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NAD^+ Metabolism in Aging and Cancer

Tyler G. Demarest,[1,2] Mansi Babbar,[1] Mustafa N. Okur,[1] Xiuli Dan,[1] Deborah L. Croteau,[1] Nima B. Fakouri,[1] Mark P. Mattson,[2] and Vilhelm A. Bohr[1]

[1]Laboratory of Molecular Gerontology, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA; email: vbohr@nih.gov

[2]Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA

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Abstract

Aging is a major risk factor for many types of cancer, and the molecular mechanisms implicated in aging, progeria syndromes, and cancer pathogenesis display considerable similarities. Maintaining redox homeostasis, efficient signal transduction, and mitochondrial metabolism is essential for genome integrity and for preventing progression to cellular senescence or tumorigenesis. NAD^+ is a central signaling molecule involved in these and other cellular processes implicated in age-related diseases and cancer. Growing evidence implicates NAD^+ decline as a major feature of accelerated aging progeria syndromes and normal aging. Administration of NAD^+ precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) offer promising therapeutic strategies to improve health, progeria comorbidities, and cancer therapies. This review summarizes insights from the study of aging and progeria syndromes and discusses the implications and therapeutic potential of the underlying molecular mechanisms involved in aging and how they may contribute to tumorigenesis.

INTRODUCTION

Aging is the leading risk factor for many diseases including cancer. Hallmarks of aging (Lopez-Otin et al. 2013) and cancer have recently been proposed (Hanahan & Weinberg 2011). The identification of hallmarks of aging and associated disease states is a key first step toward understanding complex disease processes. Metabolic decline, one hallmark of aging, can lead to obesity, insulin resistance, oxidative stress, DNA damage, and tumorigenesis (Caliskan et al. 2018, Giovannucci et al. 2010, Ligibel 2012, Nawab et al. 2017, Renehan et al. 2008). The underlying molecular mechanisms of this physiological decline are not well understood. The central metabolite, nicotinamide adenine dinucleotide (NAD^+), is emerging as an important aging metabolite that may be a common link between age-related genome instability, metabolic decline, and associated comorbidities such as diabetes, neurodegeneration, and cancer.

Aging and cancer share many common underlying features. For example, genome instability, characterized by an accumulation of oxidative DNA damage combined with a decrease in DNA repair capacity, can lead to the accumulation of mutations that initiate tumorigenesis (Bohr et al. 1998). Recruitment of DNA repair proteins is crucial to repair DNA damage. Following DNA single-strand breaks (SSBs), double-strand breaks (DSBs), and other type of DNA damage, poly(ADP-ribose) polymerases (PARPs) catalyze the poly(ADP-ribosylation) of damaged DNA and proteins as an initial recruitment signal via the consumption of NAD^+. For this reason, PARP1 is often considered a guardian of genome integrity. However, if DNA damage is not repaired, and PARP activation is persistent, declining cellular NAD^+ can impair sirtuin (SIRT) activities, thus altering epigenetic chromatin structure (Fritze et al. 1997) and gene transcription involved in mitochondrial metabolism (reviewed in Fang et al. 2016b). These pathways can lead to mitochondrial dysfunction characterized by increased oxidative stress and decreased energy production in the form of ATP. This can promote inflammation and initiate a feedforward cycle of oxidative stress that exacerbates cellular injury (Bryan et al. 2013). Many hallmarks are shared by physiological aging and cancer pathogenesis (**Figure 1**). We propose that the cellular response to these metabolic perturbations likely dictates whether cells follow the aging pathway toward senescence and apoptosis or initiate uncontrolled proliferation and tumorigenesis. With NAD^+ as the central metabolite connecting these cellular processes, we focus on the roles of the bioenergetics and redox regulation of different NAD^+ species.

NAD^+ BIOSYNTHESIS

NAD^+ metabolism is a dynamic redox cycle that functions to shuttle electrons throughout cells to maintain redox homeostasis and bioenergetics. NAD^+ is synthesized through several pathways discussed in detail in recent reviews (Fang et al. 2017, Yoshino et al. 2017) and summarized in **Figure 2**. De novo synthesis of NAD^+ accounts for a minority of the total NAD^+ pool, while the majority of NAD^+ comes from recycling the NAD^+ breakdown product nicotinamide (NAM) by the salvage pathway enzyme NAM phosphoribosyltransferase (NAMPT) to nicotinamide mononucleotide (NMN) and back to NAD^+ via NMN adenyltransferases 1–3 (NMNATs) (Chiarugi et al. 2012, Nikiforov et al. 2015).

NAD^+/NADH ALTERATIONS IN AGING

Contrary to the notion of a continual decline with age, physiological aging is accompanied by a biphasic shift in basal metabolic rate, which increases from adolescence to adulthood and only begins to decline by around the middle of the second decade of life in humans (Baker & Peleg 2017).

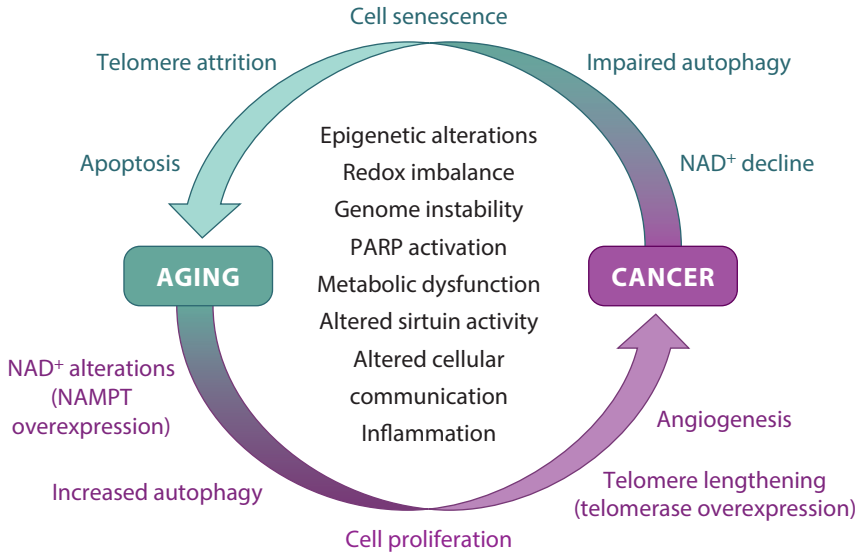

Figure 1

Interactions between hallmarks of aging and cancer. Common underlying cellular processes involved in aging and cancer (*middle*), including alterations in redox state, can initiate oxidative stress leading to genome stability, metabolic dysfunction, and poly(ADP-ribose) polymerase (PARP) activation, which can repair endogenous DNA damage or initiate persistent cellular dysfunction. Chronic PARP activation can deplete cellular nicotinamide adenine dinucleotide (NAD^+) and thus impair sirtuin activity and autophagy, which can lead to further metabolic decline and cell death or senescence, leading to age-related cellular dysfunction (*teal*). On the other hand, following persistent PARP activation, cellular maladaptation can upregulate nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting NAD^+ salvage pathway enzyme, and enhance autophagy and cellular metabolism to promote uncontrolled cellular proliferation and tumorigenesis (*purple*).

While it is still unknown at what age cellular NAD^+ decreases, it has been reported to decline with age in many tissues including liver, skin, muscle, pancreas, and adipose tissue (Fang et al. 2017). Importantly, in the human brain, there is a significant decline in the NAD^+/NADH redox state with age because of the gradual decline in NAD^+, coupled with the gradual increase in NADH (Zhu et al. 2015a). The small decline in NAD^+ with age observed via magnetic resonance spectroscopy, coupled with the increase in NADH (Zhu et al. 2015a), highlights the importance of measuring multiple NAD^+ metabolites to gain insight into age- and disease-associated alterations in redox homeostasis. Moreover, the decline in NAD^+ concomitant with the accumulation of NADH indicates a dysfunction in NAD^+ regeneration, anaerobic glycolysis, or oxidative phosphorylation, which would also result in a reduced capacity to generate ATP. The following sections highlight the interactions between NAD^+ metabolism in the context of aging, progerias, and their involvement in various cancers.

NAD^+ IN PREMATURE AGING DISORDERS AND CANCER

Premature aging syndromes, or progerias, are usually caused by mutations in DNA repair proteins that lead to profound genome instability and the accumulation of mutations. Intriguingly, despite the accumulation of DNA mutations, only some progeria syndromes have a high incidence of cancer (Vermeij et al. 2016). The major progerias include xeroderma pigmentosum (XP), Werner

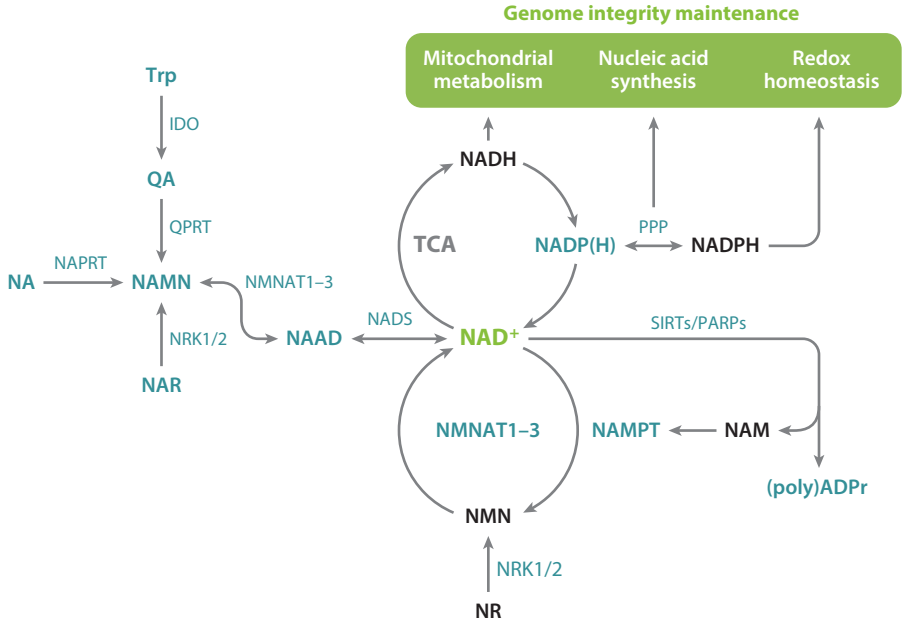

Figure 2

Convergence of nicotinamide adenine dinucleotide (NAD^+) metabolites for genome maintenance. The de novo synthesis of NAD^+ begins from the conversion of dietary precursor tryptophan (Trp) to quinolinic acid (QA) by indoleamine 2,3-dioxygenase (IDO). QA is converted to nicotinamide adenine mononucleotide (NAMN) by quinolinate phosphoribosyl transferase (QPRT). NAMN is also synthesized via nicotinic acid riboside (NAR) by nicotinamide riboside kinases 1 and 2 (NRK1/2) or indirectly via nicotinic acid (NA) by nicotinate phosphoribosyltransferase (NAPRT). NAMN is adenylated to nicotinic acid adenine dinucleotide (NAAD) via nicotinamide mononucleotide adenyltransferases 1–3 (NMNATs) before NAD^+ synthesis via NAD synthetase (NADS). NAD^+ is reduced by tricarboxylic acid (TCA) cycle enzymes to NADH, which acts as the principle electron donor to complex I of the mitochondrial electron transport chain to support mitochondrial metabolism. The corresponding phosphorylated redox pair NADP/NADPH are crucial TCA cycle intermediates that provide reducing equivalents for endogenous antioxidant defense systems to maintain redox homeostasis, while NADPH production via the pentose phosphate pathway (PPP) is critical for nucleotide synthesis. Sirtuins (SIRTs) and poly(ADP-ribose) polymerases (PARPs) consume NAD^+ to produce ADP ribose (ADPr) and nicotinamide (NAM), which is recycled to nicotinamide mononucleotide (NMN) by the salvage pathway enzyme nicotinamide phosphoribosyltransferase (NAMPT) and adenylated to NAD^+ by NMNATs. Nicotinamide riboside (NR) is an NAD^+ precursor that can bypass the NAMPT salvage pathway via conversion to NMN by NRK1/2. These factors converge to prevent DNA damage, facilitate repair of the nuclear genome, and prevent genome instability.

(WRN), Bloom (BLM), Cockayne (CS), and Hutchinson-Gilford (HG) syndromes. Of these, XP, WRN, and BLM have a high incidence of cancer, while no elevated incidence of cancer has been reported in CS and HG patients. CS and XP type A cells have decreased NAD^+ levels, in part due to the persistent activation of PARP1 (Fang et al. 2014, Scheibye-Knudsen et al. 2014). So why does WRN have a high incidence of osteosarcoma, while CS patients do not get cancer? This may be due to the different age of onset of these disorders. WRN and BLM are segmental progerias, with the onset of advanced aging symptoms presenting in the second decade of life, while CS and HG patients exhibit a failure-to-thrive phenotype from birth. CSB can promote cell proliferation via the degradation of p53, and knockdown of CSB sensitizes cancer cells to chemotherapeutic-induced apoptosis (Proietti-De-Santis et al. 2018). Additionally, CS

cells are resistant to UV-induced mutagenesis, which may explain the lack of cancer in CS (Reid-Bayliss et al. 2016). In XP, the accumulation of mutations with UV exposure to sunlight probably contributes to their susceptibility to skin cancer (Bradford et al. 2011). The compounding effect of advanced age in WRN and BLM is likely to be part of the reason an increased incidence of cancer is observed, but this requires further research (Lebel & Monnat 2018).

NAD^+ metabolism has emerged as a potential target for cancer treatments. In cancer, NAD^+ and the major NAD^+ metabolites [e.g., NAD(P)H] participate in multiple physiological processes that can modulate cancer cell metabolism, survival, progression, and invasion. Some of the many enzymes utilizing NAD^+ metabolites as substrates that are involved in various mechanisms of carcinogenesis are reviewed in **Table 1**, and major NAD^+-synthesizing and -consuming enzymes including NAMPT, NMNATs, SIRTs, PARPs, and cluster of differentiation 38 (CD38) are discussed below.

NAMPT IN CANCER

Maintenance of cellular and tissue NAD^+ in healthy cells occurs predominantly via the salvage pathway (Chiarugi et al. 2012). NAMPT is the rate-limiting enzyme of this pathway and is up-regulated in multiple cancer cell lines (Bajrami et al. 2012, Cagnetta et al. 2015, Cea et al. 2012, Hasmann & Schemainda 2003). NAMPT exists in both intracellular (iNAMPT) and extracellular (eNAMPT) forms. Multiple human malignancies exhibit increased NAMPT (extracellular and intracellular) expression, which increases cellular NAD^+ and can enhance many hallmarks of cancer, including proliferation, invasion, angiogenesis, metabolic dysfunction, inflammation, and resistance to apoptosis.

eNAMPT is also known as pre-B cell colony-enhancing factor or visfatin. It is secreted by adipocytes; by immune cells, including lipopolysaccharide-activated monocytes, leucocytes, lymphocytes, pre-B cells, and tumor cells (Grolla et al. 2016); and by cancer cells under nutrient deprivation due to limited blood supply (Zhao et al. 2014), inflammatory response, and cellular stress. Studies report that eNAMPT may act as a growth factor or cytokine; however, the underlying mechanisms and importance of extracellular NAM and NMN synthesis by eNAMPT are not completely understood.

eNAMPT and iNAMPT expressions are increased in numerous malignancies (**Table 1**). High NAMPT (intracellular and extracellular) levels are linked with higher tumor grade, metastasis, and poor survival (Long et al. 2012, Neubauer et al. 2015, Santidrian et al. 2014). These data indicate that higher cellular NAD^+ levels may represent a hallmark for some cancers that promote cancer initiation or progression. This is contrary to aged cells and tissues, which generally display a decline in NAD^+. Due to its many roles in cell health and metabolism, NAMPT has received considerable attention as a potential therapeutic target for cancer treatment.

ANTICANCER EFFECT OF NAMPT INHIBITORS

In the past two decades, inhibition of the salvage NAD^+ biosynthesis pathway has emerged as a potential anticancer strategy. Increased NAMPT expression in some tumors is a biomarker and a therapeutic target for anticancer therapies. GMX1777/CHS828 and APO866/FK866 are well-studied and specific NAMPT inhibitors (NAMPTi) with affinities in the nanomolar range. NAMPT inhibition regulates the expression of multiple genes important for predicting recurrence-free survival and may serve as a prognostic marker in breast and colorectal cancers (Zhou et al. 2014).

To achieve the full potential of NAMPTi, there is a need to identify biomarkers for patients who may respond positively to NAMPTi treatment. As outlined in **Figure 2**, multiple routes of NAD^+

Table 1 Role of NAD(P)(H) metabolism in cancer

Metabolite	Enzymes	Alterations	Cancer types	Physiological effects	References
NAD^+	NAMPT	Overexpression	iNAMPT: Pancreatic ductal adenocarcinoma, oral squamous cell carcinoma, breast cancer, colorectal carcinoma, gastric cancer, endometrial adenocarcinoma, ovarian serous adenocarcinoma, melanoma, myeloma, astrocytoma, thyroid carcinoma, malignant lymphomas, prostate cancer eNAMPT: breast cancer, bladder cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, non-small-cell lung cancer, esophageal cancer, oral squamous cell carcinoma, pancreatic cancer	Increases NAD^+ NAMPT inhibition suppresses Erk activity and causes G2/M cell cycle arrest in glioblastoma multiforme. NAMPT inhibitor–mediated glycolysis suppression is followed by reduced carbon flux through the TCA (tricarboxylic acid) cycle, leading to inhibition of aspartate/alanine and purine/pyrimidine metabolism, which eventually causes cell death. Melanoma cells release NAMPT. This eNAMPT acts as a cytokine, activating MAPK, PI3K/AKT, ERK1/2, STAT3, and NF-κB to support tumor progression and invasion. eNAMPT supports angiogenesis via increased synthesis and secretion of FGF-2 and CCL2 in human mammary epithelial cells and VEGF in human umbilical vein endothelial cells.	Bi et al. 2011; Lu et al. 2014; Nergiz Avcioğlu et al. 2015; Shackelford et al. 2013a,b; B. Wang et al. 2011; G. Wang et al. 2016; X.Y. Wang et al. 2017; Yang et al. 2016
	SIRT1 SIRT5 SIRT6	Overexpression	Colorectal cancer, thyroid cancer, hepatocellular carcinoma, leukemia, lung cancer, osteosarcoma	SIRT1 attenuates p53, PTEN, and E2F1 to avoid stress-mediated apoptosis; stabilizes oncogenes *FOXO1* and PGC1α to boost mitochondrial biogenesis; and increases N-Myc to enhance epithelial-to-mesenchymal transition and cancer cell metastasis. SIRT5 enhances amino acid metabolism and supports cancer cell proliferation. SIRT6 enhances inflammation, angiogenesis, and metastasis in pancreatic cancer. SIRT6 endorses osteosarcoma cell migration and invasion via the ERK1/2–MMP9 pathway.	Chalkiadaki & Guarente 2015, Wang et al. 2018
	SIRT1 SIRT2 SIRT3 SIRT4 SIRT6	Downregulation	Bladder cancer, breast cancer, colorectal cancer, glioblastoma multiforme, liver cancer, lung cancer, prostate cancer, ovarian cancer	SIRT1 inhibits cancer cell proliferation via suppressing β-catenin and survivin signaling. SIRT2 inhibits APC/C (anaphase-promoting complex/cyclosome). SIRT3 downregulation activates HIF1α and induces glycolysis and angiogenesis pathways. SIRT4 and SIRT6 represses glutaminolysis and tumor growth.	Chalkiadaki & Guarente 2015, Lin et al. 2017

(*Continued*)

Table 1 (*Continued*)

Metabolite	Enzymes	Alterations	Cancer types	Physiological effects	References
NAD^+	PARPs	Overexpression	Breast cancer, gastric cancer, melanoma, small-cell lung cancer	PARPs confer protection against anticancer genotoxic drugs. PARP1 boosts cancer cell proliferation by inhibiting the Sp1 signaling pathway. PARP5a enhances telomere elongation.	Green et al. 2015, Y. Liu et al. 2016, Rodriguez et al. 2013, Yang et al. 2013
	NADK	Gain-of-function mutant NADK-I90F	Pancreatic ductal adenocarcinoma	Increases transformation of normal pancreatic ductal cells NADK 10F mutation imparts increased activity to NADK, thereby elevating NADPH levels.	Tedeschi et al. 2016
	IDH3α	Overexpression	Breast cancer, lung cancer	Enhances metabolic reprogramming and angiogenesis via HIF1α activation	Zeng et al. 2015
	ALDH1	Overexpression	Cancer stem cells of lung adenocarcinoma, breast cancer, esophageal cancer, melanoma, and colorectal cancer	Enhances malignant transformation and metastasis and promotes resistance to anticancer chemo(radio)therapy	Clark & Palle 2016
	BRCA1	Downregulation (mutation or promoter methylation)	Breast cancer, ovarian cancer	Suppression modulates cell cycle checkpoint and DNA repair, contributing to genomic instability.	Wang 2012
	MDH2	Overexpression	Prostate cancer, uterine cancer	Confers prostate cancer and uterine cancer cell resistance to docetaxel and doxorubicin, respectively MDH2 inhibition suppresses tumor growth via inhibition of HIF1α, VEGF, and GLUT1 in colorectal cancer cells.	Ban et al. 2016
	NMNAT2	Overexpression	Colorectal cancer	Unknown: increased NAD^+?	Cui et al. 2016
	CD38	Overexpression	Chronic lymphocytic leukemia, prostate cancer	Promotes cancer cell proliferation and migration via activation of ZAP70 and ERK1/2 pathways	Japp et al. 2015, Malavasi et al. 2011
NADH	LDHA	Overexpression, downregulation	Breast cancer, renal cell carcinoma, esophageal squamous cell carcinoma	LDHA promotes the Warburg effect, tumorigenesis, cell growth, cell migration, and lactic acid generation, which aids in cancer cell invasion and metastasis. LDHA downregulation in hepatocellular carcinoma boosts EO9-induced DNA damage apoptosis.	Furuta et al. 2010, Miao et al. 2013

(*Continued*)

Table 1 (*Continued*)

Metabolite	Enzymes	Alterations	Cancer types	Physiological effects	References
$NADP^+$	IDH1 IDH2	Mutations (IDH1 Arg132, IDH2 Arg140 and Arg172)	Gliomas, biliary cancer, leukemia, prostate cancer, colorectal cancer	Produces oncometabolite D-2 hydroxyglutarate; increases nutrient consumption, which supports cancer cell proliferation; stabilizes HIF1α to promote angiogenesis; and suppresses differentiation via the inhibition of HNF4α	Madala et al. 2018, Reitman & Yan 2010, Saha et al. 2014
NADPH	NQO1	Downregulation: loss-of-function polymorphisms (R139W, P187S, and C609T)	Colorectal cancer, digestive tract cancer, esophageal squamous cell carcinoma	Wild-type NQO1 activates AMPK-mediated suppression of the cancer cell–proliferation mTOR/S6K/4E-BP1 pathway.	Lafuente et al. 2000, Lee et al. 2015, Yang et al. 2012, Zhang et al. 2003
		Overexpression	Breast cancer, pancreatic cancer, colorectal cancer, cholangiocarcinoma, uterine cervical cancer, melanoma, lung cancer, adrenal cancer, bladder cancer, liver cancer, ovary cancer, thyroid cancer	Stabilizes HIF1α, promotes redox homeostasis, and is selectively utilized to develop bioreductive anticancer drugs	Oh & Park 2015, Oh et al. 2016
	NOX1	Overexpression	Colorectal cancer	Increases cell proliferation and migration via activation of EGFR/PI3K/AKT and Wnt/β-catenin pathways and suppresses p53 activity via SIRT1 activation	Skonieczna et al. 2017
	NOX2	Overexpression	Gastric cancer	Increases ROS production, contributing to DNA damage and genomic instability	P. Wang et al. 2015
	NOX4	Overexpression	Lung cancer, liver cancer, melanoma, gastric cancer, pancreatic cancer, renal cell carcinoma	Enhances metastasis via TGFβ and JAK2/STAT3 signaling Upregulates AKT, NF-κB, and VEGF in pancreatic cancer to promote cancer survival and angiogenesis Promotes tumor development in chronic myeloid leukemia by activating the PI3K/AKT pathway and inhibiting PP1 phosphatase Regulates HIF2α expression in renal cell carcinoma Targeted using Fulvene-5 in mouse endothelial tumors	Bonner & Arbiser 2012, Gao et al. 2017, Skonieczna et al. 2017

(*Continued*)

Table 1 (*Continued*)

Metabolite	Enzymes	Alterations	Cancer types	Physiological effects	References
NADPH	NOX5	Overexpression	Barrett's esophagus–associated adenocarcinoma, malignant melanoma, prostate cancer, breast cancer, brain cancer, colorectal cancer, lung cancer, ovarian cancer	Activates COX2 and NF-κB signaling in Barrett's esophagus–associated adenocarcinoma	Roy et al. 2015, Si et al. 2007
	ME2	Overexpression	Melanoma, glioblastoma multiforme	Promotes cancer cell proliferation, migration, and invasion by modulating cellular ATP levels, activating AMPK and PI3K/AKT, and inhibiting acetyl-CoA carboxylase and PTEN activity Decrease in ME2 expression has been linked to induction of senescence.	Chang et al. 2015, C.P. Cheng et al. 2016
	G6PDH	Overexpression	Cervical cancer, melanoma, breast cancer, colorectal cancer, endometrial cancer, cervical cancer, prostate cancer, lung cancer	Accelerates the pentose phosphate pathway (PPP), and therefore nucleotide precursor and NADPH synthesis, thereby facilitating DNA replication/repair and redox homeostasis Aids tumorigenesis and angiogenesis in NIH3T3	Furuta et al. 2010

Abbreviations: ALDH, aldehyde dehydrogenase; BRCA, breast cancer; CD38, cluster of differentiation 38; CYP, cytochrome P450 reductase; eNAMPT, extracellular NAMPT; G6PDH, glucose-6-phosphate dehydrogenase; HIF1α, hypoxia-inducible factor 1 alpha; IDH, isocitrate dehydrogenase; iNAMPT, intracellular NAMPT; LDH, lactate dehydrogenase; MDH, malate dehydrogenase; ME, malic enzyme; NAD^+, nicotinamide adenine dinucleotide; NADK, NAD^+ kinase; NAMPT: nicotinamide phosphoribosyltransferase; NMNAT, nicotinamide mononucleotide adenylyltransferase; NOX, NADPH oxidase; NQO1, NAD(P)H quinone oxidoreductase; PARP, poly(ADP-ribose) polymerase; ROS, reactive oxygen species; SIRT, sirtuin.

biosynthesis may make NAMPTi particularly useful in certain cancer types that primarily rely on the salvage pathway. Accordingly, studies have reported that patients with increased NAMPT expression are more sensitive to NAMPTi. For example, *isocitrate dehydrogenase 1* (*IDH1*)-mutant cancers also show increased sensitivity to NAD^+ depletion (Tateishi et al. 2015). Mutant *IDH1* downregulates the Preiss-Handler pathway's enzyme nicotinate phosphoribosyltransferase, resulting in reduced NAD^+ levels and increased sensitivity to NAMPTi. Various oncogenic signals are also associated with increased NAMPT or NAD^+ levels. For instance, activation of the oncogene c-*Myc* increases NAMPT messenger RNA (mRNA) transcription, which may facilitate tumor progression in cancers (Menssen et al. 2012).

Various clinical trials have been conducted to exploit the antitumor potential of NAMPT inhibition; however, this approach has thus far shown low efficacy and high toxicities. Oral and intravenous administration of NAMPTi are associated with various toxicities, including thrombocytopenia, skin rash, lymphopenia, and gastrointestinal effects such as esophagitis, diarrhea, and vomiting. Reduced efficacy of NAMPTi may be attributed to increased NAD^+ biosynthesis via the de novo or Preiss-Handler pathways. Therefore, targeting the NMNATs as the final step in NAD^+ synthesis may represent a more effective and targeted approach for NAD^+ depletion in tumor cells.

NMNATs

Mammalian cells have three isoforms of NMNATs (NMNAT1–3), which are localized to the nucleus (NMNAT1), the cytoplasmic membrane of the Golgi apparatus (NMNAT2), and the mitochondria (NMNAT3) (Lau et al. 2010). While NAMPT has been considered the rate-limiting step of the NAD^+ salvage pathway, it is important to note that NAD^+ production from any of the biosynthetic pathways requires NMNATs as the terminal step for NAD^+ synthesis (Buonvicino et al. 2018). NMNATs have been predominantly studied for their neuroprotective role in axonal degeneration in the central nervous system (CNS) (Ali et al. 2013). Interestingly, NMNAT2, which is cytoplasmic and highly expressed in the CNS, was recently demonstrated to contribute to both the cytoplasmic and mitochondrial NAD^+ pools (Cambronne et al. 2016). This means that mitochondrial NAD^+ is critically important to maintain cell health in the CNS. Moreover, NMNAT2 mRNA levels have been reported to decline in models of Alzheimer's disease and precede neurodegeneration (Ljungberg et al. 2012), while a single-nucleotide polymorphism in NMNAT3 has been identified in a Dutch cohort of familial Alzheimer's disease (Liu et al. 2007).

In contrast to the decline in NMNAT expression implicated in age-related neurodegenerative diseases, NMNAT2 overexpression has been reported in colorectal cancer (Cui et al. 2016), melanoma, and neuroblastoma (Buonvicino et al. 2018). Therefore, targeting NMNATs could be more efficacious than targeting upstream NAMPT. Indeed, recent reports indicate that an NAD^+ analog called Vacor inhibits NAD^+ synthesis and potentiates cytotoxicity by targeting NAMPT and NMNAT2/3 in melanoma and neuroblastoma cell lines (Buonvicino et al. 2018). These results support the development of specific NMNAT inhibitors as a potentially useful clinical treatment option for cancers overexpressing multiple pathways of the NAD^+ synthesis machinery.

PARPs

PARP1–3 are major NAD^+ consumers, with PARP1 being the best understood. PARPs are involved in DNA damage repair, chromatin modification, transcription regulation, inflammation, cell death, and energy metabolism (reviewed in Dulaney et al. 2017). PARPs require NAD^+ as a substrate to generate poly(ADP-ribose) (PAR) polymers and NAM at sites of DNA damage.

PARPs are initiating components of the cellular stress response that are activated immediately following DNA damage to recruit components of the DNA repair machinery. PARP1 is involved in SSB and DSB repair by promoting the homologous recombination (HR) pathway over the error-prone nonhomologous end joining (NHEJ) pathway. For example, PARP1 activity is required for the recruitment of BRCA1 to repair DSBs via HR (Li & Yu 2013). However, in the absence of BRCA1, such as in many breast cancers, the inability to repair DNA via HR activates alternative NHEJ, which promotes the accumulation of mutations and eventual tumorigenesis.

Increases in PARP activity have been linked to both the suppression and the progression of tumorigenesis. This discrepancy may be due to PARPs' role in DNA repair, which may prevent mutation accumulation and cancer formation, but may also aid in cancer cell survival following tumor initiation. For example, high-PARP expression in patients with breast cancer (Green et al. 2015), gastric cancer (Y. Liu et al. 2016), melanoma (Rodriguez et al. 2013), and small-cell lung cancer (Kim et al. 2014) is linked with poor prognosis, whereas pancreatic cancer patients with high PARP expression exhibit improved survival (Klauschen et al. 2012). Thus, the activation of PARPs may be beneficial in pancreatic cancer, whereas inhibition of PARPs would be beneficial in other cancers.

PARP inhibitors (PARPi) represent a suitable strategy in cancer therapy when tumors are defective in HR DNA repair (i.e., loss of BRCA1 and BRCA2). Accordingly, several PARPi have reached late-stage clinical trials, and olaparib is currently approved by the US Food and Drug Administration (FDA) for the treatment of BRCA-deficient cancers (Dulaney et al. 2017). Tumor cells that lack BRCA1 are extremely dependent on repair via Polθ and alternative NHEJ for their survival (Ceccaldi et al. 2015). PARPi kill tumor cells in several different ways: (*a*) PARPi can cause synthetic lethality due to increased SSB formation during DNA replication, which can proceed to DSBs that cannot be repaired (Bryant et al. 2005); (*b*) PARP may be "trapped" on the DNA to physically impede the DNA repair machinery; and (*c*) PARPi can facilitate death by mutation accumulation due to the reliance on error-prone NHEJ. Thus, PARP1 inhibition limits the ability of tumor cells to repair DNA and proliferate when they bear mutations rendering them defective in HR (Dulaney et al. 2017). The future development of combination therapies with PARPi and other strategies to impair PARP activity with less toxicity will hopefully improve the efficacy and tolerability of PARPi treatment in cancer patients.

SIRTUINS

SIRTs were first identified as major determinants of lifespan (Tissenbaum & Guarente 2001) that are required for the robust life extension afforded by calorie restriction in multiple species [reviewed by Guarente (2005), Lin & Guarente (2003), Minor et al. (2010), and Sinclair (2005)]. There are currently seven SIRT isoforms (SIRT1–7), identified with different subcellular localizations (e.g., SIRT3–5 are mitochondrial) and functions [reviewed by Houtkooper et al. (2012) and Imai & Guarente (2014)]. SIRTs require NAD^+ as a cosubstrate to posttranslationally modify target proteins, producing ADP-ribose and NAM. Evidence demonstrates that SIRTs have dual roles in cancer and may function as tumor suppressors or initiate tumorigenesis (Song & Surh 2012). Mechanistically, most SIRT isoforms deacetylate proteins including histones and modulate the transcription of key genes, including the master regulator of mitochondrial biogenesis, PGC1α. SIRT1 also directs cell cycle progression by modulating p53 activity via deacetylation. Since SIRT activity is known to decline with age, likely as a result of declining NAD^+, the loss of SIRT-mediated tumor suppressor function may be a critical step leading to tumorigenesis. On the other hand, SIRT1 is overexpressed in multiple malignancies (**Table 1**). Activated SIRT1 diminishes tumor suppressors such as p53, PTEN, and retinoblastoma protein and stabilizes

oncogenes such as *MYCN* to enhance epithelial-to-mesenchymal transition and cancer cell metastasis (Shackelford et al. 2013b). SIRT2 is overexpressed in numerous cancers including prostate, colorectal, and hepatocellular carcinoma (Cheng et al. 2018, Yang et al. 2017). Mechanistically, SIRT2 has been demonstrated to deacetylate and activate glucose-6-phosphate dehydrogenase, thereby enhancing NADPH production and promoting cancer cell proliferation (Xu et al. 2016).

SIRT3–5 are located in mitochondria, where they play numerous roles in mitochondrial metabolic regulation. For example, SIRT3 has been identified as an essential mediator of some of the beneficial effects of caloric restriction (Qiu et al. 2010) and adaptive responses to energetic challenges in the brain (A. Cheng et al. 2016). Mechanistically, SIRT3 deacetylates IDH2 (Yu et al. 2012) and superoxide disumutase 2 (Liu et al. 2017), resulting in the increased production of NADPH for reactive oxygen species (ROS) detoxification. Accordingly, *SIRT3* modulation has been implicated as an oncogene and tumor suppressor in cancer (reviewed in Torrens-Mas et al. 2017). Similarly, SIRT4 has also been identified as a deacetylase that acts as a tumor suppressor in numerous malignancies (Zhu et al. 2014).

SIRT5 is unique among sirtuins in that it is a very weak deacetylase, but it acts predominantly as a lysine desuccinylase, demalonylase, and deglutyrase for the modulation of numerous mitochondrial metabolic enzymes (Zhang et al. 2017). The diverse roles for SIRT5 in metabolic reprogramming in cancer have been recently reviewed (Bringman-Rodenbarger et al. 2018). In brief, SIRT5 is generally overexpressed in tumor tissues relative to native normal tissues, and it demalonylates GAPDH and other glycolytic enzymes, resulting in elevated energy production via glycolysis (Nishida et al. 2015). SIRT5 also interacts with and regulates numerous TCA (tricarboxylic acid) cycle enzymes via desuccinylation including mitochondrial complex I (NADH dehydrogenase) (Marcon et al. 2015), complex II (succinate dehydrogenase) (Park et al. 2013), and IDH2 (Zhou et al. 2016).

SIRT6 deacetylase activity modulates DNA repair in telomeres and participates in nuclear DSB repair by recruiting PARP1 to DNA breaks (McCord et al. 2009, Michishita et al. 2008, Van Meter et al. 2016). SIRT6 also participates in base excision repair to remove oxidatively damaged DNA (Mostoslavsky et al. 2006). Accordingly, transgenic SIRT6-overexpressing mice display several health benefits including increased lifespan, improved glucose tolerance, and reduced adipose inflammation (Roichman et al. 2017). This suggests that SIRT6 has important roles in genome integrity maintenance and metabolic programming. The role of SIRT6 in cancer has recently been reviewed (Dong et al. 2016). Intriguingly, conflicting results have shown that SIRT6 is overexpressed or downregulated depending on cancer type (**Table 1**), and this therefore requires further investigation.

SIRT7 has been implicated in aging and cancer physiology but is relatively poorly characterized. This may be due to the relatively low enzyme activity of SIRT7. Despite the limitations in our current understanding of SIRT7, it is thought to play a role in RNA metabolism by regulating RNA polymerase expression and is localized to the nucleoli, where ribosomal RNA is transcribed (Ford et al. 2006). Like other SIRTs, SIRT7 plays a key role in metabolic regulation. For example, SIRT7-knockout mice develop fatty liver disease, and overexpression of SIRT7 can reverse these effects (Yoshizawa et al. 2014). Increasing our understanding of SIRT7 regulatory mechanisms may provide insight into mechanisms of metabolic dysregulation in age-related disorders and comorbidities like cancer.

Overall, the involvement of many SIRT isoforms highlights the complex relationships between the epigenetic modulation of cellular transcription, cell cycle progression, and metabolic regulation. Importantly, these processes are nearly all influenced by NAD^+ bioavailability and posttranslational modifications of key metabolic enzymes. Since SIRTs play numerous crucial roles in the aging process, future research should focus on understanding the SIRT-mediated

regulation of metabolic pathways in relation to age-related diseases and the proclivity for cancer development and progression.

CD38 IN AGING AND CANCER

CD38 is an NAD^+-consuming ectoenzyme originally discovered for its extracellular role in innate immune activation. Emerging evidence demonstrates that CD38 is the major enzyme responsible for NAD^+ decline in physiological aging (Camacho-Pereira et al. 2016). CD38-knockout mice have elevated NAD^+ levels in multiple tissues (Camacho-Pereira et al. 2016, Sahar et al. 2011, Young et al. 2006). Contrary to the idea that elevated NAD^+ may facilitate cancer formation, CD38 knockout impedes tumorigenesis and halts the progression of lung cancer in murine models (Bu et al. 2018). This implicates a tumorigenic role for CD38 in inflammatory immune system activation. Indeed, low-CD38 expression has been associated with proinflammatory prostate cancer cells (X. Liu et al. 2016). Moreover, recent research also proposes that CD38 is a diagnostic marker for aggressive prostate cancer (Sahoo et al. 2018) and is involved in the pathophysiology of other cancers such as multiple myelomas (Chini et al. 2018). Accordingly, the FDA has approved the monoclonal antibody targeted to CD38, daratumumab, for the treatment of patients with relapsed or refractory multiple myeloma (Raedler 2016). These data suggest a role for CD38 modulation of the immune response in cancer development/progression, a possibility that requires further research.

METABOLIC AND MITOCHONDRIAL (DYS)FUNCTION IN AGING AND CANCER

Mitochondrial metabolism declines with age, and cells may adapt by utilizing alternative biofuels depending on local bioavailability within the given cellular and tissue environment. Cell fate is largely determined by mitochondria, which dictate whether cells survive or die by necrotic or apoptotic cell death pathways. Mitochondria can initiate cell death through the release of apoptosis-inducing factor (AIF) or cytochrome c, which initiates the formation of the apoptosome and caspase activation. Intriguingly, AIF release is downstream of persistent PARP activation, in which PAR polymer accumulation can permeabilize the outer mitochondrial membrane that results in cell death known as parthanatos (Andrabi et al. 2008).

If cells enduring age-related metabolic decline do not die, they could persist in a metabolically dysfunctional state or they may exit the cell cycle and enter senescence (discussed in detail below). If cells persist in a dysfunctional state, they could initiate a maladaptive metabolic switch toward the utilization of glucose and upregulate NAD^+ synthesis pathways, which initiates a series of incompletely understood events that may initiate tumorigenesis. Since there are a myriad of metabolic signaling pathways modulated by NAD^+ metabolites, we focus on the roles of other NAD^+ metabolites as putative determinants of aging and cancer.

NADH

NAD^+ is reduced to NADH by pyruvate dehydrogenase and the TCA cycle enzymes malate dehydrogenase and α-ketoglutarate dehydrogenase (αKGDH). NADH acts as the principle electron donor to complex I (NADH dehydrogenase) of the mitochondrial electron transport chain to support mitochondrial oxidative phosphorylation to generate ATP. Mitochondrial function, including complex I function, declines with age (Stefanatos & Sanz 2011). The resulting decline in NAD^+/NADH redox state has been reported to initiate a pseudohypoxic state that upregulates many oncogenic signaling pathways such as the canonical hypoxia-inducible factor 1 alpha

(HIF1α) pathway (Gomes et al. 2013). HIF1α can upregulate the expression of many stress response genes such as vascular endothelial growth factor, which promotes angiogenesis and can provide nutrients to malignant cells and encourage metastasis. Moreover, the production of more NADH may force cells to rely on glycolysis via NADH utilizing the enzyme lactate dehydrogenase to produce lactate and also regenerate NAD^+. This characteristic Warburg shift in metabolism promotes tumorigenesis (Warburg 1956).

Lactate dehydrogenase (LDH) is encoded by two genes, *LDHA* and *LDHB*. The gene products of *LDHA* and *LDHB* combine to form five isozymes of tetrameric LDH. Tetrameric structures containing a majority of LDHA proteins primarily drive the forward reaction, reducing pyruvate to lactate by consuming NADH to regenerate NAD^+. Isozymes containing the majority of LDHB proteins catalyze the reverse reaction (Ross et al. 2010). Elevated lactate is observed with aging and has been proposed to be a hallmark of the aging process (Houtkooper et al. 2011, Ross et al. 2010). Since LDH is a critical component of anaerobic glycolysis and the Warburg shift is a key observation in cancer cells, it is not surprising that LDH is also overexpressed in several forms of cancer (Furuta et al. 2010). Elevated LDH has also been associated with poor prognosis for cancer patients (Thonsri et al. 2017). Increased NADH production implies a mitochondrial deficit; however, many TCA cycle enzymes also act as NAD(P)H redox cycling enzymes and are implicated in aging and cancer development.

NADPH

NADPH is an essential TCA cycle intermediate for endogenous antioxidant defense systems (e.g., glutathione and thioredoxin peroxidase systems) to maintain redox homeostasis. As a substrate for many important enzymes, NADPH is involved in the regulation of cell growth, differentiation, antioxidant systems, immune cell activation, and nucleic acid synthesis. NADPH production via the pentose phosphate pathway is critical for nucleotide synthesis support of DNA replication and repair. Given that NADPH plays numerous crucial roles in maintaining metabolic homeostasis, perturbations in NADPH redox state and mutations in NADP(H)-dependent enzymes are associated with age-related pathologies and cancer.

Isocitrate Dehydrogenases

IDH1 and IDH2 reduce $NADP^+$ to NADPH to catalyze the decarboxylation of isocitrate to α-ketoglutarate (αKG) in the TCA cycle. IDH1 and IDH2 are commonly mutated in gliomas at sites Arg132 and Arg140/172, respectively. Mutations at the arginine residue alters substrate (isocitrate) binding to the enzyme's active site, which results in a decline in αKG. Intriguingly, mutant IDH isoforms produce oncometabolite D-2 hydroxyglutarate (2-HG) using NADPH as a substrate, resulting in reduced αKG levels and an altered NADP/NADPH redox ratio. Corresponding increases in 2-HG inhibit αKG-dependent dioxygenases, including prolyl hydroxylase (PHD), which promotes the stabilization of HIF1α. The phenomenon where alterations in redox state or TCA cycle activity occurs has been described as pseudohypoxia (Gomes et al. 2013, MacKenzie et al. 2007). Interestingly, the addition of a cell-permeable derivative of αKG can reverse the pseudohypoxic state by reactivating the degradation of HIF1α by PHD (MacKenzie et al. 2007).

The consumption of NADPH by IDH may also compromise endogenous antioxidant defense systems, resulting in more oxidatively damaged proteins, lipids, and DNA (Madala et al. 2018). Therefore, elevated oncometabolite 2-HG levels may serve as a diagnostic and prognostic marker, specifically in gliomas. Enasidenib, an IDH2-R140Q and IDH2-R172H inhibitor, is currently used as a treatment for acute myeloid leukemia, and glioma-specific vaccines targeting

IDH1-R132H are also in clinical trials (Madala et al. 2018). Since IDH mutations result in diminished NADPH for antioxidant defense enzymes and αKG levels, downstream αKGDH function may also be compromised; the resulting redox imbalance and HIF1α stabilization can facilitate tumorigenesis and could serve as a promising therapeutic target.

α-Ketoglutarate Dehydrogenase

αKGDH reduces NAD^+ to NADH for the decarboxylation of α-ketoglutarate to succinyl-coenzyme A, the precursor to succinate, which is the principle substrate for cellular energy generation at mitochondrial complex II (succinate dehydrogenase). Intriguingly, supplementation with αKG has been demonstrated to extend lifespan in *Caenorhabditis elegans* by as much as 50% (Chin et al. 2014). Lifespan extension by αKG was mediated by a reduction in cell metabolic rate via the inhibition of ATP synthase and the activation of autophagy (Chin et al. 2014). Moreover, αKGDH dysfunction is implicated in age-related pathology such as neurodegenerative disorders (Gibson et al. 2005). This may be because αKGDH has been identified as a major source of ROS generation (Starkov et al. 2004) and plays an important role in regulating cancer cell metabolic plasticity (Vatrinet et al. 2017).

αKGDH has been reported to possess ADP-ribosyltransferase activity (Pankotai et al. 2009) and therefore may act within the mitochondria to regulate metabolic activities through post-translational modifications. Despite the observation of polyADP-ribosylation in mitochondrial extracts (Lai et al. 2008, Masmoudi & Mandel 1987) and PARP localization to the mitochondria (Rossi et al. 2009, Du et al. 2003), the presence of a mitochondrial PARP isoform remains controversial. Given the role of αKGDH in generating substrates necessary for mitochondrial energy metabolism, the production of ROS, and the potential ADP-ribosyltransferase activity of αKGDH, more attention is warranted to the role and putative therapeutic value of targeting αKGDH and αKG in the regulation of age-related pathologies and cancer.

AUTOPHAGY, MITOPHAGY, AND NAD^+

Autophagy is activated in response to nutrient deprivation, via inhibition of the mTOR pathway, to recycle damaged cellular components to amino acid building blocks, while mitophagy may be triggered in nutrient-rich conditions to remove damaged mitochondria that adversely affect cell health (Youle & Narendra 2011). Accumulating evidence advocates that rates of autophagy and mitophagy decline with age (Fang et al. 2017, Moreira et al. 2017, Shi et al. 2017). NAD^+ precursor treatment may improve age-related pathology by restoring autophagy/mitophagy (Fang et al. 2014, 2016a; Kerr et al. 2017; Lin & Qin 2013; Scheibye-Knudsen et al. 2014). Intriguingly, an excellent review detailing the role of autophagy in cancer reports that the initiation of cancer occurs under conditions where autophagy is also compromised (Santana-Codina et al. 2017). This indicates that the decline in autophagy observed during aging may be a key factor that predisposes aged individuals to cancer. Following cancer cell initiation, autophagy is vastly upregulated to provide the amount of amino acids and nutrients required to support uncontrolled cellular proliferation (Kimmelman & White 2017, Santana-Codina et al. 2017). Interestingly, malignant cells not only upregulate autophagy to meet these bioenergetic needs but also have been reported to sequester extracellular metabolites through a process known as macropinocytosis. Collectively, these data imply that the metabolic adaption in response to the aging process may dictate cell fate and represent a therapeutic opportunity to treat age-related diseases and cancer.

Mitochondrial quality control, the balance between mitochondrial biogenesis and mitophagy, is critical to maintain cellular energy and redox homeostasis. The turnover of damaged

mitochondria helps prevent excessive generation of ROS, which protects the nuclear and mitochondrial genome from DNA damage, thus preventing DNA mutations and promoting cell survival under energetic stress (Chourasia et al. 2015). Research from the Finkel group demonstrated that mitophagy drastically declines in the hippocampus with age (Sun et al. 2015). Since neuronal activity is bioenergetically demanding, the age-dependent decline in mitophagy may contribute to metabolic decline and neurodegeneration. Contrarily, diminished mitochondrial function combined with an increase in oxidative damage may promote a metabolic shift toward glycolysis, which could predispose aged tissues toward tumorigenesis. Importantly, mitophagy has been shown to promote mitochondrial health in age-related disorders (Ryu et al. 2016). Interestingly, two main regulatory proteins of mitophagy, parkin and NIX/BNIP3L, are frequently deleted or silenced in a variety of human cancers (Springer & Macleod 2016), implying that the induction of mitophagy may represent a therapeutic strategy to help restore a healthy mitochondrial pool and improve metabolic dysfunction in aging and cancer.

SENESCENCE AND NAD^+

As we age, senescent cells accumulate and wreak havoc in our body. Senescent cells are metabolically active but irreversibly cell cycle–arrested cells that degrade organ function, promote inflammation, and have both pro- and anticancer properties. Senescent cells are also a hallmark of aging (Lopez-Otin et al. 2013). They secrete proinflammatory markers, extracellular matrix proteases, and chemokines to surrounding cells, and collectively this phenotype is called secretory-associated senescence phenotype (SASP) (Coppe et al. 2010). SASP promotes cancer and aging. There are many stimuli that encourage the development of senescent cells, including oncogene expression, DNA damage exposure, replication stress, telomere erosion, and mitochondrial dysfunction (van Deursen 2014, Wiley et al. 2016). Senescent cells also display a protective role because cells can enter a senescent state after DNA damage, and this represents a major tumor-suppressor mechanism (Rodier et al. 2007, Campisi & d'Adda di Fagagna 2007). Consequently, senescent cells possess both pro- and anticancer properties depending on the biological context.

A recent study established a causal role for senescent cells in age-related physical deterioration and decreased lifespan in mice (Xu et al. 2018). Since the health and lifespan of mice have been shown to be improved by the removal of senescent cells (Baker et al. 2011, Xu et al. 2018), investigators have sought out drugs that could preferentially kill senescent cells. These drugs are called senolytics. Two of the first compounds identified were dasatinib and quercetin; each individually killed senescent cells, but with different efficiencies depending on cell type. Consequently, senescent cell killing was more effective if the two drugs were combined (Zhu et al. 2015b). Dasatinib is a tyrosine kinase inhibitor and known to induce apoptosis (Montero et al. 2011, Xue et al. 2012). Quercetin was also described as a kinase inhibitor (Bruning 2013) but is also a CD38 inhibitor (Escande et al. 2013). This raises the question of whether modulation of NAD^+ contributes to the senolytic activity of this drug and, further, if other NAD^+ modulators may attenuate senescence.

Interestingly, in cells with mitochondrial dysfunction–associated senescence, a modified SASP program was executed (Wiley et al. 2016). These cells were characterized as having lower NAD^+/NADH ratios and lacking the IL-1 (interleukin 1)-associated inflammation due to 5′ AMP-activated protein kinase (AMPK)-mediated p53 activation. Consequently, high NAD^+ may be negatively associated with the development of senescent cell phenotypes. In support of this concept, a recent paper demonstrated that AMPK activation could lead to increased NAD^+ and prevent oxidative stress–induced senescence (Han et al. 2016). Further, they showed that NAMPT was significantly decreased in H_2O_2-induced senescent cells and that AMPK activation reversed this. Additionally, there are other lines of evidence that indicate that low NAD^+ may be a

common feature found in senescent cells (Ziegler et al. 2015), and thus NAD^+ is a druggable target. Since senescence and mitochondrial dysfunction are both intimately associated with cancer and aging, additional research is needed to more thoroughly investigate their relationship to NAD^+ biosynthesis and decomposition.

NAD^+ AS A THERAPEUTIC TARGET IN CANCER AND AGING DISORDERS

Although emerging data support the beneficial and protective role of NAD^+ supplementation in age-related neurodegenerative and premature aging diseases (Fang et al. 2016a, Hou et al. 2018, Scheibye-Knudsen et al. 2014), its role in preventing or treating cancer remains controversial. There are conflicting studies on the effect of NAD^+ on cancer cell proliferation and death. For example, a high dose (1000 mg/kg) of NAM can inhibit breast tumor growth in mice, whereas in pancreatic islet cells, 350 mg/kg of NAM increased the incidence of streptozotocin-induced cancer (Surjana et al. 2010). Further studies are needed to eliminate unwanted effects of NAD^+ administration in cancerous cells or the toxicity from NAMPT inhibition to neighboring healthy cells.

Subsequent studies have revealed that NAMPT inhibition results in the attenuation of glycolysis and the activation of autophagy, indicating that NAD^+-depleted cancer cells experience an energy crisis, which may ultimately result in cell death (Cea et al. 2012, Sharif et al. 2016, Tan et al. 2015). The multifaceted roles of NAD^+ on energy production, DNA repair, antioxidant defenses, and many other signal transduction pathways make this metabolite a gem-like substance for cell survival and homeostasis. However, processes like DNA repair and energy metabolism are also hijacked by cancer cells to enhance their survival and proliferation capacity without activating cell death pathways, making NAD^+ a potential contributing factor for tumorigenesis as well. Thus, maintaining NAD^+ at optimum levels throughout the lifespan might be essential to prevent metabolic maladaptation, age-related neurodegeneration, and cancer formation. In scenarios which are at low risk for cancer development, such as in CS patients, the benefits of NAD^+ precursor treatment would be predicted to largely outweigh the risks. Therefore, interventions modulating NAD^+ levels should be considered with caution, as they may either promote or suppress cancer formation and progression, depending on the timing of treatment and biological context.

COMMENTARY

NAD^+ metabolism serves as a central signaling hub that links numerous bioenergetic, redox, transcription, and DNA repair processes. The reviewed evidence suggests that the metabolic adaptation to cellular stressors encountered during the aging process may alter redox homeostasis to facilitate the progression of cellular senescence or neoplastic transformation (**Figure 3**). The recognition and increasing study of the diverse roles of NAD^+ metabolites may uncover novel therapeutic targets for age-related pathologies and cancer. Moreover, while NAD^+ precursor treatment is emerging as an efficacious intervention for the prevention of numerous age-related pathologies, the therapeutic potential for NAD^+ precursors in cancer is not well understood. It is possible in some instances that boosting NAD^+ metabolism could fuel cell proliferation and exacerbate cancer progression and metastasis. On the other hand, supplementation with NAD^+ precursors could also prevent or shift cancer cell metabolism in a favorable manner and decrease uncontrolled proliferation. Therefore, the most optimal anticancer clinical strategy will likely involve individual patient profiling to identify treatments with maximal efficacy for the particular metabolic and genetic profile of the patient's cancer.

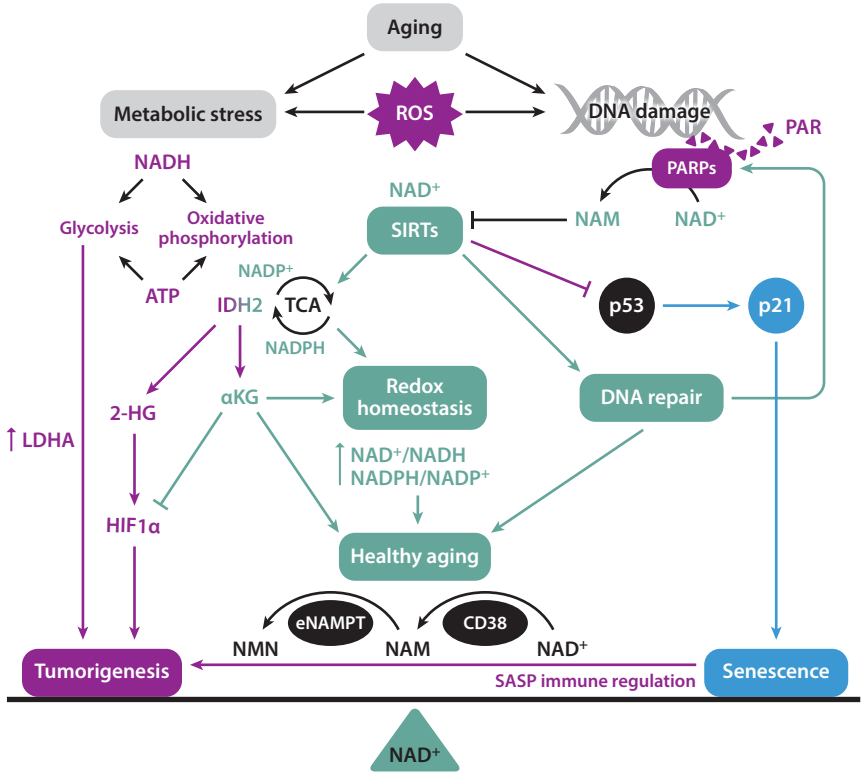

Figure 3

Metabolic adaptation to cellular stress associated with aging dictates cell fate. ROS cause DNA damage, and metabolic stress initiates alterations in metabolism and cell signaling pathways toward repair and the restoration of redox homeostasis (*teal*). Failure to restore homeostasis can lead to a decline in metabolism associated with cellular senescence (*blue*) or can upregulate tumorigenic metabolic pathways (*purple*), such as glycolysis. Senescent cells also release inflammatory cytokines, which may also lead to tumor formation. Abbreviations: 2-HG, D-2 hydroxyglutarate; αKG, α-ketoglutarate; eNAMPT, extracellular NAMPT; HIF1α, hypoxia-inducible factor 1 alpha; IDH2, isocitrate dehydrogenase 2; LDHA, lactate dehydrogenase A; NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide; NAMPT, nicotinamide phosphoribosyltransferase; NMN, nicotinamide mononucleotide; PAR, poly(ADP-ribose); PARPs, poly(ADP-ribose) polymerases; ROS, reactive oxygen species; SASP, secretory-associated senescence phenotype; SIRTs, sirtuins; TCA, tricarboxylic acid cycle.

DISCLOSURE STATEMENT

The Bohr Laboratory has cooperative research and development agreements with ChromaDex to study the effects of nicotinamide riboside (NR) supplementation on neurodegeneration.

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