal muscle. A treatment with IL-6, TNFα and TGFβ increases *NNMT* expression in human skeletal muscle myoblasts: activity of NNMT and production of MNAM are thought to play a protective compensatory response to injury [139].

3.2. Intermediates restoring or regulating NAD levels in cells for therapeutic approaches

NAD intermediates regulate and restore NAD^+ levels in cells, and have been tested in several therapeutic approaches**.** Extracellular NAD^+ is degraded by CD73 to NMN and successively to nicotinamide riboside (NR). Exogenous NMN could decrease AD-associated pathological characteristics in a mouse model of AD [26, 140]. Abnormal protein aggregation is a pathological feature of several neurodegenerative diseases, such as in Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Huntington's disease (HD), and causes brain ageing and neuronal cell death: NAD^+ and its precursors could delay and block the development of these diseases [141, 142]. NAD supplementation was used to improve mitochondrial function, leading to a significant increase in lifespan [19, 143, 144]. NAD^+ synthesis precursors such as nicotinamide (NAM), NMN or nicotinamide riboside (NR) [145-149] can improve cell conditions: NAD^+ boosters protect mice against high fat diet [145], and may prevent age-related diseases and increase longevity [31]. A recent clinical trial on healthy overweight adults to test the safety of NIAGEN (Nicotinamide Riboside Chloride) was positively concluded [146].

NAD^+ precursors, including NMN and nicotinamide riboside (NR), are drug candidates in AD for their ability to induce autophagy [31, 47]. *De novo* NAD^+ synthesis or increased availability of NAD precursors may support health quality during aging [147] and improve cognitive functions through a decrease of Aβ fibrils. Nicotinamide or NMN treatment preserved mitochondrial integrity in mouse models of AD [62, 148], and may function in the therapy of pathological processes such as diabetes, ischemia-reperfusion injury, heart failure are age-related diseases [25, 149]. The application of NMN and NR may sustain the need for higher levels of NAD^+, either due to higher consumption, or to reduced synthesis. NAD^+ synthesis intermediates have been associated with stilbenes to exert beneficial effects on NAD-dependent enzymes such as sirtuins. NAD^+ availability supports a proper function of sirtuins, required either in cellular signaling, mitochondrial energy, and mitophagy.

Salidroside, a bioactive from *Rhodiola rosea*, protected PC12 cells from $A\beta_{140}$ induced cytotoxicity [150], by regulating the NAPRT signaling pathway [6]. NAMPT expression levels decline with aging [151]: NAMPT depletion aggravates, while NAMPT overexpression prevents age-related changes [6]. It is worth noting that a calibration of NAD^+ synthesis and regulation of NAMPT and NAPRT may be required in chronic disease treatment and in anticancer therapy. Quercetin and apigenin, among flavonoids, are potent inhibitors of CD38, with the effect to increase NAD levels: administration to obese mice increased NAD^+ levels, decreased protein acetylation, and improved glucose and lipid homeostasis [152].

NAM, proposed for the treatment of early AD; NAM can affect and inhibit sirtuins and PARPs when NAD salvage enzymes (i.e. NAMPT) are downregulated, therefore its use needs to be evaluated considering the possible side effects [153].

Several diseases have been proposed to receive beneficial effects from administration of PARP1 inhibitors. Olaparib was tested in the treatment of amyotrophic lateral sclerosis, protected cardiomyocytes against oxidative stress, improved functionality in various organs, suppressed inflammatory responses and accelerated wound healing in a murine model of third-degree burn injury, so it may be repurposed for treating non-oncological diseases [154, 155].

PARP1/2 inhibitors used in cancer therapeutics are unlikely to be of therapeutic value for neurodegenerative diseases, due to the trapping effect: this effect locks the enzyme on DNA. Inhibitors are screened for the ability to mimic genetic deletion of PARP1[53, 156].

A scheme in Table 3 shows the use of NAD boosters and Sirt1 regulators in therapeutic applications. Table 4 shows the potential use of NAD synthesis inhibitors in disease treatment and in combined therapies.

3.3. Combined approaches and association of drugs boosting mitochondrial metabolism

In search for chemicals and bioactive compounds stimulating mitochondrial function, a huge number of publications can be retrieved. Catalpol is an iridoid glycoside able to exert a hypoglycemic action and to improve mitochondrial function [157]. Catalpol increases

mitochondria biogenesis, leading to upregulation of three genes: PGC-1α, mitochondrial transcription factor A (TFAM) and nuclear respiratory factor 1 (NRF1). Catalpol increases glucose uptake and ATP production in C2C12 myotubes as cells related to skeletal mass [157]. This effect was linked to activation of AMPK-mediated mitochondrial biogenesis.

Noteworthy, drugs for treatment of neurodegenerative disease require to be transported through the blood-brain-barrier (BBB). The passage of solutes through the BBB may be facilitated by exploiting formulations with protein tags able to be transported into the brain circulation. Additionally, delivery systems able to allow the transport of drugs into mitochondria have been developed, such as dequalinium-based liposome-like vesicles [158, 159].

KL1333 is an orally available derivative of lapachones, organic molecules isolated from the bark of the lapacho tree. Using human fibroblasts from patients with mitochondrial encephalomyopathy, lactic acidosis and stroke (MELAS), the study showed that KL133 was effective in increasing NAD^+ levels, through oxidation of NADH by NAD(P)H:quinone oxidoreductase 1 [160]

Among the new drugs and chemical entities for mitochondrial diseases, Mitoquinone (MitoQ, ubiquinoyldecyltriphenylphosphonium) has been studied in a clinical trial for ageing as NCT 02597023, while in other trials has been included as a dietary supplement. A similar drug, plastoquinone triphenyl phosphonium (SKQ1) has been tested with positive effect in treatment of mitochondrial induced oxidative damage in dry eye disease [161-163]. Among redox-active molecules, EPI-743 treatment showed improvement in disease state of individuals, patients at risk for progressing to end-of-life care for mitochondrial diseases (Leigh syndrome, MELAS, Friedreich's ataxia) and treated with EPI-743, showed a slower disease progression, improved their quality-of-life and showed positive clinical evaluation, based on noninvasive brain-imaging [160].

Mitochondria are required to be cleared from protein aggregates and damaged DNA, so mitophagy boosters may offer a first line of therapeutics [161].

MitoQ (ubiquinone),MitoVitE, MCAT (catalase), SKQ (plastoquinone)[159],MitoTEMPO (SOD mimetic), MitoPBN (coenzyme Q and phenyltertbutylnitrone conjugate), concentrate within mitochondria where they scavenge free-radicals and improve mitochondrial function [160].

Novel molecules including Szeto-Schiller (SS) peptides target the inner mitochondrial membrane stability. SS-31 is a member of the Szeto-Schiller (SS) peptides binding selectively to cardiolipin via electrostatic and hydrophobic interactions. SS-31 prevents cardiolipin from converting cytochrome c into a peroxidase while protecting its electron carrying function [164]. MTP-131 is a tetrapeptide that targets cardiolipin, a modulator of the inner mitochondrial membrane (IMM) essential for formation of cristae and for good functioning of the respiratory complex. In a reperfusion injury assay, MTP-131 was shown to load into the IMM, inhibiting mitochondrial swelling and oxidative cell death [160].

Diethyl 3,4-dihydroxyphenethyl aminoquinolin-4-yl methylphosphonate (DDQ) can improve cell energy, reducing mitochondrial fragmentation [160].

a-Tocopherolquinone (EPI-A0001), Indole-3-propionic acid (SHP622) and another quinone derivative (EPI-589) were tested in Friedreich's ataxia patients, in A3243G mtDNA mutation and Parkinson's disease, respectively. One completed phase III trial (NCT02652780) has been published, showing that elamipretide prevented disease progression or alleviated symptoms, significantly improving the quality of life for patients.

Dichloroacetate (DCA) inhibits pyruvate dehydrogenase kinase (PDK), thus preventing the inhibition of PDH, thereby acting as a metabolic modulator. DCA increases the flux of pyruvate into mitochondria and boosts mitochondrial respiration and generation of ATP [160]. Phase II study (NCT02255435) was designed to assess the dose-dependent safety and potential benefits of RTA408 (omaveloxolone) in Friedreich's ataxia patients, able to improve neurological functions [160]. RTA408 is a synthetic oleanane triterpenoid derivative that activates Nrf2 and suppresses NF-kB. RTA408 improves mitochondrial function, increasing ATP generation, and suppresses uncontrolled inflammatory cellular reactions [160]. Dexpramipexole, with good brain permeability and binding to F_1F_o ATP synthase to increase mitochondrial ATP production, was tested in patients with amyotrophic lateral sclerosis (ALS) and found effective in treatment of ischaemic brain injury [165].

Recently, metformin has been studied as an anti-ageing compound, in association with NAM or NMN [166]. Metformin may directly act on mitochondria to reestablish a balance between glycolysis intermediates and oxidative phosphorylation [167, 168]. Metformin may inhibit complex I of the respiratory chain, by means of ubiquinone reduction. It induces mitochondrial biogenesis, oxidizes mitochondrial NADH, suppresses oxidative stress, inhibits gluconeogenesis, and prevents gentamicin-induced nephrotoxicity. Metformin exerts pleiotropic effects on metabolic hallmarks of aging, such as the insulin/ILGF-1 and AMPK1/mTOR signaling pathways [169].

A scheme showing the therapeutic potential of energy boosters is presented in Table 5.

3.4. Neurodegenerative disease and cancer: targeting cell metabolism regulating glycolysis and oxphos

Links between cancer and Alzheimer's disease have been proposed via oxidative stress and mitochondrial damage [170]. While PARP inhibition in DNA repair defective cancers has been based on PARP trapping inhibitors, novel PARPi could be efficient in therapies of wound

healing [154], heart failure, cardiovascular protection [193], emphysema [205], retinal degeneration [206], diet-induced obesity and various inflammatory states [208] and asthma [209]. NAD boosters have been applied in diabetes, ischemia-reperfusion injury, heart failure are age-related diseases [25, 149, 193]. NAD consumption by PARPs and CD38 reduces NAD levels, while at the same time NAD salvage enzymes (i.e. NAMPT) may be downregulated, such as during aging. Quercetin and apigenin, as CD38 inhibitors, rescued from high fat diet damages in animal models. Thus, NAD protection and NAD boosters may be associated in therapies, improving cognitive functions, decreasing Aβ fibrils, and protecting from other neurodegeneration-related modifications. Increased NAD availability may allow proper function of sirtuins (Sirt1, Sirt3, Sirt4, Sirt6, Sirt7), with a positive effect on mitochondria and energy production, metabolism, PARP1 activation, functions that need to be regulated since in aging these enzymes are downregulated.

The balance between NAD^+ synthesis and activity of NAMPT and NAPRT must be taken in consideration when deciding the type of anticancer therapy. The LDH inhibitor FX11 produced an effect additive to FK866 in reducing the growth of the human P493 B cell line, used as a model for Burkitt's lymphoma. The combined administration of FK866 and FX11 has been tested for dual inhibition of metabolic pathways [171]. A distinct NAMPT inhibitor (CHS828) showed anti-tumor properties in various xenograft models. In triple-negative (TN) breast cancers, NAMPT was found as a non-redundant modifier of olaparib response: association of FK866 with olaparib was more effective for therapy of the tumors [172]. In a subtype of BRCA1/BRCA2 defective ovarian cancers showing NAMPT-dependent glycolysis, FK866 was coadministered in the therapy with PARPi [175]. Some tumor types show defects or deregulation in NAD synthesis enzymes. In tumor cell lines lacking NAPRT1 enzyme, nicotinic acid was supplemented to restore NAD^+ levels in normal tissues in *vivo*, to alleviate the toxicity of NAMPT inhibitors [135]. Wilm's tumor 1 (WT1) is a transcription factor that binds to the *QPRT* gene inducing its transcription. Quinolinate phosphoribosyltransferase is a key enzyme in the *de novo* NAD synthesis pathway (kynurenine pathway): when overexpressed, QPRT may confer resistance to imatinib, an anti-leukemic drug, so it may have anti-apoptotic functions in leukemic K562 cells [173]. The screening and selection of tumors with specific vulnerabilities that can be co-targeted with NAMPT inhibitors is a prerequisite to avoid the failure of NAMPT inhibitors in clinical trials [174], combining it to therapies targeting sirtuin function, DNA repair machinery, redox homeostasis, cellular stemness, molecular signaling and immune processes.

Various cancers showed to respond well to PARP inhibitors. Prostate cancers, in which androgen signaling is out of control, are responsive toUPF-1069, a PARP2 specific inhibitor [199, 200]. Wnt-driven cancers may benefit from Tankyrase inhibitors [71, 86]. Homologous recombination (HR) defective cancers, with *BRCA1*,*BRCA2*, *ATM*, *ATR*, *FANC*, *PALB2* mutation, respond to PARPi, that were tested also in *RNASEH2B* deleted cancers, in HER negative cancers, in few cases as pretreatment with adjuvant taxanes, or anthracycline [66, 179, 180, 194, 195, 198]. PARP14 macrodomain 2 inhibitor may be applied to treatment of lymphoma and myeloma [92, 98].

However, PARPi therapies should be carefully considered when co-administered with other types of anticancer drugs. Homologous recombination defective (HRD) cells are sensitive to metformin and changes in NAD^+ concentration [176]. HRD tumors show a metabolic profile that includes enhanced oxidative phosphorylation (OXPHOS) with low glycolytic activity [176]. Shifting from an OXPHOS metabolism to increased glycolysis, i.e. by rotenone or dichloroacetate addition, may interfere with the sensitivity to PARP inhibitors (PARPi) in HRD cells. The treatment of HRD cancers with OXPHOS inhibitors (such as metformin) does not support a favorable response to PARP inhibitors, but could be effective on cancers with high oxidative phosphorylation metabolism. PARPi can be effective in HRD cells in combination to NAD^+ boosters that activate mitochondrial respiration.

CONCLUSION

The application of NAD precursors may prevent mitochondrial failure and cell death in neurodegenerative and metabolic diseases. PARP inhibitors may be associated with regulators of NAD salvage enzymes, in treatment of various cancers and degenerative A great improvement in therapeutic applications is under progress, through application of drugs sustaining mitochondrial functions. Further studies and clinical trials may give rise to targeted therapies for various chronic diseases, applying PARP inhibitors and sirtuin modulators to cell metabolic profiles.

FUNDING

The authors declare they have not been funded.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

1. Wallace D.C. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annu. Rev. Genet*., **2005**, *39*:359-407.
2. Wu Y.T., Wu S.B., Lee W.Y., Wei YH. Mitochondrial respiratory dysfunction-elicited oxidative stress and posttranslational protein modification in mitochondrial diseases. *Ann. N.Y. Acad. Sci. U.S.A*., **2010**, *1201*:147-156.
3. Wallace D.C. Bioenergetic origins of complexity and disease. *Cold Spring Harb. Symp. Quant. Biol.***2011**, *76*:1–16.
4. Wang C.H., Wu S.B., Wu Y.T., Wei Y.H. Oxidative stress response elicited by mitochondrial dysfunction: implication in the pathophysiology of aging. *Exp. Biol. Med. (Maywood*), **2013**, *238*:450-460.
5. Yang H., Yang T, Baur J.A., Perez E., Matsui T., Carmona J.J., Lamming D.W., Souza-Pinto N.C., Bohr V.A., Rosenzweig A., de Cabo R., Sauve A.A., Sinclair D.A. Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. *Cell*, **2007**, *130*:1095-1107.
6. Pehar M., Harlan B.A., Killoy K.M., Vargas M.R. Nicotinamide Adenine Dinucleotide Metabolism and Neurodegeneration. *Antioxid. Redox Signal*., **2018**, *28*:1652-1668.
7. Koch-Nolte, F., Fischer, S., Haag, F., Ziegler, M. Compartmentation of NAD+-dependent signalling. *FEBS Lett*., **2011**, *585*:1651-1656.
8. Cohen M.S. Interplay between compartmentalized NAD+ synthesis and consumption: a focus on the PARP family. *Genes Dev***.,** **2020**, *34*:254-262.
9. Hopp A.-K., Grüter P., Hottiger M.O. Regulation of Glucose Metabolism by NAD+ and ADP-Ribosylation. *Cells* (MDPI), **2019**, *8*:890.
10. Mendelsohn A.R., and Larrick J.W. The NAD+/PARP1/SIRT1 Axis in Aging. Rejuvenation Res. 2017, 20:244-247.
11. Fatokun A.A., Bawson V.L., Dawson T.M. Parthanatos: mitochondrial-linked mechanisms and therapeutic opportunities. *British J. Pharmacol*., **2014**, *171*:2000–2016.
12. Verdin E. NAD+ in aging, metabolism, and neurodegeneration. *Science*, **2015**, *350*:1208-1213.
13. Adiele R.C., and Adiele C.A. Mitochondrial Regulatory Pathways in the Pathogenesis of Alzheimer's Disease. *J. Alzheimers Dis.*, **2016**, *53*:1257-1270.
14. Strømland Ø., Niere M., Nikiforov A.A., VanLinden M.R., Heiland I., Ziegler M. Keeping the balance in NAD metabolism. *Biochem. Soc. Trans*., **2019**, *47*:119–130.
15. Massudi H,, Grant R,, Guillemin G,J,, Braidy N. NAD+ metabolism and oxidative stress: the golden nucleotide on a crown of thorns. *Redox Rep*., **2012**, *17*:28-46.
16. Wang X., Zhang Z., Zhang N., Li H., Zhang L., Baines C.P., Ding S. Subcellular NAMPT-mediated NAD+ salvage pathways and their roles in bioenergetics and neuronal protection after ischemic injury. *J. Neurochem*., **2019**, *151*:732-748.
17. Ramsey K.M., Yoshino J., Brace C.S., Abrassart D., Kobayashi Y., Marcheva B., Hong H.K., Chong J.L., Buhr E.D., Lee C., Takahashi J.S., Imai S., Bass J. Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. *Science*, **2009**, *324*:651-654.
18. Peek C.B., Affinati A.H., Ramsey K.M., Kuo H.Y., Yu W., Sena L.A., Ilkayeva O., Marcheva B., Kobayashi Y., Omura C., Levine D.C., Bacsik D.J., Gius D., Newgard C.B., Goetzman E., Chandel N.S., Denu J.M., Mrksich M., Bass J. Circadian clock NAD+ cycle drives mitochondrial oxidative metabolism in mice. *Science*, **2013**, *342*:1243417
19. Asher G., Gatfield D., Stratmann M., Reinke H., Dibner C., Kreppel F., Mostoslavsky R., Alt F.W., Schibler U. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell*, **2008**, *134*:317-328.
20. Chang H.C., and Guarente L. SIRT1 mediates central circadian control in the SCN by a mechanism that decays with aging. *Cell*, **2013**, *153*:1448–1460.
21. Poljsak B., and Milisav I. NAD+ as the Link Between Oxidative Stress, Inflammation, Caloric Restriction, Exercise, DNA Repair, Longevity, and Health Span. *Rejuvenation Res*., **2016**, *19*:406-415.
22. Wang P., and Miao C.-Y. NAMPT as a Therapeutic Target against Stroke. *Trends Pharmacol. Sci*., **2015**, *36*:891-905.
23. Xing S., Hu Y., Huang X., Shen D., Chen C. Nicotinamide phosphoribosyltransferase-related signaling pathway in early Alzheimer's disease mouse models. *Mol. Med. Rep*., **2019**, *20*:5163-5171.
24. Roh E., and Kim M.-S. Hypothalamic NAD+-Sirtuin Axis: Function and Regulation. *Biomolecules* (MDPI), **2020**, *10*:396.
25. Felici R., Lapucci A., Ramazzotti M., Chiarugi A. Insight into Molecular and Functional Properties of NMNAT3 Reveals New Hints of NAD Homeostasis within Human Mitochondria. *PLoS One*, **2013**, *8*:e76938.
26. Rajman L., Chwalek K., Sinclair D.A. Therapeutic Potential of NAD-Boosting Molecules: The *In Vivo* Evidence. *Cell Metab*., **2018**, *27*:529-547.
27. Orlandi I., Alberghina L., Vai M. Nicotinamide, Nicotinamide Riboside and Nicotinic Acid-Emerging Roles in Replicative and Chronological Aging in Yeast. *Biomolecules* (MDPI), **2020**, *10*:604.

28. Mehmel M., Jovanovic N., Spitz U. Nicotinamide Riboside-The Current State of Research and Therapeutic Uses. *Nutrients* (MDPI), **2020**, *12*, 1616.
29. Sampath D., Zabka T.S., Misner D.L., O'Brien T., Dragovich P.S. Inhibition of nicotinamide phosphoribosyltransferase (NAMPT) as a therapeutic strategy in cancer. *Pharmacol. and Therapeutics*, **2015**, *151*:16–31.
30. Buonvicino D., Mazzola F., Zamporlini F., Resta F., Ranieri G., Camaioni E., Muzzi M., Zecchi R., Pieraccini G., Dölle C., Calamante M., Bartolucci G., Ziegler M., Stecca B., Raffaelli N., Chiarugi A. Identification of the Nicotinamide Salvage Pathway as a New Toxification Route for Antimetabolites. *Cell. Chem. Biol*., **2018**, *25*:471-482.e7.
31. Gaudino F., Manfredonia I., Managò A., Audrito V., Raffaelli N., Vaisitti T., Deaglio S. Subcellular Characterization of Nicotinamide Adenine Dinucleotide Biosynthesis in Metastatic Melanoma by Using Organelle-Specific Biosensors. *Antioxid Redox Signal*., **2019**, *31*:1150-1165.
32. Pittelli M., Formentini L., Faraco G., Lapucci A., Rapizzi E., Cialdai F., Romano G., Moneti G., Moroni F., Chiarugi A. Inhibition of Nicotinamide Phosphoribosyltransferase: cellular bioenergetics reveals a mitochondrial insensitive NAD pool. *J. Bol. Chem*., **2010**, *285*:34106–34114.
33. Grolla A.A., Travelli C., Genazzani A.A., Sethi J.K. Extracellular nicotinamide phosphoribosyl transferase, a new cancer metabokine. *British J. Pharmacol*., **2016**, *173*:2182–2194.
34. Managò A., V. Audrito, F. Mazzola, L. Sorci, F. Gaudino, K. Gizzi, N. Vitale, Incarnato D., Minazzato G., A. Ianniello, Varriale A., D'Auria S., Mengozzi G., Politano G., Oliviero S., Raffaelli N., Deaglio S. Extracellular nicotinate phosphoribosyltransferase binds Toll like receptor 4 and mediates inflammation. *Nature Comm*., **2019**, *10*:4116.
35. Galli U., Colombo G., Travelli C., Tron G.C., Genazzani A.A., Grolla A.A. Recent Advances in NAMPT Inhibitors: A Novel Immunotherapic Strategy. *Front. Pharmacol*., **2020**, *11*:656.
36. Audrito V., Messana V.G., Deaglio S. NAMPT and NAPRT: Two Metabolic Enzymes With Key Roles in Inflammation. *Front. Oncol*., **2020**, *10*:358.
37. Vaisitti T., Arruga F., Guerra G., Deaglio S. Ectonucleotidases in Blood Malignancies: A Tale of Surface Markers and Therapeutic Targets. *Front. Immunol*., **2019**, *10*:2301.
38. Goueli S.A., and Hsiao K. Monitoring and characterizing soluble and membrane-bound ectonucleotidases CD73 and CD39. *PLoS One*, **2019**, *14*: e0220094.
39. Deaglio S., and Robson S.C. Ectonucleotidases as regulators of purinergic signaling in thrombosis, inflammation, and immunity. *Adv. Pharmacol*., **2011**, *61*:301-332.
40. Fliegert R., Heeren J., Koch-Nolte F., Nikolaev V.O., Lohr C., Meier C., Guse A.H. Adenine nucleotides as paracrine mediators and intracellular second messengers in immunity and inflammation. *Biochem. Soc. Trans*., **2019,***47*:329-337.
41. Grozio A., Sociali G., Sturla L., Caffa I., Soncini D., Salis A., Raffaelli N., De Flora A., Nencioni A., Bruzzone S. CD73 Protein as a Source of Extracellular Precursors for Sustained NAD+ Biosynthesis in FK866-treated Tumor Cells. *J. Biol. Chem.*,**2013**, *288*:5938-49.
42. Camacho-Pereira J, Tarragó MG, Chini CC, Nin V, Escande C, Warner GM, Puranik AS, Schoon RA, Reid JM, Galina A, Chini EN. CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. *Cell Metab*., **2016**, *23*:1127–1139.
43. Fang E.F. Mitophagy and NAD+ inhibit Alzheimer disease. *Autophagy*, **2019**, *15*:1112–1114.
44. Aksoy P., White T.A., Thompson M., Chini E.N. Regulation of intracellular levels of NAD: a novel role for CD38. *Biochem. Biophys. Res. Commun*., **2006**, *345*:1386-92.
45. Brazill J.M., Li C., Zhu Y., Zhai R.G. NMNAT: It's an NAD+ synthase… It's a chaperone… It's a neuroprotector. *Curr. Opin. Genet. Dev*., **2017**, *44*:156-162.
46. Tarragó M.G., Chini C.C.S., Kanamori K.S., Warner G.M., Caride A., de Oliveira G.C., Rud M., Samani A., Hein K.Z., Huang R., Jurk D., Cho D.S., Boslett J.J., Miller J.D., Zweier J.L., Passos J.F., Doles J.D., Becherer D.J., Chini E.N. A Potent and Specific CD38 Inhibitor Ameliorates Age-Related Metabolic Dysfunction by Reversing Tissue NAD+ Decline. *Cell Metab*., **2016**, *27*:1081-1095.
47. Poltronieri P., and Čerekovic N. Roles of Nicotinamide Adenine Dinucleotide (NAD+) in Biological Systems. *Challenges* (MDPI), **2018**, *9*:3.
48. Tóth B., Iordanov I., Csanády L. Ruling out pyridine dinucleotides as true TRPM2 channel activators reveals novel direct agonist ADP-ribose-2'-phosphate. *J. Gen. Physiol*., **2015**, *145*:419-30.
49. Poltronieri P., and Miwa M. Editorial (Thematic Issue: Overview on ADP Ribosylation and PARP Superfamily of Proteins). *Curr. Protein Pept. Sci*., **2016**, *17*:630-632.
50. Hoch N.C., and Polo L.M. ADP-ribosylation: from molecular mechanisms to human disease. *Genet. Mol. Biol*., **2019**, *43*:e20190075.
51. Verheugd P., Bütepage M., Eckei L., Lüscher B. Players in ADP-ribosylation: Readers and Erasers. *Curr. Protein Pept. Sci*., **2016**, *17*:654-667.
52. Palazzo L., Daniels C.M., Nettleship J.E., Rahman N., McPherson R.L., Ong S.E., Kato K., Nureki

O., Leung A.K., Ahel I. ENPP1 processes protein ADP-ribosylation in vitro. *FEBS J*., **2016**, *283*:3371-3388.
53. Li J., Bonkowski M.S., Moniot S., Zhang D., Hubbard B.P., Ling A.J., Rajman L.A., Qin B., Lou Z., Gorbunova V., Aravind L., Steegborn C., Sinclair D.A. A conserved NAD+ binding pocket that regulates protein-protein interactions during aging. *Science*, **2017**, *355*:1312-1317.
54. Martire S., Fuso A., Mosca L., Forte E., Correani V., Fontana M., Scarpa S., Maras B., D'Erme M. Bioenergetic Impairment in Animal and Cellular Models of Alzheimer's Disease: PARP-1 Inhibition Rescues Metabolic Dysfunctions. *J. Alzheimers Dis.*, **2016**, *54*:307-324.
55. Yamashita S., Tanaka M., Nodono H., Hamada A., Hamada T., Hasegawa M., Nishi Y., Moss J., Miwa M. Human alcohol dehydrogenase 1 is an acceptor protein for polyADP-ribosylation. *Biochem. Pharmacol*., **2019**, *167*:27-32.
56. Fouquerel E, Goellner EM, Yu Z, Gagné JP, Barbi de Moura M, Feinstein T, Wheeler D, Redpath P, Li J, Romero G, Migaud M, Van Houten B, Poirier GG, Sobol R.W. ARTD1/PARP1 negatively regulates glycolysis by inhibiting hexokinase 1 independent of NAD+ depletion. *Cell Rep*., **2014**, *8*:1819-1831.
57. Andrabi S.A., Umanah G.K.E., Chang C., Stevens D.A., Karuppagounder S.S., Gagné J.-P., Poirier G.G., Dawson V.L., Dawson T.M. Poly(ADP-ribose) polymerase-dependent energy depletion occurs through inhibition of glycolysis. *Proc. Natl. Acad. Sci. U.S.A.*, **2014**, *111*:10209-10214.
58. Feng X., Wang Y., Chen W., Xu S., Li L., Geng Y., Shen A., Gao H., Zhang L., Liu S. SIRT3 inhibits cardiac hypertrophy by regulating PARP-1 activity. *Aging* (Albany NY), **2020**, *12*:4178-4192.
59. Liu C., and Phang Y. New insights of poly(ADP-ribosylation) in neurodegenerative diseases: a focus on protein phase separation and pathologic aggregation. *Biochem. Pharmacol.*,**2019**, *167*:58-63.
60. Banasik M., Stedeford T., Strosznajder R.P. Natural inhibitors of poly(ADP-ribose) polymerase-1. *Molecular Neurobiol.*, **2012**, *46*:55–63.
61. Sodhi R.K., Singh N., Jaggi A.S. Poly(ADP-ribose) polymerase-1 (PARP-1) and its therapeutic implications. *Vascul. Pharmacol.*, **2010**, *53*:77-87.
62. Feng F.Y., de Bono J.S., Rubin M.A., Knudsen K.E. Chromatin to Clinic: The Molecular Rationale for PARP1 Inhibitor Function. *Mol. Cell*, **2015**, *58*(6):925-34.
63. Lord C.J. and Ashworth A. PARP Inhibitors: The First Synthetic Lethal Targeted Therapy. *Science*, **2017**, *355*:1152-1158.
64. Bottino C., Peserico A., Simone C., Caretti G. SMYD3: An Oncogenic Driver Targeting Epigenetic Regulation and Signaling Pathways. *Cancers* (MDPI), **2020,***12*:142.
65. Rottenberg S., Jaspers J.E., Kersbergen A., van der Burg E., Nygren A.O., Zander S.A., Derksen P.W., de Bruin M., Zevenhoven J., Lau A., Boulter R., Cranston A., O'Connor M.J., Martin N.M., Borst P., Jonkers J. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. *Proc. Natl. Acad. Sci. U.S.A*., **2008**, *105*:17079-17084.
66. Yasukawa M., Fujihara H., Fujimori H., Kawaguchi K., Yamada H., Nakayama R., Yamamoto N., Kishi Y., Hamada Y., Masutani M. Synergetic Effects of PARP Inhibitor AZD2281 and Cisplatin in Oral Squamous Cell Carcinoma in Vitro and in Vivo. *Int. J. Mol. Sci.* (MDPI), **2016**, *17*:272.
67. Karpova Y., C. Wu, A. Divan, M.E. McDonnell, E. Hewlett, P. Makhov, J. Gordon, M. Ye, A.B. Reitz, W.E. Childers, T. Skorski, V. Kolenko, Tulin A.V. Non-NAD-like PARP-1 inhibitors in prostate cancer treatment. *Biochem. Pharmacol.*, **2019**, *167*:149-162.
68. Thorsell AG, Ekblad T, Karlberg T, Löw M, Pinto AF, Trésaugues L, Moche M, Cohen MS, Schüler H. Structural Basis for Potency and Promiscuity in Poly(ADP-ribose) Polymerase (PARP) and Tankyrase Inhibitors. *J. Med. Chem*., **2017**, *60*:1262-1271.
69. Zha S., Li Z., Cao Q., Wang F., Liu F. PARP1 inhibitor (PJ34) improves the function of aging-induced endothelial progenitor cells by preserving intracellular NAD+ levels and increasing SIRT1 activity. *Stem Cell Res. Ther*., **2018**, *9*:224.
70. Bai P, Cantó C, Oudart H, Brunyánszki A, Cen Y, Thomas C, Yamamoto H, Huber A, Kiss B, Houtkooper RH, Schoonjans K, Schreiber V, Sauve AA, Menissier-de Murcia J, Auwerx J. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. *Cell Metab*., **2011**, *13*:461-468.
71. Cseh A.M., Fabian Z., Quintana-Cabrera R., Szabo A., Eros K., Soriano M.E., Gallyas F., Scorrano L., Sumegi B. PARP Inhibitor PJ34 Protects Mitochondria and Induces DNA-Damage Mediated Apoptosis in Combination With Cisplatin or Temozolomide in B16F10 Melanoma Cells. *Front Physiol*., **2019**, *10*:538.1.
72. Grundy G.J., Polo L.M., Zeng Z., Rulten S.L., Hoch N.C., Paomephan P., Xu Y., Sweet S.M., Thorne A.W., Oliver A.W., Matthews S.J., Pearl L.H., Caldecott K.W. PARP3 is a sensor of nicked nucleosomes and monoribosylates histone H2B(Glu2). *Nat. Commun.***2016**, *7*:12404.
73. Boehler C., Gauthier L.R., Mortusewicz O., Biard D.S., Saliou J.M., Bresson A., Sanglier-Cianferani S., Smith S., Schreiber V., Boussin F., Dantzer F. Poly(ADP-ribose) polymerase 3 (PARP3), a newcomer in cellular response to DNA damage and mitotic progression. *Proc. Natl. Acad. Sci. U.S.A*. **2011**, *108*:2783-8.
74. Beck C, Rodriguez-Vargas JM, Boehler C, Robert I, Heyer V, Hanini N, Gauthier LR, Tissier A,

Schreiber V, Elofsson M, Reina San Martin B, Dantzer F. PARP3, a new therapeutic target to alter Rictor/mTORC2 signaling and tumor progression in BRCA1-associated cancers. *Cell Death Differ.* **2019**, *26*:1615-1630.
75. Karlberg T., Hammarström M., Schütz P., Svensson L., Schüler H. Crystal structure of the catalytic domain of human PARP2 in complex with PARP inhibitor ABT-888. *Biochemistry*, **2010**, *49*:1056-1058.
76. Kirby I.T., and Cohen M.S. Small-Molecule Inhibitors of PARPs: From Tools for Investigating ADP-Ribosylation to Therapeutics. Pp. 212-231. In: Activity-Based Protein Profiling. Cravatt B.F., Hsu K.-L., Weerapana E. (Eds.). *Current Topics Microbiol. Immunol.*, **2019**, *420*:211-231.
77. Sherstyuk Y.V., Ivanisenko N.V., Zakharenko A.L., Sukhanova M.V., Peshkov R.Y., Eltsov I.V., Kutuzov M.M., Kurgina T.A., Belousova E.A., Ivanisenko V.A., Lavrik O.I., Silnikov V.N., Abramova T.V. Design, Synthesis and Molecular Modeling Study of Conjugates of ADP and Morpholino Nucleosides as A Novel Class of Inhibitors of PARP-1, PARP-2 and PARP-3. *Int. J. Mol. Sci.* (MDPI), **2019**, *21*:214.
78. Zhang X-N., Cheng Q., Chen J., Lam A.T., Lu Y., Dai Z., Pei H., Evdokimov N.M., Louie S.G., Zhang Y. A ribose-functionalized NAD+ with unexpected high activity and selectivity for protein poly-ADP-ribosylation. *Nat. Commun*., **2019**, *10*:4196.
79. Ekblad T., Lindgren A.E., Andersson C.D., Caraballo R., Thorsell A.G., Karlberg T., Spjut S., Linusson A., Schüler H., Elofsson M. Towards small molecule inhibitors of mono-ADP-ribosyltransferases. *Eur. J. Med. Chem*., **2015**, *95*:546-51.
80. Venkannagari H., Verheugd P., Koivunen J., Haikarainen T., Obaji E., Ashok Y., Narwal M., Pihlajaniemi T., Lüscher B., Lehtiö L. Small-Molecule Chemical Probe Rescues Cells from Mono-ADP-Ribosyltransferase ARTD10/PARP10 -Induced Apoptosis and Sensitizes Cancer Cells to DNA Damage. *Cell. Chem. Biol*., **2016**, *23*:1251-1260.
81. Murthy S., Desantis J., Verheugd P., Maksimainen M.M., Venkannagari H., Massari S., Ashok Y., Obaji E., Nkizinkinko Y., Lüscher B., Tabarrini O., Lehtiö L. 4-(Phenoxy) and 4-(benzyloxy)benzamides as potent and selective inhibitors of mono-ADP-ribosyltransferase PARP10/ARTD10. *Eur. J. Med. Chem*., **2018**, *156*:93-102.
82. Kirby I.T., Kojic A., Arnold M.R., Thorsell A.G., Karlberg T., Vermehren Schmaedick A., Sreneevasan R., Schultz C., Schuler H., Cohen M.S. A Potent and Selective PARP11 Inhibitor Suggests Coupling between Cellular Localization and Catalytic Activity. *Cell. Chem. Biol.*, **2018**, *25*:1547-1553.e12.
83. Peng B., Thorsell A.G., Karlberg T., Schüler H., Yao S.Q. Small Molecule Microarray Based Discovery of PARP14 Inhibitors. *Angew. Chem. Int. Ed. Engl*., **2017**, *56*:248-253.
84. Upton K., Meyers M., Thorsell A.G., Karlberg T., Holechek J., Lease R., Schey G., Wolf E., Lucente A., Schüler H., Ferraris D. Design and synthesis of potent inhibitors of the mono(ADP-ribosyl)transferase, PARP14. *Bioorg. Med. Chem. Lett*., **2017**, *27*:2907-2911.
85. Yoneyama-Hirozane M., Matsumoto S-I., Toyoda Y., Saikatendu K.S., Zama Y., Yonemori K., Oonishi M.,, Ishii T., Kawamoto T. Identification of PARP14 inhibitors using novel methods for detecting auto-ribosylation. *Biochem. Biophys. Res. Commun*., **2017**, *486*:626–631.
86. Ferri M., Liscio P., Carotti A., Asciutti S., Sardella R., Macchiarulo A., Camaioni E. Targeting Wnt-driven cancers: Discovery of novel tankyrase inhibitors. *Eur. J. Med. Chem*., **2017**, *142*:506-522.
87. Barkauskaite E., Jankevicius G., Ahel I. Structures and Mechanisms of Enzymes Employed in the Synthesis and Degradation of PARP-Dependent Protein ADP-Ribosylation. *Mol. Cell*, **2015**, *58*:935-946.
88. Dani N., Stilla A., Marchegiani A., Tamburro A., Till S., Ladurner A.G., Corda D., Di Girolamo M. Combining affinity purification by ADP-ribose-binding macro domains with mass spectrometry to define the mammalian ADP-ribosyl proteome. *Proc. Natl. Acad. Sci. USA*, **2009**, *106*:4243–4248.
89. Vivelo C., Wat R., Agrawal C., Tee H.Y., Leung A.K.L. ADPriboDB: The database of ADP-ribosylated proteins. *Nucl. Acids Res.*, **2017**, *45*:D204–D209.
90. Di Girolamo M., and Fabrizio G. Overview of the mammalian ADP-ribosyl-transferases clostridia toxin-like (ARTCs) family. *Biochem. Pharmacol*., **2019**, *167*:86-96.
91. Mehrotra P., Riley J.P., Patel R., Li F., Voss L., Goenka S. PARP-14 functions as a transcriptional switch for Stat6-dependent gene activation. *J. Biol. Chem*., **2011**, *286*:1767-76.
92. Qin W., Wu H.J., Cao L.Q., Li HJ, He C.X., Zhao D., Xing L., Li P.Q., Jin X., Cao H.L. Research Progress on PARP14 as a Drug Target. *Front. Pharmacol*., **2019**, *10*:172.
93. Palazzo L., Mikolčević P., Mikoč A., Ahel I. ADP-ribosylation signalling and human disease. *Open Biol.*, **2019**, *9(*4):190041.
94. Di Paola S., Micaroni M., Di Tullio G., Buccione R., Di Girolamo M. PARP16/ARTD15 is a novel endoplasmic reticulum- associated mono-ADP-ribosyltransferase that interacts with, and modifies karyopherin-ß1. *PLoS One*, **2012**, *7*:e37352.
95. Di Girolamo M., Fabrizio G., Scarpa E.S., Di Paola S. NAD^+-dependent enzymes at the endoplasmic reticulum. *Curr. Top. Med. Chem.*, **2013**, *13*:3001-3010.
96. Di Girolamo M.; and Fabrizio G. The ADP-Ribosyl-Transferases Diphtheria Toxin-Like (ARTDs) Family: An Overview. *Challenges* (MDPI), **2018**, *9*:24.
97. Lu A.Z., Abo R., Ren Y., Gui B., Mo J.R., Blackwell D., Wigle T., Keilhack H., Niepel M. Enabling

drug discovery for the PARP protein family through the detection of mono-ADP-ribosylation. *Biochem. Pharmacol*., **2019**, *167*:97-106.
98. Moustakim M., Riedel K., Schuller M., Gehring A.P., Monteiro O.P., Martin S.P., Fedorov O., Heer J., Dixon D.J., Elkins J.M., Knapp S., Bracher F., Brennan P.E. Discovery of a novel allosteric inhibitor scaffold for polyadenosine-diphosphate-ribose polymerase 14 (PARP14) macrodomain 2. *Bioorg. Med. Chem*., **2018**, *26*:2965-2972.
99. Katsyuba E., and Auwerx J. Modulating NAD+ metabolism, from bench to bedside. *EMBO J*., **2017**, *36*:2670-2683.
100. Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cantó C, Mottis A, Jo YS, Viswanathan M, Schoonjans K, Guarente L, Auwerx J. The NAD(+)/Sirtuin Pathway Modulates Longevity through Activation of Mitochondrial UPR and FOXO Signaling. *Cell*, **2013**, *154*:430-441.
101. Poltronieri P., Xu B., Giovinazzo G. Resveratrol and other Stilbenes: Effects on Dysregulated Gene Expression in Cancers and Novel Delivery Systems. *Anticancer Agents Med. Chem*., **2020** Jul 5, doi: 10.2174/1871520620666200705220722. Online ahead of print.
102. Aliev G., Palacios H.H., Walrafen B., Lipsitt A.E., Obrenovich M.E., Morales L. Brain mitochondria as a primary target in the development of treatment strategies for Alzheimer disease. *Int. J. Biochem. Cell Biol.*, **2009**, *41*:1989-2004.
103. Aliev G., Palacios H.H., Gasimov E., Obrenovich M.E., Morales L., Leszek J., Bragin V., Solís Herrera A., Gokhman D. Oxidative Stress Induced Mitochondrial Failure and Vascular Hypoperfusion as a Key Initiator for the Development of Alzheimer Disease. *Pharmaceuticals* (MDPI), **2010**, *3*:158-187.
104. Desler C., Lillenes M.S., Tønjum T., Rasmussen L.J. The Role of Mitochondrial Dysfunction in the Progression of Alzheimer's Disease. *Curr. Med. Chem.*, **2018**, *25*:5578-5587
105. Sweeney G., and Song J. The association between PGC-1α and Alzheimer's disease. *Anat. Cell Biol*. **2016**, *49*:1-6.
106. Donmez G., Arun A., Chung C.Y., McLean P.J., Lindquist S., Guarente L. SIRT1 protects against α-synuclein aggregation by activating molecular chaperones. *J. Neurosci*., **2012**, *32*:124-32.
107. Kim D., Nguyen M.D., Dobbin M.M., Fischer A., Sananbenesi F., Rodgers J.T., Delalle I., Baur J.A., Sui G., Armour S.M., Puigserver P., Sinclair D.A., Tsai L.H. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. *EMBO J*., **2007**, *26*:3169-79.
108. Jeong H., Cohen D.E., Cui L., Supinski A., Savas J.N., Mazzulli J.R., Yates J.R.3rd, Bordone L., Guarente L., Krainc D. Sirt1 mediates neuroprotection from mutant huntingtin by activation of the TORC1 and CREB transcriptional pathway. *Nat. Med*., **2011**, *18*:159-65.
109. Imai S., and Guarente L. NAD+ and Sirtuins in Aging and Disease. *Trends Cell Biol*., **2014**, *24*: 464–471.
110. Roh E., and Kim M.-S. Hypothalamic NAD+-Sirtuin Axis: Function and Regulation. Biomolecules (MDPI), 2020, 10(3):396.
111. Kulkarni S.S., and Cantó C. The molecular targets of resveratrol. Biochim. Biophys. Acta, 2015, 1852:1114-23.
112. Hong S., Zhao B., Lombard D.B., Fingar D.C., Inoki K. Cross-talk between sirtuin and mammalian target of rapamycin complex 1 (mTORC1) signaling in the regulation of S6 kinase 1 (S6K1) phosphorylation. *J. Biol. Chem*., **2014**, *289*:13132-41.
113. Andreux P.A., Houtkooper R.H., Auwerx J. Pharmacological approaches to restore mitochondrial function. *Nat. Rev. Drug Discov*., **2013**, *12*:465-83.
114. Houtkooper R.H., Schoonjans K., Schreiber V., Sauve A.A., Menissier-de Murcia J., Auwerx J. PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. *Cell Metab*., **2011**, *13*:461-468.
115. Grathwol C.W., Wössner N., Swyter S., Smith A.C., Tapavicza E., Hofstetter R.K., Bodtke A., Jung M., Link A. Azologization and repurposing of a hetero-stilbene-based kinase inhibitor: towards the design of photoswitchable sirtuin inhibitors. *Beilstein J. Org. Chem*., **2019**, *15*:2170-2183.
116. Wang Q., Li L., Li C.Y., Pei Z., Zhou M., Li N. SIRT3 protects cells from hypoxia via PGC-1α- and MnSOD-dependent pathways. *Neuroscience*,**2015**, *286*:109-21
117. Meng H., Yan W-Y., Y-H. Lei, Wan Z., Hou Y-Y., Sun L-K., Zhou J-P. SIRT3 Regulation of Mitochondrial Quality Control in Neurodegenerative Diseases. *Front. Aging Neurosci*., **2019**, *11*:313.
118. Park J-H., Burgess J.D., Faroqi A.H., De Meo N.N., Fiesel F.C., Springer W., Delenclos M., McLean P.J. Alpha-synuclein-induced mitochondrial dysfunction is mediated via a sirtuin 3-dependent pathway. *Mol. Neurodegener*., **2020**, *15*:5.
119. Papa L., and Germain D. Sirt3 regulates the mitochondrial unfolded protein response. *Mol. Cell Biol*., **2014**, *34*:699–710.
120. Saunders L.R., and Verdin E. Sirtuins: critical regulators at the crossroads between cancer and aging. Oncogene, 2007, 26:5489-504.
121. Harkcom W.T., Ghosh A.K., Sung M.S., Matov A., Brown K.D., Giannakakou P., Jaffrey S.R. NAD+ and SIRT3 control microtubule dynamics and reduce susceptibility to antimicrotubule agents. *Proc. Natl. Acad. Sci. USA*, **2014**, *111*:E2443–E2452.
122. Haigis M.C., Mostoslavsky R., Haigis K.M., Fahie K., Christodoulou D.C., Murphy A.J., Valenzuela

D.M., Yancopoulos G.D., Karow M., Blander G., Wolberger C., Prolla T.A., Weindruch R., Alt F.W., Guarente L. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic β cells. *Cell*, **2006**, *126*:941-954.

123. Farooqi A.A., Fayyaz S., Poltronieri P., Calin G., Mallardo M. Epigenetic deregulation in cancer: Enzyme players and non-coding RNAs. *Semin. Cancer Biol*., **2020**, Jul 30 Online ahead of print, doi: 10.1016/j.semcancer.2020.07.013

124. Sociali G., Grozio A., Caffa I., Schuster S., Becherini P., Damonte P., Sturla L., Fresia C., Passalacqua M., Mazzola F., Raffaelli N., Garten A., Kiess W., Cea M., Nencioni A., Bruzzone S. SIRT6 deacetylase activity regulates NAMPT activity and NAD(P)(H) pools in cancer cells. *FASEB J*., **2019**, *33*:3704-3717.

125. Mohamad Nasir N.F., Zainuddin A., Shamsuddin S. Emerging Roles of Sirtuin 6 in Alzheimer's Disease. *J. Mol. Neurosci.*, **2018**, *64*:157-161.

126. Beauharnois J.M., Bolívar B.E., Welch J.T. Sirtuin 6: a review of biological effects and potential therapeutic properties. *Mol. Biosyst.,***2013**, *9*:1789-1806

127. Mao Z., Hine C., Tian X., Van Meter M., M. Au, Vaidya A., Seluanov A., Gorbunova V. SIRT6 promotes DNA repair under stress by activating PARP1. *Science*, **2011**, *332*:1443-1446.

128. Rezazadeh S., Yang D., Biashad S.A., Firsanov D., Takasugi M., Gilbert M., Tombline G., Bhanu N.V., Garcia B.A., Seluanov A., Gorbunova V. SIRT6 mono-ADP ribosylates KDM2A to locally increase H3K36me2 at DNA damage sites to inhibit transcription and promote repair. *Aging* (Albany NY), **2020**, *12*:11165-11184.

129. Tasselli L., Zheng W., Chua K.F. SIRT6: Novel Mechanisms and Links to Aging and Disease. *Trends Endocrinol. Metab*., **2017**, *28*:168-185.

130. Van Meter M., Kashyap M., Rezazadeh S., Geneva A.J., Morello T.D., Seluanov A., Gorbunova V. SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nat. Commun*., **2014**, *5*:5011.

131. Rezazadeh, S., Yang, D., Tombline, G., Simon, M., Regan, S.P., Seluanov, A., Gorbunova, V. SIRT6 promotes transcription of a subset of NRF2 targets by mono-ADP-ribosylating BAF170. *Nucleic Acids Res*., **2019**, *47*:7914-7928.

132. Ghosh S., Liu B., Wang Y., Hao Q., Zhou Z. Lamin A Is an Endogenous SIRT6 Activator and Promotes SIRT6-Mediated DNA Repair. *Cell Reports*, **2015**, *13*:1396-1406.

133. Van Meter M., Mao Z., Gorbunova V., Seluanov A. SIRT6 overexpression induces massive apoptosis in cancer cells but not in normal cells. *Cell Cycle*, **2011**, *10*:3153–3158.

134. Miteva Y.V. and Cristea I.M. A Proteomic Perspective of Sirtuin 6 (SIRT6) Phosphorylation and Interactions and Their Dependence on Its Catalytic Activity. *Molecular & Cellular Proteomics* **2014**, *13*:168-183.

135. Simonet N.G., Thackray J.K., Vazquez B.N., Ianni A., Espinosa-Alcantud M., Morales-Sanfrutos J., Hurtado-Bagès S., Sabidó E., Buschbeck M., Tischfield J., De La Torre C., Esteller M., Braun T., Olivella M., Serrano L., Vaquero A. SirT7 auto-ADP-ribosylation regulates glucose starvation response through mH2A1. *Sci. Adv*., **2020**, *6*:eaaz2590.

136. Ryu D., Jo Y.S., Lo Sasso G., Stein S., Zhang H., Perino A., Lee J.U., Zeviani M., Romand R., Hottiger M.O., Schoonjans K., Auwerx J. A SIRT7-dependent acetylation switch of GABPβ1 controls mitochondrial function. *Cell Metab.* **2014**, *20*:856–869.

137. Vazquez B.N., Thackray J.K., Simonet N.G., Kane-Goldsmith N., Martínez-Redondo P., Nguyen T., Bunting S., Vaquero A., Tischfield J.A., Serrano L. SIRT7 promotes genome integrity and modulates non-homologous end joining DNA repair. *EMBO J*., **2016**, *35*:1488–1503.

138. Preyat N., and Leo O. Complex role of nicotinamide adenine dinucleotide in the regulation of programmed cell death pathways. *Biochem. Pharmacol*., **2016**, *101*:13–26.

139. Mellini P., Itoh Y., Elboray E.E., Tsumoto H., Li Y., Suzuki M., Takahashi Y., Tojo T., Kurohara T., Miyake Y., Miura Y., Kitao Y., Kotoku M., Iida T., Suzuki T. Identification of Diketopiperazine -Containing 2-Anilinobenzamides as Potent Sirtuin 2 (SIRT2)-Selective Inhibitors Targeting the "Selectivity Pocket", Substrate-Binding Site, and NAD+-Binding Site. *J. Med. Chem*., **2019**, *62*:5844-5862.

140. Schmeisser K., Mansfeld J., Kuhlow D., Weimer S., Priebe S., Heiland I., Birringer M., Groth M., Segref A., Kanfi Y., Price N.L., Schmeisser S., Schuster S., Pfeiffer A.F.H., Guthke R., Platzer M., Hoppe T., Cohen H.Y., Zarse K., Sinclair D.A., Ristow M. Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. *Nat. Chem. Biol.,* **2013**, *9*:693-700.

141. Chen D., Li L., Diaz K., Iyamu I.D., Yadav R., Noinaj N., Huang R. Novel Propargyl-Linked Bisubstrate Analogues as Tight-Binding Inhibitors for Nicotinamide N-Methyltransferase. *J. Med. Chem*., **2019**, *62*:10783-10797.

142. Pissios P. Nicotinamide N-methyltransferase: more than a vitamin B3 clearance enzyme. *Trends Endocrinol. Metab*., **2017**, *28*:340-353.

143. Yao Z., Yang W., Gao Z., Jia P. Nicotinamide mononucleotide inhibits JNK activation to reverse Alzheimer disease. *Neurosci. Lett*., **2017**, *647*:133-140.

144. Lautrup S., Sinclair D.A., Mattson M.P., Fang E.F. NAD+ in Brain Aging and Neurodegenerative Disorders. *Cell Metab*. **2019**, *30*:630-655.

145. Gilmour B.C., Gudmundsrud R., Frank J., Hov A., Lautrup S., Aman Y., Røsjø H., Brenner C., Ziegler M., Tysnes O.B., Tzoulis C., Omland T., Søraas A., Holmøy T., Bergersen L.H., Storm-Mathisen J., Nilsen H., Fang E.F. Targeting NAD+ in translational research to relieve diseases and conditions of metabolic stress and ageing. *Mech. Ageing Dev*., **2020**, *186*:111208.

146. Hou Y., Lautrup S., Cordonnier S., Wang Y., Croteau D.L., Zavala E., Zhang Y., Moritoh K., O'Connell J.F., Baptiste B.A., Stevnsner T.V., Mattson M.P., Bohr V.A. NAD+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. *Proc. Natl. Acad. Sci. U.S.A.*, **2018**, *115*:E1876-E1885.

147. Guerreiro S., Privat A.L., Bressac L., Toulorge D. CD38 in Neurodegeneration and Neuroinflammation. *Cells* (MDPI), **2020**, *9*:471.

148. Cantó C., Houtkooper R.H., Pirinen E., Youn D.Y., Oosterveer M.H., Cen Y., Fernandez-Marcos P.J., Yamamoto H., Andreux P.A., Cettour-Rose P., Gademann K., Rinsch C., Schoonjans K., Sauve A.A., Auwerx J. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab*. **2012**, *15*:838-47.

149. Conze D., Brenner C., Kruger C.L. Safety and Metabolism of Long-term Administration of NIAGEN (Nicotinamide Riboside Chloride) in a Randomized, Double-Blind, Placebo-controlled Clinical Trial of Healthy Overweight Adults. *Sci. Rep*orts, **2019**, *9*:9772.

150. Garrido A., and Djouder N. NAD+ Deficits in Age-Related Diseases and Cancer. *Trends Cancer*, **2017**, *3*:593-610.

151. Long A.N., Owens K., Schlappal A.E., Kristian T., Fishman P.S., Schuh R.A. Effect of nicotinamide mononucleotide on brain mitochondrial respiratory deficits in an Alzheimer's disease-relevant murine model. *BMC Neurology*, **2015**, *15*:19.

152. Hong W., Mo F., Zhang Z., Huang M., Wei X. Nicotinamide Mononucleotide: A Promising Molecule for Therapy of Diverse Diseases by Targeting NAD+ Metabolism. *Front. Cell Devel. Biol*., **2020**, *8*:246.

153. Jang S.I., Pae H.O., Choi B.M., Oh G.S., Jeong S., Lee H.J., Kim H.Y., Kang K.J., Yun Y.G., Kim Y.C., Chung H.T. Salidroside from *Rhodiola sachalinensis* protects neuronal PC12 cells against cytotoxicity induced by amyloid-beta. *Immunopharmacol. Immunotoxicol*., **2003**, *25*:295-293.

154. Zhang M., and Ying W. NAD+ Deficiency Is a Common Central Pathological Factor of a Number of Diseases and Aging: Mechanisms and Therapeutic Implications. *Antioxid. Redox Signal*., **2019**, *30*:890-905.

155. Escande C, Nin V, Price NL, Capellini V, Gomes AP, Barbosa MT, O'Neil L, White TA, Sinclair DA, Chini EN. Flavonoid apigenin is an inhibitor of the NAD+ ase CD38: implications for cellular NAD+ metabolism, protein acetylation, and treatment of metabolic syndrome. *Diabetes*, **2013**, *62*:1084-1093.

156. Salech F., Ponce D.P., Paula-Lima A.C., SanMartin C.D., Behrens M.I. Nicotinamide, a Poly [ADP-Ribose] Polymerase 1 (PARP-1) Inhibitor, as an Adjunctive Therapy for the Treatment of Alzheimer's Disease. *Front. Aging Neurosci*., **2020**, *12*:255.

157. Ahmad A., Olah G., Herndon D.N., Szabo C. The clinically used PARP inhibitor olaparib improves organ function, suppresses inflammatory responses and accelerates wound healing in a murine model of third-degree burn injury. *Br. J. Pharmacol*., **2018**, *175*:232–245.

158. Berger N.A., Besson V.C., Boulares A.H., Bürkle A., Chiarugi A., Clark R.S., Curtin N.J., Cuzzocrea S., Dawson T.M., Dawson V.L., Haskó G., Liaudet L., Moroni F., Pacher P., Radermacher P., Salzman A.L., Snyder S.H., Soriano F.G., Strosznajder R.P., Sümegi B., Swanson R.A., Szabo C. Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases. *Br. J. Pharmacol*., **2018**, *175*:192-222.

159. Kauppinen T.M., Suh S.W., Higashi Y., Berman A.E., Escartin C., Won S.J., Wang C., Cho S.H., Gan L., Swanson R.A. Poly(ADP-ribose)polymerase-1 modulates microglial responses to amyloid β. *J. Neuroinflammation*, **2011**, *8*:152.

160. Xu D.Q., Li C.J., Jiang Z.Z., Wang L., Huang H.F., Li Z.J., Sun L.X., Fan S.S., Zhang L.Y., Wang T. The hypoglycemic mechanism of catalpol involves increased AMPK-mediated mitochondrial biogenesis. *Acta Pharmacol. Sin*., **2020**, *41*:791-799.

161. Weissig V. DQAsomes as the prototype of mitochondria-targeted pharmaceutical nanocarriers: preparation, characterization, and use. *Methods Mol. Biol*., **2015**, *1265*:1-11.

162. Guzman-Villanueva D., and Weissig V. Mitochondria-Targeted Agents: Mitochondriotropics, Mitochondriotoxics, and Mitocans. *Handb. Exp. Pharmacol*.,**2017**, *240*:423-438.

163. Weissig V. Drug development for the therapy of mitochondrial diseases. *Trends Mol. Med*.,**2020**, *26*:40-57.

164. Skulachev V.P., Anisimov V.N., Antonenko Y.N.., Bakeeva L.E., Chernyak B.V., Erichev V.P., Filenko O.F., Kalinina N.I., Kapelko V.I., Kolosova N.G., Kopnin B.P., Korshunova G.A., Lichinitser M.R., Obukhova L.A., Pasyukova E.G., Pisarenko O.I., Roginsky V.A., Ruuge E.K., Senin I.I., Severina I.I., Skulachev M.V., Spivak I.M., Tashlitsky V.N., Tkachuk V.A., Vyssokikh M.Y., Yaguzhinsky L.S., Zorov D.B. An attempt to prevent senescence: a mitochondrial approach. *Biochim. Biophys. Acta*, **2009,***1787*:437-461.

165. Oliver D.M.A., and Reddy P.H. Small molecules as therapeutic drugs for Alzheimer's disease. *Mol. Cell. Neurosci*., **2019**, *96*:47-62.

166. Stefanova N.A., Muraleva N.A., Skulachev V.P., Kolosova N.G. *J. Alzheimers Dis*., **2014**, *38*:681–694.
167. Szeto H.H., James L.P., Atkinson AJ. Mitochondrial pharmacology: its future is now. *Clin. Pharmacol. Ther*., **2014**, *96*:629-633.
168. Muzzi M., Gerace E., Buonvicino D., Coppi E., Resta F., Formentini L., Zecchi R., Tigli L., Guasti D., Ferri M., Camaioni E., Masi A., Pellegrini-Giampietro D.E., Mannaioni G., Bani D., Pugliese A.M., Chiarugi A. Dexpramipexole improves bioenergetics and outcome in experimental stroke. *Br. J. Pharmacol*., **2018**, *175*:272-283.
169. Menendez J.A. Metformin: Sentinel of the Epigenetic Landscapes That Underlie Cell Fate and Identity. *Biomolecules* (MDPI), **2020**, *10*:780.
170. Hur K.Y., and Lee M.S. New mechanisms of metformin action: Focusing on mitochondria and the gut. *J. Diabetes Investig*., **2015**, *6*:600-609.
171. Yaribeygi H., Atkin S.L., Sahebkar A. Mitochondrial dysfunction in diabetes and the regulatory roles of antidiabetic agents on the mitochondrial function. *J. Cell Physiol*., **2019**, *234*:8402-8410.
172. Vitali E., Boemi I., Tarantola G., Piccini S., Zerbi A., Veronesi G., Baldelli R., Mazziotti G., Smiroldo V., Lavezzi E., Spada A., Mantovani G., Lania A.G. Metformin and Everolimus: A Promising Combination for Neuroendocrine Tumors Treatment. *Cancers* (MDPI), **2020**, *12*:2143.
173. Aliev G., Obrenovich M.E., Tabrez S., Jabir N.R., Reddy V.P., Li Y., Burnstock G., Cacabelos R., Kamal M.A. Link between cancer and Alzheimer disease via oxidative stress induced by nitric oxide-dependent mitochondrial DNA overproliferation and deletion. *Oxid. Med. Cell Longev*., **2013**, *2013*:962984.
174. Roulston A., and Shore G.C. New strategies to maximize therapeutic opportunities for NAMPT inhibitors in oncology. *Mol. Cell Oncol*., **2015**, *3*:e1052180.
175. Bajrami I., Kigozi A., Van Weverwijk A., Brough R., Frankum J., Lord C.J., Ashworth A. Synthetic lethality of PARP and NAMPT inhibition in triple-negative breast cancer cells. *EMBO Mol. Med*., **2012**, *4*:1087-1096.
176. Ullmark T., Montano G., Järvstråt L., Jernmark Nilsson H., Håkansson E., Drott K., Nilsson B., Vidovic K., Gullberg U. Anti-apoptotic quinolinate phosphoribosyltransferase (QPRT) is a target gene of Wilms' tumor gene 1 (WT1) protein in leukemic cells. *Biochem. Biophys. Res. Commun*., **2017**, *482*:802-807.
177. Heske C.M. Beyond Energy Metabolism: Exploiting the Additional Roles of NAMPT for Cancer Therapy. *Front. Oncol*., **2020**, *9*:1514.
178. Kudo K., Nomura M., Sakamoto Y., Ito S., Morita M., Kawai M., Yamashita Y., Ito K., Yamada H., Shima H., Yaegashi N., Tanuma N. Divergent metabolic responses dictate vulnerability to NAMPT inhibition in ovarian cancer. *FEBS Lett*., **2020**, *594*:1379-1388.
179. Lahiguera Á., Hyroššová P., Figueras A., Garzón D., Moreno R., Soto-Cerrato V., McNeish I., Serra V., Lazaro C., Barretina P., Brunet J., Menéndez J., Matias-Guiu X., Vidal A., Villanueva A., Taylor-Harding B., Tanaka H., Orsulic S., Junza A., Yanes O., Muñoz-Pinedo C., Palomero L., Pujana M.À., Perales J.C., Viñals F. Tumors defective in homologous recombination rely on oxidative metabolism: relevance to treatments with PARP inhibitors. *EMBO Mol. Med*., **2020**, *12*:e11217.
180. Zimmermann M., Murina O., Reijns M.A.M., Agathanggelou A., Challis R., Tarnauskaitė Ž., Muir M., Fluteau A., Aregger M., McEwan A., Yuan W., Clarke M., Lambros M.B., Paneesha S., Moss P., Chandrashekhar M., Angers S., Moffat J., Brunton V.G., Hart T., de Bono J., Stankovic T., Jackson A.P., Durocher D. CRISPR screens identify genomic ribonucleotides as a source of PARP-trapping lesions. *Nature*, **2018**, *559*:285-289.
181. Villalba J.M., and Alcaín F.J. Sirtuin activators and inhibitors. *Biofactors*, **2012**, *38*:349-359.
182. Han H., Li C., Li M., Yang L., Zhao S., Wang Z., Liu H., Liu D. Design, Synthesis, and Biological Evaluation of 8-Mercapto-3,7-Dihydro-1H-Purine- 2,6-Diones as Potent Inhibitors of SIRT1, SIRT2, SIRT3, and SIRT5. *Molecules* (MDPI), **2020**, *25*:2755.
183. Barber M.F., Michishita-Kioi E., Xi Y., Tasselli L., Kioi M., Moqtaderi Z., Tennen R.I., Paredes S., Young N.L., Chen K., Struhl K., Garcia B.A., Gozani O., Li W., Chua K.F. SIRT7 links H3K18 deacetylation to maintenance of oncogenic transformation. *Nature*, **2012**, *487*:114–118.
184. Kim J.K., Noh J.H., Jung K.H., Eun J.W., Bae H.J., Kim M.G., Chang Y.G., Shen Q., Park W.S., Lee J.Y., Borlak J., Nam S.W. Sirtuin7 oncogenic potential in human hepatocellular carcinoma and its regulation by the tumor suppressors MiR-125a-5p and MiR-125b. *Hepatology*, **2013**, *57*:1055–1067.
185. Asaba T., Suzuki T., Ueda R., Tsumoto H., Nakagawa H., Miyata N. Inhibition of human sirtuins by in situ generation of an acetylated lysine-ADP-ribose conjugate. *J. Am. Chem. Soc*., **2009**, *131*:6989–6996.
186. Gertz M., and Steegborn C. Using mitochondrial sirtuins as drug targets: disease implications and available compounds. *Cell. Mol. Life Sci*., **2016**, *73*:2871-2896.
187. Hu J., Jing H., Lin H. Sirtuin inhibitors as anticancer agents. *Future Med. Chem*., **2014**, *6*:945-966.
188. Lin Z.F., Xu H.B., Wang J.Y., Lin Q., Ruan Z., Liu F.B., Jin W., Huang H.H., Chen X. SIRT5 desuccinylates and activates SOD1 to eliminate ROS. *Biochem. Biophys. Res. Commun*., **2013**, *441*:191-195.
189. Klein M.A., and Denu J.M. Biological and catalytic functions of sirtuin 6 as targets for small-molecule modulators. *J. Biol. Chem.***2020**, *295*:11021-11041.
190. Heras-Sandoval D., Pérez-Rojas J.M., Pedraza-Chaverri J. Novel compounds for the modulation of mTOR

and autophagy to treat neurodegenerative diseases. *Cell Signal*., **2020**, *65*:109442.
191. Norwitz N.G., and Querfurth H. mTOR Mysteries: Nuances and Questions About the Mechanistic Target of Rapamycin in Neurodegeneration. *Front. Neurosci*., **2020**, *14*:775.
192. Hill C.S., Menon D.K., Coleman M.P. P7C3-A20 neuroprotection is independent of Wallerian degeneration in primary neuronal culture. *Neuroreport*, **2018**, *29*:1544-1549.
193. Henning R.J., Bourgeois M., Harbison R.D. Poly(ADP-ribose) Polymerase (PARP) and PARP Inhibitors: Mechanisms of Action and Role in Cardiovascular Disorders. *Cardiovasc. Toxicol*., **2018**, *18*:493-506.
194. Murai J., Huang S.Y., Das B.B., Renaud A., Zhang Y., Doroshow J.H., Ji J., Takeda S., Pommier Y. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res.***2012**, *72*:5588-5599.
195. Min A. and Im S.A. PARP Inhibitors as Therapeutics: Beyond Modulation of PARylation. *Cancers* (MDPI), **2020**, *12*:394.
196. Xie N., Zhang L., Gao W., Huang C., Huber P.E., Zhou X., Li C., Shen G., Zou B. NAD+ metabolism: pathophysiologic mechanisms and therapeutic potential. *Signal Transduct. Target. Ther*. **2020**, *5*:227.
197. Jęśko H., Wencel P., Strosznajder R.P., Strosznajder J.B. Sirtuins and Their Roles in Brain Aging and Neurodegenerative Disorders. *Neurochem. Res*. **2017**, *42*:876-890.
198. Singh N., Pay S.L., Bhandare S.B., Arimpur U., Motea E.A. Therapeutic Strategies and Biomarkers to Modulate PARP Activity for Targeted Cancer Therapy. *Cancers* (MDPI), **2020**, *12*:972.
199. Gui B., Gui F., Takai T., Feng C., Bai X., Fazli L., Dong X., Liu S., Zhang X., Zhang W., Kibel A.S., Jia L. Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. *Proc. Natl. Acad. Sci. U.S.A.***2019**, *116*:14573-14582.
200. Ekblad T., and Schüler H. Sirtuins are Unaffected by PARP Inhibitors Containing Planar Nicotinamide Bioisosteres. *Chem. Biol. Drug Des.* **2016**, *87*:478-482.
201. Wencel P.L., Lukiw W.J., Strosznajder J.B., Strosznajder R.P. Inhibition of Poly(ADP-ribose) Polymerase-1 Enhances Gene Expression of Selected Sirtuins and APP Cleaving Enzymes in Amyloid Beta Cytotoxicity. *Mol. Neurobiol*. **2018**, *55*:4612-4623.
202. Luo X., and Kraus W.L. A One and a Two … Expanding Roles for Poly(ADP-Ribose) Polymerases in Metabolism. *Cell Metabol*. **2011**, *4*:353-355.
203. Hopp A.K., Grüter P., Hottiger M.O. Regulation of Glucose Metabolism by NAD+ and ADP-Ribosylation. *Cells* (MDPI), **2019**, *8*:890.
204. Vyas S., Chesarone-Cataldo M., Todorova T., Huang Y.H., Chang P. A systematic analysis of the PARP protein family identifies new functions critical for cell physiology. *Nat. Commun.* **2013**, *4*:2240.
205. Vyas S., Matic I., Uchima L., Rood J., Zaja R., Hay R.T., Ahel I., Chang P. Family-wide analysis of poly(ADP-ribose) polymerase activity. *Nat. Commun*. **2014**, *5*:4426.
206. Dharwal V., Sandhir R., Naura A.S. PARP-1 inhibition provides protection against elastase-induced emphysema by mitigating the expression of matrix metalloproteinases. *Mol. Cell. Biochem*.**2019**, *457*:41-49.
207. Jang K.H., Hwang Y., Kim E. PARP1 Impedes SIRT1-Mediated Autophagy during Degeneration of the Retinal Pigment Epithelium under Oxidative Stress. *Mol. Cells*, **2020**, *43*:632-644.
208. Abd Elmageed Z.Y., Naura A.S., Errami Y., Zerfaoui M. The poly(ADP-ribose) polymerases (PARPs): new roles in intracellular transport. *Cell Signal.* **2012**, *24*:1-8.
209. Ghonim M.A. Pyakurel K., Ibba S.V., Wang J., Rodriguez P., Al-Khami A.A., Lammi M.R., Kim H., Zea A.H., Davis C., Okpechi S., Wyczechowska D., Al-Ghareeb K., Mansy M.S., Ochoa A., Naura A.S, Boulares A.H. PARP is activated in human asthma and its inhibition by olaparib blocks house dust mite-induced disease in mice. *Clin. Sci.* (Lond), **2015**, *129*:951-162.
210. Poltronieri P., Xu B., Giovinazzo G. Resveratrol and other Stilbenes: Effects on Dysregulated Gene Expression in Cancers and Novel Delivery Systems. *Anticancer Agents Med Chem.***2020** Jul 5. Epub ahead of print. doi: 10.2174/1871520620666200705220722
211. Hwang E.S., and Song S.B. Nicotinamide is an inhibitor of SIRT1 in vitro, but can be a stimulator in cells. *Cell. Mol. Life Sci.***2017**, *74*:3347–3362.
212. Yanez M., Jhanji M., Murphy K., Gower R.M., Sajish M., Jabbarzadeh E. Nicotinamide augments the anti-inflammatory properties of resveratrol through PARP1 activation. *Sci Rep*. **2019**, *9*:10219.
213. Cantó C., Sauve A.A., Bai P. Crosstalk between poly(ADP-ribose) polymerase and sirtuin enzymes. *Mol. Aspects Med.***2013**, *34*:1168-11201.

Drug	Activity	Therapeutic application	Refs
PARPi (PARP1, PARP2) Olaparib, Rucaparib, Niraparib, Talazoparib FDA/EMA approved Veliparib, completed phase III clin trial	PARP inhibition and trapping on DNA	*BRCA1,BRCA2, ATM, ATR, FANC, PALB2* mutated,HR defective cancers; *RNASEH2B* deleted cancers; HER negative cancers; pretreatment with adjuvant taxanes, or anthracycline	66, 179, 180, 194, 195, 198
PARPi, olaparib	PARP inhibition	Cardiomyocytes protection against oxidative stress, improvement of organ functionality; suppression of inflammatory responses, accelerated wound healing during burn injury; treatment of ALS	154
non-NAD-like PARP-1 inhibitor, 5F02 (no FDA/EMA)	PARP1 inhibition	Prostate cancers (hormone dependent and independent); PARG mutated cancers	70
UPF-1069	selective PARP2 inhibitor	Prostate cancers, block androgen receptor signaling	199, 200
IWR1, AZ-6102 (no FDA/EMA)	Tankyrases: ARTD5-6/PARP5a, b	Wnt-driven cancers	86, 71
ARTD8/PARP14 inhibitors N-(2(-9H-carbazol-1-yl) phenyl)acetamide (GeA-69) (no FDA, EMA)	PARP14 macrodomain 2 inhibitor	Lymphoma, myeloma, therapeutic approach in asthma	92, 98
4-benzyloxybenzimide derivatives (no FDA/EMA)	PARP10/ARTD10 inhibition	Neurodegenerative disorders	81
in progress	ARTD17/PARP6	Colorectal cancer	96,
in progress	ARTD17/PARP16	Various cancers	95, 96
in progress	ARTC1	Various cancers	90

Table 1. PARP/ADP-ribosyltransferases inhibitors and therapeutic targets

Drug	Activity	Therapeutic application	Refs
pan-sirtuin inhibitors	Block NAD^+ binding site, potential for ADP-ribosylation inhibition	In certain types of cancer	112, 181, 182
Selisistat (EX-527), indoles, nicotinamide mimics	Sirt1 deacetylase inhibitor	Passed phase II clinical trials as a disease-modifying therapeutic for early stage Huntington's disease	112
AGK2, AK-1, AK-7, sirtinol, SirReal2, SRT1720, SRT2104	Sirt2 deacetylase inhibitors	reduced α-synuclein-induced cytotoxicity in fruitfly, neuroprotective in Huntington's disease and HD models; SIRT2 inhibition improves neurological and behavioral deficits in a PD model induced by MPTP in old mice; prevent cell death, induce growth arrest in colon cancer	135, 196, 197
diketopiperazine-containing 2-anilinobenzamides double site inhibitors	Sirt2 "selectivity pocket" in substrate-binding site and the NAD^+-binding site	neuroprotective	136
tenovins	Sirt1 inhibitors	chronic myelogenous leukemia (CML), suppressing growth of xenograft tumors derived from human lung and colon cancer	181
cambinol	Sirt1–Sirt2 inhibitor	inducing apoptosis by hyperacetylation of p53 and Bcl-6, in Bcl-6 expressing Burkitt's lymphoma	181
Suramin non-specific sirtuin inhibitor	Sirt1, Sirt5 deacylase inhibitor	bladder cancer, antiproliferative	181
Salermide	Sirt1 and Sirt2	p53-induced apoptosis, epigenetic reactivation of tumor suppressing pro-apoptotic genes	181
thieno[3,2-d]pyrimidine-6-carboxamide derivatives, SDX-437, ELT-31, ELT-11c	Sirt1, 2, 3 inhibitor	inhibiting A549 lung carcinoma and MCF-7 breast carcinoma cell growth	182, 139
thieno[3,2-d]pyrimidine-6-carboxamide-15, indole GW5074, inhibiting peptide3-methyl-3-phenyl-succinyl-CPS1	Sirt5 deacylase inhibitors	Regulation of SOD1 deacylation and growth of a cancer cell line	182, 184
Sirt1 activating compounds (STACs), fisetin (7-3'-4' flavon-3-ol), stilbenes	AMPK1-dependent signaling, regulation of mTOR and autophagy	Increase oxidative phosphorylation and longevity, block PI3K/Akt/mTOR signaling, Sirt1 deacetylase inhibits NF-kB and inflammation	101, 191, 212
Activators: quercetin, cyanidin, fatty acids, polyphenols	Sirt6 modulation	In most cases Sirt6 is a tumor suppressor. When Sirt6 is overexpressed, reduces cancer cell susceptibility to doxorubicin or H2O2	124, 189, 196, 197
PARP inhibitors and NAD boosters to increase SIRT1 activity	PARP1 inhibition, NAD increase restore autophagy mediated by Sirt1	effects on sirtuin levels; protection against diet-induced obesity; NAD boosting effect; protection against retinal pigment epithelial (RPE) degeneration	201, 202, 206
acetylated lysine-ADP-ribose conjugates	Sirt7 inhibition	hepatocellular carcinoma, histone H3K18 deacetylation and oncogenic transformation	183, 184, 185

Table 2. Sirtuins inhibitors and therapeutic targets

Molecule	Activity	Therapeutic potential	Refs
Kynurenine, quinolinic acid, NMN	NAD precursors	preserved mitochondrial integrity in mouse models of AD, neurodegenerative diseases, such as in Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Huntington's disease (HD), protecting from brain ageing, neuronal cell death, age-related pathological processes such as diabetes, ischemia-reperfusion injury, heart failure	26, 62, 143, 151, 152
NR, NRH		clinical trial of healthy overweight adults, AD protection through the induction of autophagy; protected mice against a high fat diet prevent age-related diseases and increase longevity	148, 149
Nicotinic acid	NAD precursor	tumor cells deficient in NAPRT	139
NAM	Supports NAD synthesis, can inhibit PARPs and sirtuins when NAD salvage enzyme levels are low; substrate for NNMT to produce MNAM	treatment of early AD	156, 211
1-methylnicotinamide (MNAM)	Sirt1 regulation, substrate for GAD-3 activity producing H2O2	MNAM activates Sirt1 through deubiquitination; lifespan extension, mitohormetic signaling, protects from lipotoxicity in renal tubular kidney cells, protective compensatory response to injury in skeletal muscle	139, 141, 142
Salidroside	Activates NAPRT and NAPRT signaling pathway (and chaperone role)	protects PC12 cells from $A\beta_{140}$induced cytotoxicity; clear α-sinuclein aggregates by autophagy and mTOR regulation, antiapoptotic effect	153, 190
Quercetin, apigenin, pelargonidin, 78c,	CD38 inhibition	Increase in NAD levels; in obese mice decrease global protein acetylation, and improve several aspects of glucose and lipid homeostasis	155
5-aminoimidazole -4-carboxamide-1-β-d-ribofuranoside (AICAR)	AMPK agonist	higher sirt3 levels, restoring mitochondrial respiration, decrease of α-synuclein oligomers	10
Sirt1 activating compounds (STACs), stilbenes	AMPK1-dependent signaling, regulation of mTOR and autophagy	Increase oxidative phosphorylation, and longevity	101, 191, 212
β-hydroxybutyrate	regulation of mTOR and autophagy	improves brain network stability, a biomarker for brain aging in adults	191

Table 3. NAD, Sirtuins and mTOR regulators with therapeutic potential

Molecule	Activity	Therapeutic potential	Refs
Substrate analogs	NNMT inhibition/regulation	increase of S-adenosyl methionine for epigenetic regulation; treatment of chronic obstructive pulmonary disease (COPD)	142
Substrate analogs	QPRT inhibition	Restore sensitivity to imatinib in WT1 expressing K562 leukemic cells	176
aminopropyl carbazole agents, P7C3-A20; SB-797812; nutrition stress, oxidative stress	NAMPT enzyme activation (through phosphorylation) *NAMPT* expression	neuroprotection in Wallerian degeneration (WD) and SOD1 mouse model for ALS	192, 196
FK-866, CHS-828	NAMPT inhibitor	anti-tumoral properties in various xenograft models, NAMPT-dependent glycolysis in BRCA1 negative ovarian cancers	175, 178
FX-11	LDH inhibitor	effect additive to that obtained with FK866 in reducing the growth of the human P493 B cell line, used as a model for Burkitt's lymphoma	176
PARP inhibitor + NAD salvage activators (P7C3-A20; SB-797812)	activation of myocyte survival enzymes protein kinase B (Akt) and protein kinase C epsilon, restores the myocardial concentrations of NAD+	Acute myocardial infarction, atherosclerosis, coronary disease, heart failure, cardiovascular protection, limits ventricular remodeling and fibrosis, and prevents significant decreases in myocardial contractility; protects cardiomyocytes against oxidative stress, improves functionality in various organs, suppresses inflammatory responses	193 155
PARPi, olaparib	PARP1/PARP2/PARP3 inhibition,	treatment of amyotrophic lateral sclerosis; accelerated wound healing in a murine model of third-degree burn injury	154, 155
PARP inhibitors and NAD boosters	PARP1 inhibition, avoidance of NAD decrease restores autophagy, inhibited by activated PARP1 in oxidative stress	effects on sirtuin levels; protection against diet-induced obesity; increase in NAD levels ; protection against retinal pigment epithelial (RPE) degeneration	201, 202, 206
PARPi	block of PAR-dependent activation of proteases	protection from emphysema in mouse models, decrease matrix metalloproteinases	205
PARPi	allergen triggered asthma	block inflammation, asthma, hyper-responsiveness	209
PARPi	inflammation	inhibition of PARylation of nuclear factor-kappa B (NF-κB), mitigation of inflammation	208
FK-866 + olaparib	Potentiation of PARP inhibition by NAMPT inhibition (NAMPT as a non-redundant modifier of olaparib response)	association of FK866 with olaparib in triple-negative (TN) breast cancers, proposed as adjuvant to ovarian cancers showing NAMPT-dependent glycolysis, in cells defective in BRCA1/BRCA2	179

Table 4. NAD synthesis regulation in disease treatment and in combined therapies

Energy boosters	Activity and targets	Therapeutic potential	Refs
Dexpramipexole	mitochondria	treatment of ischaemic brain injury	169
boosting NAD synthesis (by inhibition of Quinolinic acid pathway)	ACMSD expressed in kidney and liver	protects against acute kidney injury after renal ischemia-reperfusion	196, 197
metformin	Stimulates AMPK, that inhibits mTOR and mTORC1 activity	candidate for an mTOR- targeting therapy for Multiple Sclerosis. Promotingmitochondrial biogenesis, suppress oxidative stress, inhibits oxidative phosphorylation, regulates pleiotropically metabolic hallmarks of ageing, insulin/ILGF-1 and AMPK1/mTOR signaling pathways	191
RTA408(omaveloxolone), an oleanane triterpenoid derivative	Energy production, anti-inflammatory	improves mitochondrial function, increase ATP generation, suppresses uncontrolled inflammatory cellular reaction, suppresses NF-kB pathway, beneficial in Friedreich's ataxia patients, improving neurological functions	163
Dichloroacetate (DCA)	inhibits pyruvate dehydrogenase kinase (PDK)	a metabolic modulator, increases the flux of pyruvate into mitochondria and boosts mitochondrial respiration, ATP generation	163
Mitoquinone (MitoQ, ubiquinoyl decyl triphenylphosponium) MitoTEMPO (SOD mimetic), MitoPBN (coenzyme Q phenyl tertbutylnitrone), MitoVitE, MCAT (catalase), SKQ1 (plastoquinone)	Redox-active compounds	clinical trials for ageing scavengers of free-radicals and improvement of mitochondrial function SKQ1 for treatment of mitochondrial induced oxidative damage in dry eye disease	163 162, 163, 164-166
EPI-743	Redox-active	improvement in disease state and neurological functions, slowing down disease progression	163
Szeto-Schiller (SS) peptide SS-31, MTP-131 tetrapeptide	bind selectively to cardiolipin	Stabilize inner mitochondrial membrane, inhibit membrane swelling, block oxidative cell death	162, 163
Catalpol, iridoid glucoside	Increase in PGC-1α, mitochondrial transcription factor A (TFAM), NRF1 nuclear respiratory factor 1	hypoglycemic; activate AMPK1-dependent mitochondrial biogenesis	163
KL1333 lapachone derivative	increases NAD^+ levels, NADH oxidation by NAD(P)H:quinone oxidoreductase 1	Beneficial in MELAS diseases	163

Table 5. Chemical compounds with energy- and NAD- boosting activity

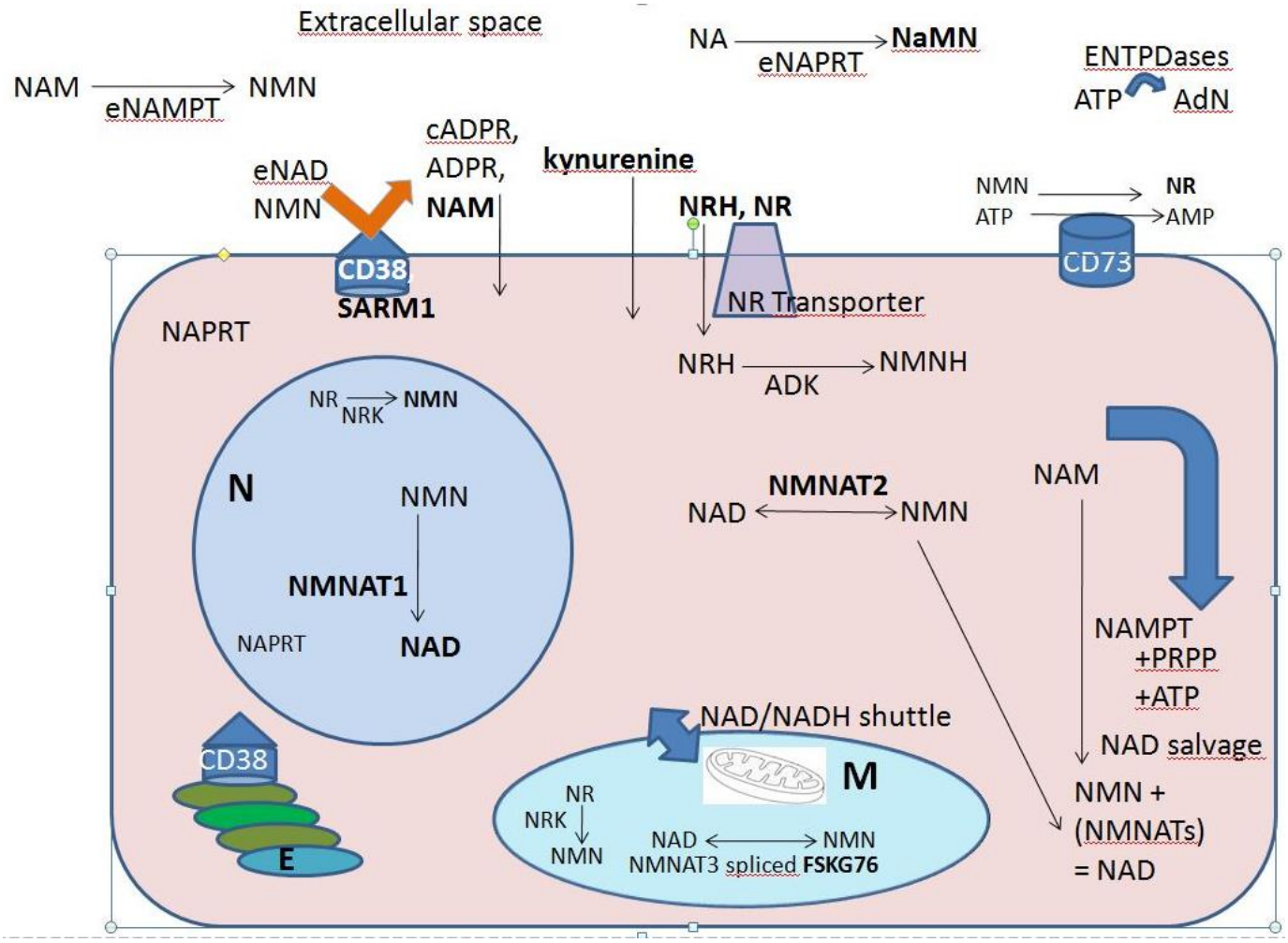
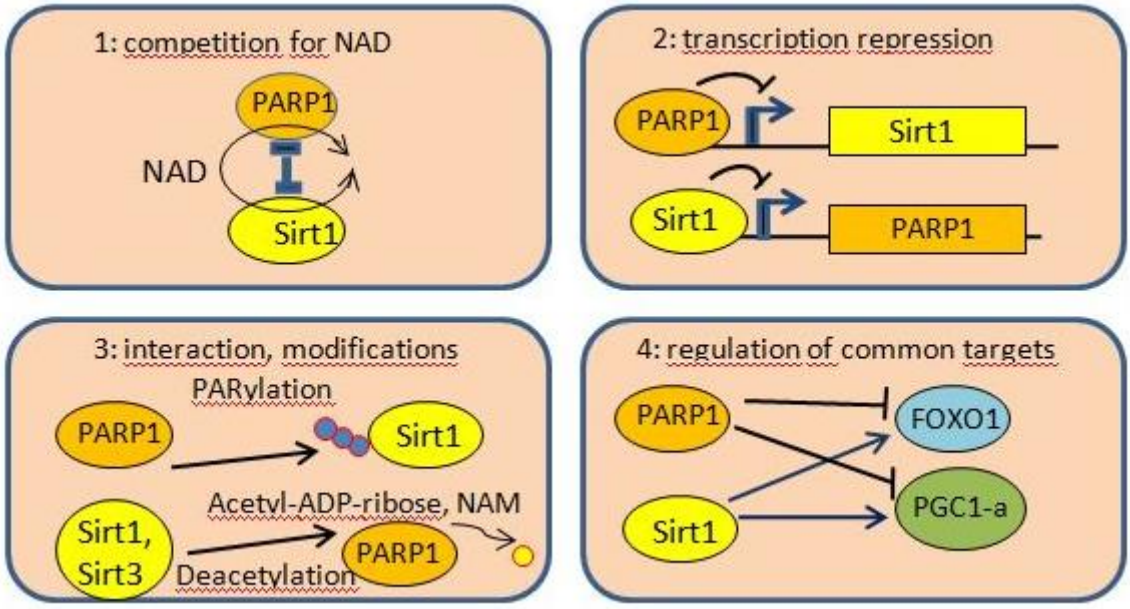


Figure 1. Schematic overview of NAD salvage pathway, NAD precursors and uptake systems. N: Nuclei; M: mitochondria; E: endosome/endoplasmic compartment. Acronyms: NR: nicotinamide riboside; NRH: NR reduced form; NRK: nicotinamide riboside kinase; NA: Nicotinic acid; NAM: nicotinamide; NMN: nicotinamide mononucleotide; NAMPT: nicotinamide phosporibosyltransferase; NaNMN: Nicotinic acid mononucleotide; NAPRT: nicotinic acid phosphoribosyltransferase; NMNATs: nicotinamide mononucleotide adenilyltransferase; ADK: adenosine kinase; CD38: NAD glycohydrolase (ADPR hydrolase); CD73: ecto-5′-nucleotidase.

Figure 2. PARP1/Sirt1 and Sirt3/PARP1 interconnections



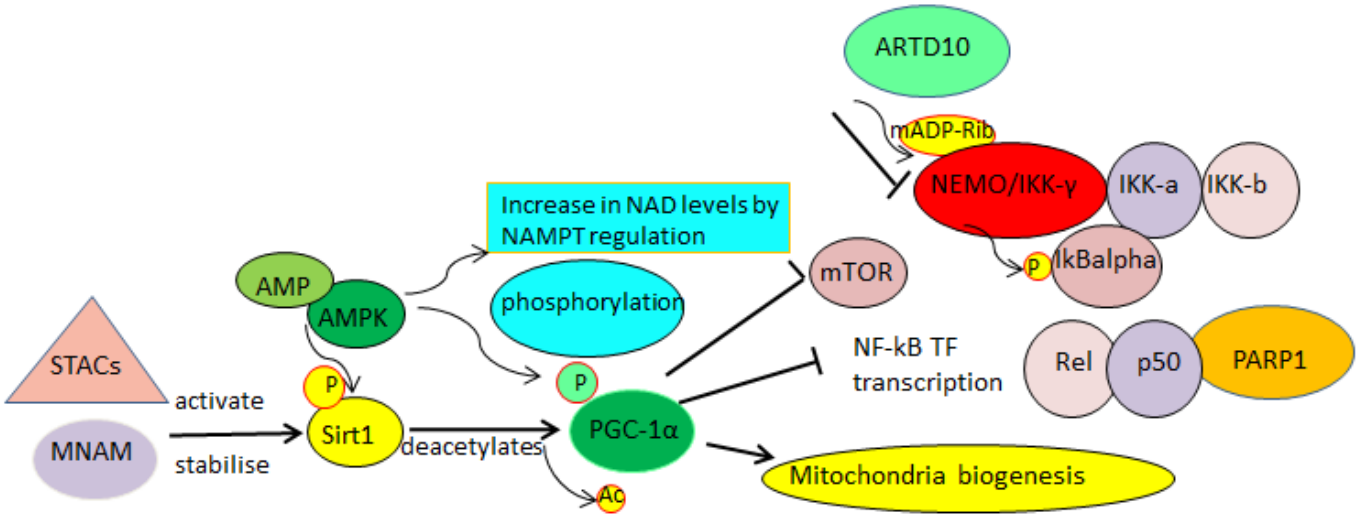


Figure 3. PARP1 and SIRT1 upstream regulators and downstream effectors