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Review Article

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NAD$^+$ in Cancer Prevention and Treatment: Pros and Cons

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Abstract

Oxidized form of cellular nicotinamide adenine dinucleotide (NAD+) is currently intensively investigated topic in longevity science. However, if ageing is considered a defense mechanism against cancer, caution should be implemented regarding the use of NAD+ and its precursors. In the hypothesis presented NAD+ is shown as an important factor related to cancer formation and prevention. NAD+ depletion with age may play a major role in the process of cancer formation by limiting (1) energy production, (2) DNA repair, (3) genomic stability and signaling. Disruption of any of these processes could increase the cancer risk due to impaired genomic stability. NAD+ content is a critical protective factor in early carcinogenesis and can become detrimental factor later in cancer progression and promotion phase. Namely, NAD+ restoration could prevent or reverse the phenotype of malignant cells at early stages by inducing cellular repair and stress adaptive response as well as regulate cell cycle arrest and apoptotic removal of damaged cells. Contrary, during cancer promotion, progression and treatment increased NAD+ levels could have deleterious effects on the malignancy process due to growth advantage, increased resistance and greater cell survival. NAD+ levels can be increased with exercise, caloric restriction and ingestion of NAD+ precursors and intermediates or could be increased by using PARP and CD 38 inhibitors. The evidence indicating that modulation of NAD+ levels could be important in cancer prevention, initiation and progression phase is presented.

Keywords

Nicotinamide adenine dinucleotide (NAD+); Cancer formation and prevention; Cancer treatment; Carcinogenesis; NAD+/NADH ratio; PARPs; Sirtuins

Introduction

Nicotinamide adenine dinucleotide NAD$^+$, a coenzyme required for DNA synthesis, is involved in cellular redox reactions and plays integral role in basic energy metabolism such as glycolysis, citric acid cycle, and mitochondrial electron transport [1]. NAD$^+$ is a substrate for many NAD-dependent enzymes and is a key substrate for signaling enzymes such as polyADPribosyl-polymerases, sirtuins, and ADPribosyltransferases [2]. Over 200 enzymes require NAD (H) and NADP (H) due to their reversible oxidation-reduction properties. The ratio of NAD$^+$/NADH regulates many aspects of metabolism, including DNA repair, stress resistance, and cell death [3]. By regulating diverse pathways [4] and by inducing apoptosis, DNA repair and increasing cell defence the amount of available NAD$^+$ could influence the malignant transformation. Namely, NAD$^+$ is involved in molecular processes which are important early in cancer development, including DNA repair, stress responses, signaling, transcription, apoptosis, metabolism, differentiation, chromatin structure, and increased life span [5]. In human subjects, NAD$^+$ content has been inversely correlated with malignant phenotype [6,7].

NAD$^+$ and its precursor nicotinamide mononucleotide (NMN) levels decline with age and NADH level increase [8-10], as well the incidence of many types of cancer increase with ageing [11,12]. Although causal relationship remains to be elucidated, stimulating the NAD$^+$ biosynthesis in second half of human lives with NAD$^+$ intermediates or by stimulation of NAD$^+$ synthesis could represent a novel strategy for preventing the incidence of malignant diseases.

Pathways of NAD$^+$ synthesis

Aerobic exercise, caloric restriction (CR) and fasting increase NAD$^+$ levels, mitochondrial and sirtuin activity and lowers the NADH levels [13-15]. Baseline requirements for NAD$^+$ synthesis can be met either with dietary tryptophan or with less than 20 mg of daily niacin, which consists of nicotinic acid and/or nicotinamide [16]. 60 mg of Trp is considered the equivalent of 1 mg of niacin [17]. Greater rates of NAD$^+$ synthesis may be obtained also by supplementation with nicotinamide riboside (NR), and possibly nicotinic acid riboside (NaR) which are NAD$^+$ precursors and utilized through distinct metabolic pathways to form NAD$^+$ [16]. Besides, O-ethylnicotinate riboside, O-methylnicotinate riboside, and several N-alkyl derivatives can increase NAD$^+$ concentrations *in vivo* [18]. For example, mitochondria in muscles of elderly mice were reversed to a youthful state after injections with NMN (nicotinamide mononucleotide), thus raising NAD$^+$ levels in old mice restored mitochondrial function to that of a young mouse in a SIRT1-dependent manner [19]. Additionally, in the recent experiment Khan et al., [20] treated mitochondrial myopathy mice with NR that effectively delayed early- and late-stage disease progression, by inducing mitochondrial biogenesis in skeletal muscle and brown adipose tissue. The work on genetically engineered mouse models indicates that enhanced SIRT1 activity (which requires NAD$^+$) would be protective against the development of some types of metabolic syndrome-associated cancers [21].

DNA damage and repair

Cancer evolves through a multi-step process, where DNA damage, genetic mutations and altered metabolism act as drivers of cancer. In cancer cells, genes are either modified by mutations that alter the function of the encoded proteins or the expression patterns of oncogenes / tumor suppressor genes can be affected through the epigenetic changes (including acetylation, methylation, phosphorylation and ubiquitylation) [22]. Evidence will be presented that NAD$^+$ or NAD$^+$/NADH ratio can influence DNA mutation frequency (Figure 1), epigenetic changes in DNA and can influence metabolic programming.

DNA damage response senses different types of DNA damage and coordinates a response that includes activation of transcription, cell

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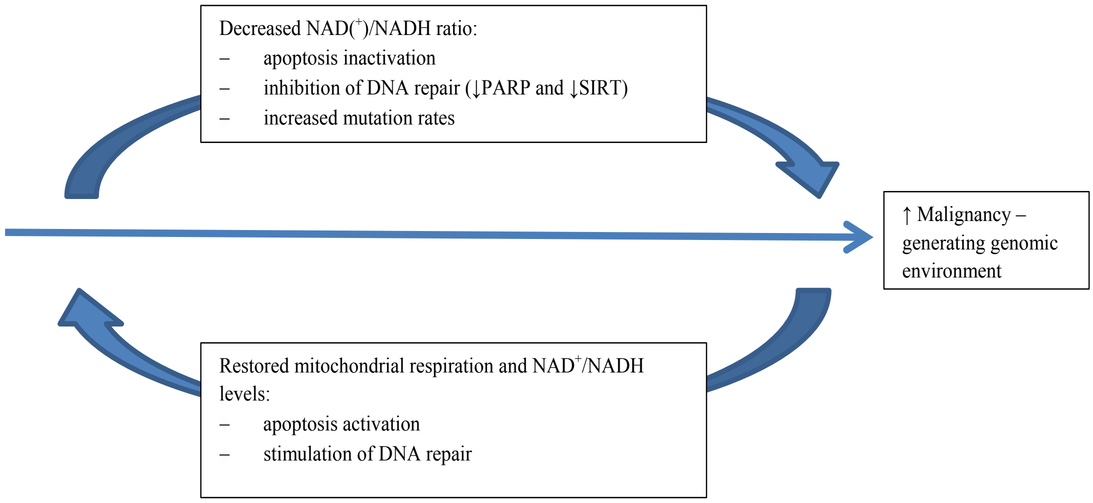

Figure 1: Possible mechanisms of NAD+ depletion and restoration in relation to apoptosis, DNA repair and mutation frequency. NAD+/NADH levels can be restored by converting NADH to NAD+; stimulating NADH-quinone oxidoreductase 1 (NQO1) that modulates cellular NAD+/NADH ratio; by dichloroacetic acid (DCA), 3-bromopyruvate (3BroP), 2-deoxyglucose (2-DG), nicotinamide riboside and nicotinamide precursors; by upregulating NAMPT with fasting and exercise, etc.

cycle control, DNA repair pathways, apoptosis, senescence, and cell death [23]. A major determinant of the quality of repair is the speed of repair, especially if mutation is replicated before being repaired, which leads to the formation of a permanent mutation. The activity of DNA repair systems decline with age [24]. The observed increase of DNA damage with age may be the consequence of a) an increased ROS generation and b) a decline of DNA repair mechanisms and clearance. For example, increased DNA damage and mutation level with age could be explained also by the depletion of NAD+ [8], which is necessary for the activity of sirtuins and PARPs involved in the genomic maintenance and repair of DNA. PARP activity increases with age in human cells and correlates with both age and NAD+ depletion in males [8,25]. The NAD+ as the link between oxidative stress, inflammation, caloric restriction, exercise, DNA repair, longevity and health span was described elsewhere by Poljšak and Milisav, [26].

ROS as the main cause of oxidative damage and the role of NAD+

ROS can cause severe damage to DNA, proteins and lipids, when produced at high levels. The major superoxide-producing component of the mammalian respiratory chain is NADH:ubiquinone oxidoreductase (Complex I). Redox state of complex I is the major source of ROS under pathological circumstances [27]. Redox state of complex I depends on numerous factors like substrate supply, ATP use and uncoupling which increase the oxidation of complex I and the flow of electrons down the respiratory chain, resulting in lowered electron leakage. Faster and more efficient electron transport may lead to a lower production of ROS by mitochondria. This occurs because of reduced leakage of electrons from the respiratory chain and/or lower oxygen concentrations in the mitochondrial microenvironment [28,29]. Deactivation of Complex I results in almost complete loss of its NADH-ubiquinone reductase activity and in increase in NADH-dependent superoxide generation [30]. This theoretical postulate was confirmed observationally in mice when it was shown that across individuals it was those individuals with the highest energy metabolic rates that lived the longest, and such individuals had greater uncoupling of their muscle mitochondria [31].

The reduction state of complex I depends strongly on the NAD and NADH levels. Ameliorating the NAD+/NADH ratio would influence the intensity of superoxide-generation from the transfer of electrons to molecular oxygen at mitochondrial complexes I/III and from the plasma membrane redox system and can thus regulate a) the formation of reductive/oxidative stress [26] and b) the intensity of oxidative damage. Increased levels of oxidative damage of proteins, DNA and lipids were observed in animal models and aged human tissues [32] however, there was decreased oxidative damage and increased resistence to oxidative stress in long-lived compared to short-lived animals [32-34]. While oxidative damage increases with age [35-37], some data imply that the rate of oxidative DNA repair and other cell repair mechanisms decrease with age [38,39] as well as the level of antioxidative defense [40,41]. The duration of life-span and health-span as well as cancer prevention may thus be improved by manipulating cellular repair and maintenance systems. Approach to neutralize free radicals with antioxidants should be changed into triggering an adaptive stress response in order to increase the damage repair processes [42]. Regulation of the redox state of mitochondrial NAD+ is an essential antioxidant defensive system. Moderate stress induced by CR, physical activity or mimetic compounds, which all influence the level of NAD+, may induce such activation of endogenous antioxidative defense and cellular repair and maintenance processes [42,43]. Aerobic exercise, caloric restriction (CR), fasting and low glucose availability increase NAD+ levels, mitochondrial and sirtuin activity, while lowering the NADH levels [44-47]. NAD+ levels are also involved in the circadian clock regulation and this might be the missing link between the circadian clock, cell cycle control, DNA damage repair and cellular metabolism [48,49]. What is more, abnormal metabolism and aberrant cellular proliferation in cancer could be linked to a disrupted circadian clock [50].

It seems that increased ROS formation protects tested animals from cancer by increasing oxidative stress/damage and killing the

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tumor cells [51] and conversely antioxidants stimulate cancer growth by decreasing oxidative stress and apoptosis [52]. Antioxidant treatment reduces ROS and DNA damage levels but increases cell proliferation. By reducing oxidative stress and oxidative DNA damage also p53 is reduced, resulting in decreased p53 surveillance and accelerated tumor proliferation [53-55]. Additionally, the tumor suppressor Nrf2 that controls many enzymes involved in antioxidative defense can actually promote cancer growth in some circumstances. Namely, Nrf2 is strongly activated in many tumors resulting in decreased oxidative stress [54,56]. Mendelsohn and Larrick [57] stressed the scenario when antioxidant treatment can reduce Nrf2 expression and down regulate p53 leading to decreased oxidative damage protection of already altered (pre-malignant and malignant) cells leading to tumor promotion. Thus, approaches resulting in increased absolute NAD^+ level are important for maintaining optimal cellular functioning. However, the increases of NAD^+ pool might cause double-edged effects - what might increase the longevity of normal cells can be harmful when the cells are already malignantly transformed. Namely, by lowering ROS leakage, e.g. by tighter control over the NADH pool, ROS damage and mutations are prevented, but also apoptosis is repressed; the latter is an essential defensive mechanism for elimination of damaged cells, including those that are precancerous and cancerous. What is more, NAD^+ depletion may have a major role in the process of tumor development by limiting 1) energy production, 2) DNA repair and 3) genomic stability and signaling [3].

NAD^+/NADH ratio regulates many cellular processes

Cancer cells are characterized by altered mitochondrial bioenergetic and biosynthetic state (excessive proliferation, impaired cell death signaling, and deregulated metabolism). The NAD^+/NADH ratio plays an important role in regulating the intracellular redox state and several enzymes involved in regulation of metabolism are influenced by the NAD^+/NADH ratio. The NAD/NADH ratio itself is regulated by small changes in NAD^+ concentration [58,59]. Changes in NAD^+ concentration and/or the NAD^+/NADH ratio can induce DNA repair and increase cell defence, by regulating diverse signalling pathways [60-62] and transcriptional events and thus play important role in cancer prevention (Figure 2). By increasing cellular NAD^+ levels AMPK enhances SIRT1 activity, resulting in the deacetylation and modulation of the activity of downstream SIRT1 targets. It seems that NAD^+ can activate PARPs, sirtuins and regulate the genes involved in the DNA repair and maintenance process [63]. This is especially true for the mammalian sirtuin 1 (SIRT1) whose activity depends on NAD^+/NA(H) ratio. The DNA repair enzyme PARPs also use large amounts of intracellular NAD^+ and are thereby in competition with sirtuins for the limited supply of NAD^+ (Figure 3). NAD^+ is the substrate for the synthesis of poly (ADP-ribose) (pADPr) by poly (ADP-ribose) polymerase (PARP). Poly(ADP)-ribosylation is a DNA strand-break-driven posttranslational modification of nuclear proteins that is catalyzed by PARP-1, with NAD^+ serving as substrate and a key player in the immediate cellular response to ROS-induced DNA damage in eukaryotic cells. Upon DNA damage, PARP activity in the cell is highly enhanced. The activation PARP-1, the enzyme responsible for most PARP activity, would lead to NAD^+ depletion, therefore limiting SIRT1 activity by lowering the bioavailability of this crucial coenzyme [64]. This reduced cellular NAD^+ then reduces the effectiveness of sirtuins (SIRT1) which can deacetylate tumor-suppressor proteins such as p53 [65] (Figure 3). p53 selectively regulates a set of its target genes, including cell cycle arrest, apoptosis, autophagy, and/or senescence, to exert its function in DNA damage and tumor suppression. Loss of p53 thus provides growth advantage to tumor cells; it enables cell survival under limiting nutrient conditions [66]. It was observed that NAD^+ concentration can modulate expression of the tumor suppressor protein, p53, in human breast, skin, and lung cells [6,67]. Tummala et al., (2014) reported that replenishing the NAD^+ levels by nicotinamide riboside (NR) prevented and abolished DNA damage and aggressive tumor formation [68]. Additionally, Tummala and Djouder propose that NAD^+ depletion is a common molecular mechanistic basis for oncogene-induced DNA damage and tumor development [69]. Additionally, NAD^+ dependend tankyrases (also known as PARP-5a and PARP-5b), which regulate telomererase activity and telomere maintenance, may also influence the carcinogenic process [70]. The NAD/NADH redox state regulates also the co-repressor CtBP (C-terminal binding protein) activity, component of critical complexes for specific repression events in cells, and therefore plays significant role in carcinogenesis [71] due to epigenetic reprogramming. The C-terminal binding protein (CtBP) is a NADH-dependent transcriptional repressor and requires NAD^+ binding for activity, indicating that NAD^+ plays a role in repression at a step subsequent to CtBP recruitment to the promoter. In situations of low glycolytic rates NADH will decrease, destabilizing CtBP/HIC1/SIRT1 inhibitory complexes and allow the induction of SIRT1 mRNA levels [71].

PARPs, sirtuins, CD38 and Nampt inhibitors in cancer treatment

Failure to repair the DNA damage leads to a loss of genomic integrity, carcinogenesis or cell death. Decreased availability of NAD^+ in cancer cells might influence cancer treatment. Namely, the amount of NAD^+ available for PARPs and sirtuins regulates the quality of DNA repair. Selective inhibition of NAD^+ synthesis demonstrated induction of apoptosis of tumor cells [72]. For example, inhibiting nicotinamide-recycling enzyme nampt/PBEF with NAD biosynthesis inhibitor, FK866, resulted in anticancer effect [73] as tumor apoptosis inducer due to NAD^+ depletion [72].

Sirtuin inhibitors are also emerging as antitumor drugs, and this function has been ascribed to the inhibition of SIRT1, which deacetylases p53 to promote cell survival [74]. SIRT1 inhibition induces growth arrest and reduces drug resistance of cancer cells *in vitro* [75,76]. Additionally, SIRT2 inhibition was reported to trigger apoptosis in C6 glioma cells and HeLa cells [74,77]. Contrary, Van Meter et al., (2011) proposed SIRT6 overexpression in cancer therapy, since it induces apoptosis in cancer cell lines but not in non-transformed cells through its ADP-ribosyltransferase activity [78].

Also PARP1 inhibitors affect NAD^+ concentration and could increase the effectives of cancer treatment. Certain tumors defective in homologous recombination mechanisms, may rely mostly on PARP-mediated DNA repair for survival, and are sensitive to its inhibition [79]. Namely, fast growing cancer cells observed in tumours with BRCA1, BRCA2 or PALB2 are low in oxygen and sensitive to PARP inhibitors [80]. BRCA1, BRCA2 and PALB2 proteins are important for double-strand DNA breaks repair (DSBs). PARP-1 is involved in repairing single strand breaks (SSBs) and the replication of unrepaired SSBs causes the formation of double strand breaks [81]. If DSBs in tumors with BRCA1, BRCA2 or PALB2 cannot be repaired due to PARP1 inactivation, cell deat is stimulated. PARP-1 inhibition can thus sensitize cancer cells to anti-cancer therapies, for example, chemotherapy and radiation therapy [82], since poly (ADP-ribose)

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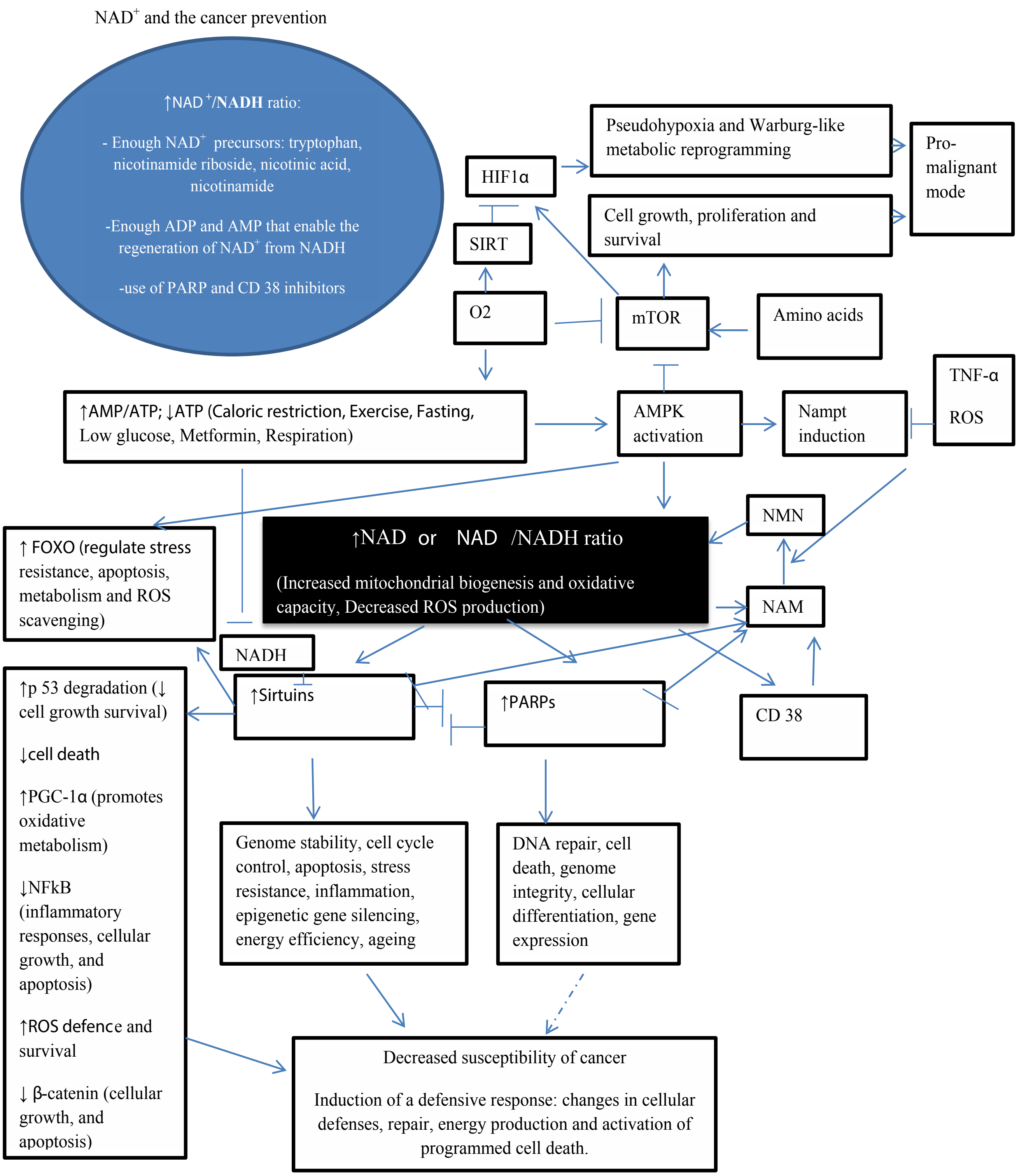

Note*: adenosine-monophosphate-(AMP-) activated protein kinase (AMPK); the target of rapamycin pathway (TOR); tumor necrosis factor-α (TNF-α); Forkhead Box O (FOXO); hypoxia-inducible factor 1 (HIF1); Sirtuin 1 (SIRT1); transcriptional coactivator peroxisome proliferator-activated receptor (PPAR)γ coactivator 1α (PGC-1α), nicotinamide phosphorybosyltransferase (Nampt); nicotinamide mononucleotide (NMN); nicotinamide (NAM); nicotinamide phosphoribosyltransferase (Nampt); nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)

Figure 2: NAD⁺ in cancer prevention: NAD⁺/NADH ratio in relation to cell energy availability, cell metabolism, DNA repair, genomic stability, cell signaling, cell survival and fate. Arrows indicate positive regulation while hash-marks indicate negative regulation; dashed lines indicate putative interaction. Note: some interactions have been omitted for simplicity.

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polymerase-1 (PARP-1) facilitates the repair of DNA strand breaks. Contrary, Ethier et al., (2012) reported that pharmacologic inhibition of PARP-1 promotes Akt activity and mTOR signaling resulting in decreased (cancer) cell death [83]. However, these results were contradicted by Wang et al., (2011) reporting PHLPP1-mediated downregulation of Akt activity and increased cell death following PARP inhibition [84].

By using the PARP or CD38 inhibitors NAD^+ bioavailability could be increased and more NAD^+ becomes available for sirtuins. Namely, SIRT1 activity is reduced when PARP1 is activated since NAD^+ is the rate-limiting factor for the activation of SIRT1. PARP-1 inhibition was shown to prevent NAD^+ depletion, restore the ATP levels, activate SIRT1 and induce gene expression program that stimulates mitochondrial metabolism (Figure 3) [85-87]. Initially, PARP inhibitors were thought to work primarily by blocking PARP enzyme activity, thus preventing the repair of DNA damage and ultimately causing cell death. Muray et al., (2012) revealed that PARP inhibitors have an additional mode of action: trapped PARP–DNA complexes are more toxic to cells than the unrepaired single-strand DNA breaks that accumulate in the absence of PARP activity, indicating that PARP inhibitors act as PARP poisons [88].

Basal NAD^+ turnover was prolonged threefold to fourfold by an inhibitor of poly(ADP-ribose) synthetase in resting human lymphocytes [89]. For example, nicotinamide (NAM) is PARP-1 inhibitor and inducer of sister chromatid exchanger [90,91]. Low levels of NAM are beneficial for SIRT1 activity, because NAM can act as an NAD^+ precursor, but accumulation of NAM could be deleterious through the inhibition of SIRT1 [64,92]. NAM between 100-1000 mg kg-1 caused a high level of *in vivo* DNA strand breaks in tumour bearing mice and normal tissue cells. After cessation of NAM treatment a delay in repair of DNA strand breaks and regeneration of NAD^+ was observed [93]. Additionally, large doses of oral niacin (nicotinic acid (NA) plus nicotinamide (NAM)) supplementation increase NAM levels in the body, which may result in inhibition of PARP-1 and increased genomic instability [94]since PARP-1 helps to stabilize genetic material with its role in DNA repair pathways including nucleotide excision repair (NER) [95] and base excision repair (BER) [96]. On the other hand, niacin is an oxygen radical scavenger and might increase the antioxidant defence against ROS [97,98], but as already mentioned, increased antioxidative stress influences intensity of proliferation. Besides, increased mutation rate and the diversity of cancer might be a consequence of niacin deficiency due to abnormal pairing of bases and its requirement for DNA synthesis [99]. It was observed that certain populations, including cancer patients (due to cachexia), could have subclinical deficiency in niacin [100,101].

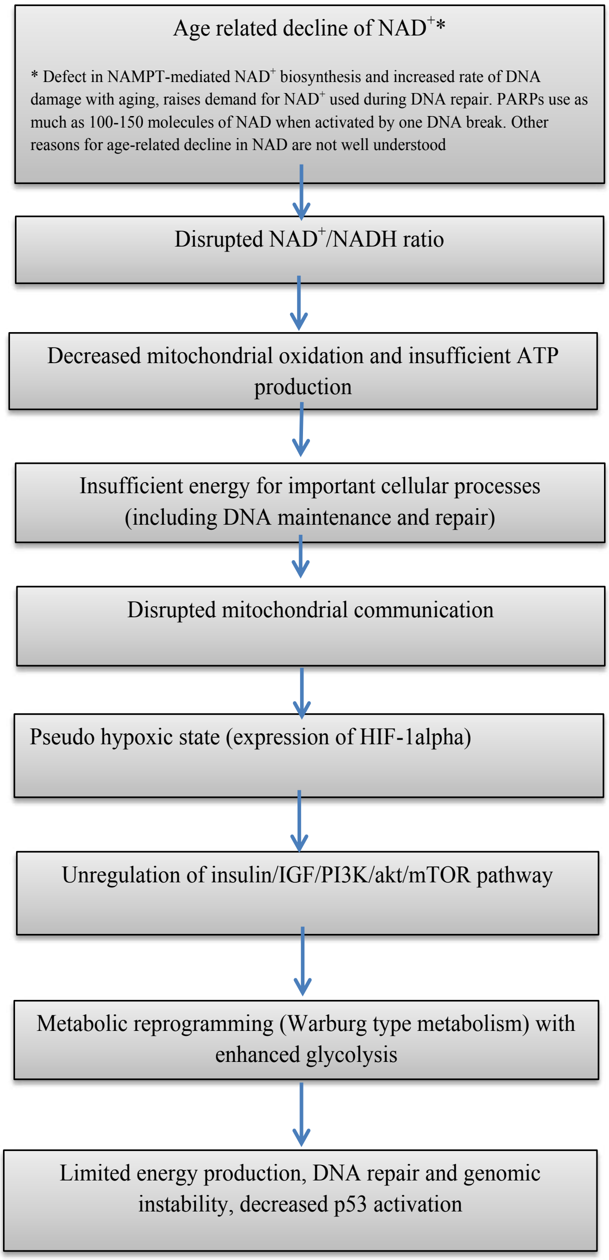

Figure 3: A vicious cycle created by a decline of NAD^+.

The age dependent mitochondrial vicious cycle and aerobic glycolysis

Mitochondrial dysfunction is a hallmark of cancer formation, but its causes are still not well understood. Previous hypothesis speculated about free radical-induced oxidative stress as the main cause of mitochondrial inner membrane damage, which creates a positive feedback-loop. Namely, induction of ROS generates mtDNA mutations [102-104] in turn leading to a defective respiratory chain and stimulation of glycolysis. During glycolysis NAD^+ accepts hydride equivalents to form the reduced dinucleotide, NADH. Glycolysis can function with or without the presence of oxygen. In humans, aerobic conditions produce pyruvate and anaerobic conditions produce lactate. When oxygen is present, acetyl-CoA is produced from the pyruvate molecules created from glycolysis. Enzyme involved in catalyzing the conversion of pyruvate to acetyl CoA is pyruvate dehydrogenase and high levels of NADH and acetyl CoA inhibit this enzyme, while NAD^+, CoA, or AMP can speed up the reaction. When oxygen is present, the mitochondria will undergo aerobic respiration which stimulates the Krebs cycle. However, if oxygen is not present, fermentation of the pyruvate molecule will occur. The goal of anaerobic glycolysis is to reduce pyruvate, thus regenerating NAD^+ in the absence of O2. In the absence of oxygen, fermentation prevents the buildup of NADH in the cytoplasm and provides NAD^+ for glycolysis. Defective respiratory chain and anaerobic glycolysis generates significant amount of ROS and forming a vicious cycle.

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This vicious cycle creates even more damage to mtDNA and reduces energy formation from oxidative phosphorylation and further stimulates aerobic glycolysis, thus reducing the available energy for DNA repair and maintenance processes (Figure 3).

Gene mutations and chromosomal abnormalities [105] determine the Warburg effect and compromised function of respiratory system. The metabolic impairment theory/mitochondrial theory of cancer [106-111] claims that cancer can be best defined as a type of mitochondrial disease. The gene theory of cancer indicates that dysfunctional mitochondria would be the result and not the causal factor of cancers, while the contrary is suggested by the metabolic impairment theory. Although some studies challenged the Warburg hypothesis of aerobic glycolysis as the universal property of tumor cells [112], claiming that tumor mitochondria do respire and produce ATP, the important fact remains that cancer cells do exhibit high rates of glycolysis in aerobic or anaerobic conditions [113]. Even under conditions of plentiful oxygen, cancer cells choose to switch glucose metabolism from respiration to lactic acid formation. Since the nuclear genome integrity is largely dependent on mitochondrial energy homeostasis, damage to cellular respiration precedes and underlies the genome instability that accompanies tumor development. Once established, genome instability contributes to further respiratory impairment, genome mutability, and tumor progression [106]. Tumors display aerobic glycolysis partly through activation of oncogenes or loss of tumor suppressors, which are then further enhanced by stabilization of the hypoxia-associated transcription factor, the hypoxia-inducible factor (HIF-1a) [114]. Increased ROS stabilize (HIF) 1-alpha, resulting in metabolic reprogramming toward glycolysis and thus facilitating tumor development [115-117]. For example, Gomes et al. proposed a model linking decreased NAD+ to loss of nuclear SIRT1 activity to stabilization of the HIF 1-alpha. HIF-1alpha promotes hypoxic-like (Warburg effect) state in the cell (Figure 3). Abnormal energy metabolism is a consistent feature of most tumor cells across all tissue types [106] and genes for glycolysis are overexpressed in the majority of cancers examined [118,119]. Numerous studies show that tumor mitochondria are structurally and functionally abnormal and incapable of generating normal levels of energy [120-128].

Could re-activation of mitochondrial oxidative metabolism in glycolytic tumors with altered mitochondria be obtained by the administration of NAD+?

The altered metabolism of tumor cells confers a selective advantage for survival and proliferation, and studies have shown that targeting such metabolic shifts may be a useful therapeutic strategy. According to Mouchiroud et al. [129], boosting oxidative metabolism through modulating NAD+ levels could in itself prove to be a powerful anti-cancer regimen and actually inhibit the "Warburg effect" [129]. For example, different inhibitors can act as anti-Warburg agents by raising NAD+ levels and promote oxidative metabolism [64]. Additionally, it was reported that SIRT3 can repress the *Warburg effect* by regulating HIF - 1α and reprogramming cancer cell metabolism; from highly glycolytic to a shift toward oxidative phosphorylation [117,118,130,131]. Also SIRT1 inactivates HIF-1alpha, consequently represses HIF-1 target genes and has negative effects on tumor growth and angiogenesis [132].

Here we introduce also the role of NAD+/NAD(H) ratio in regulating mitochondrial functions, as the bioavailability of NAD+ is the limiting factor for maximal oxidative capacity of mitochondria (Figure 2). As NAD+ levels decline with age, mitochondrial function is impaired [133] and the DNA repair activity declines as well [24] (Figure 3). The increase of DNA damage with age may therefore be the result of (a) an increased ROS generation and (b) a decline of DNA repair mechanisms and clearance affected also by lower substrate NAD+ for sirtuins and PARPs. Sirtuins and PARPs enhance cellular repair mechanisms while buying time for efficient repair of the damage (Figure 3). To sum up, the availability of free NAD+ and the perturbation of key redox couples such as the NAD(H)/NAD+ ratio can have profound effects on cells by regulating the apoptosis [134,135], accelerated ageing and cancer process (Figure 1, 2, 3).

During the aging process, increased DNA damage accumulates in the nucleus, causing PARP over-activation and decreased NAD+/NADH ratio. As NAD+ is the substrate for sirtuins, SIRT1 activity is reduced, resulting in increased PGC-1α acetylation and decreased mitochondrial transcription factor A levels. According to Imai and Guarente, these nuclear events reduce mitochondrial function in old mitochondria by affecting mitochondrial complex I and other mitochondrial components, or blocking the entry of electrons from NADH into the ETC, thereby creating an NAD deficiency [136]. NAD+ deficiency results in insufficient ATP production; metabolic reprogramming and limited DNA repair – the vicious cycle generation presented in Figure 3.

Role of NAD+ in cell protection against oxidative and genotoxic damage

The processes of cell division, differentiation, senescence and apoptosis, as well as DNA damage recognition and velocity of repair are important for cancer prevention due to their involvement in maintenance of genomic stability. Many of these processes could be influenced by perturbations in NAD+ concentration or/and NAD+/NADH ratio (Figure 2). It will be shown the opposite effect of NAD+ on the cancer prevention and cancer treatment process. For example, decreased oxidative stress and damage can have positive effect on damaged (but non-malignant) cells during cancer prevention phase while detrimental effect on malignant cells or during malignant cellular transformation. The amount of ROS and oxidative stress can namely regulate apoptosis, cancer growth and invasion – the processes influenced by NAD+ concentration.

NAD+ plays a protective role in genomic stability, as well as in mutation formation and cancer prevention. Many studies revealed that NAD+ protects cells against oxidative stress [137] or insults caused by oxygen-glucose deprivation [138]. DNA damage appears to stimulate NAD+ biosynthesis and recovery from DNA damage occurs several hours earlier in the presence of higher NAD+ or in cells undergoing active NAD+ biosynthesis [6]. Cells depleted in NAD+ were more sensitive to cytotoxic effects when exposed to DNA damaging compounds [139,140]. Namely, increased (oxidative) damage to DNA leads to PARP activation and the enzyme PARP-1 is highly activated by DNA strand breaks during the cellular oxidative and genotoxic stress response [95]. Increased cytotoxicity of many carcinogens was observed when PARP was inhibited [139,141,142] and PARP-1 defective mice had increased spontaneous genetic rearrangements and increased sensibility to DNA damage [141,143,144]. PARP family of proteins is (directly or indirectly) involved not only in DNA repair but also in programmed cell death (apoptosis), cellular differentiation, proliferation, tumor transformation and gene expression (e.g. p53 expression/ function) [143,145-150]. When activated, PARP-1 consumes NAD+ to form ADP-ribose polymers on acceptor proteins. Chen et al., (2013) were the first to observe that the oxidative stress-

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induced reduction of intracellular ATP is mediated by the oxidative stress-induced reduction of the intracellular NAD^+ [151]. Extensive activation of PARP-1 leads to glycolytic blockade, energy failure, and cell death [152]. ATP depletion in a cell leads to lysis and cell death by necrosis. PARP also has the ability to induce programmed cell death, via the production of PAR, which stimulates mitochondria to release apoptosis inducing factor (AIF) [153] and is prevented by PARP inhibitors or disruption of the PARP-1 gene [154].

The mammalian sirtuin family of enzymes is formed by paralogues Sirt1 to Sirt7 and some of them can regulate oxidative stress and programmed cell death. The function of human sirtuins has not been fully determined. Sirtuins were reported to be involved in many cellular processes, like: genome stability, cell cycle control, apoptosis, stress resistance, inflammation, energy efficiency and ageing through regulation of different metabolic regulatory transcription factors. The ability of mitochondrial NAD^+ to prevent cell death caused by genotoxic agents is linked to a mitochondrial sirtuin, SIRT3, which is required for this protection [117-155] have shown that the SIRT3 acts as a tumor suppressor via its ability to suppress ROS and regulate 1α (HIF-1α). SIRT3 can regulate also oxidative stress by activating enzymatic antioxidative defence of MnSOD [115,156-158]. SIRT2 may have a tumor suppressor role also through the regulation of microtubule network [159] and by preventing chromosomal instability during mitosis [160]. SIRT2 overexpression decreases oxidative stress-induced death of murine macrophages [161], decreases cellular levels of reactive oxygen species by increasing FOXO DNA binding and elevating the expression of FOXO target genes [162] and increases the expression of the antioxidant enzymes including MnSOD, glutathione peroxidase, and catalase [163].

Niacin (vitamin B3 or nicotinic acid) is one of B-complex vitamins and precursor of NAD^+. Niacin deficiency was reported to increase the susceptibility of DNA to oxidative and alkylating agents and is associated with an increased risk of cancer [165-166]. Contrary, it was observed that NAD^+ [167], as well as NADH [168] and NADPH [169], has negative effect on survival of different types of tumor cells by increasing oxidative stress and PARP activation, opening of P2X7 receptors (NAD^+ can be transported across the plasma membranes of murine astrocytes by P2X7 receptors) and altering calcium homeostasis [170]. What is more, increasing the level of NAD^+ resulted in beneficial survival of normal cells under stress conditions. Niacin deficiency in rats decreases bone marrow NAD^+ and limits pADPr synthesis in response to DNA damage. Altered p53 expression was observed in niacin depleted rat bone marrow cells, too. Expression of downstream p53-target genes was misregulated in niacin deficient bone marrow and apoptotic efficiency and cell cycle arrest were impaired following treatment with the chemotherapy drug etoposide (ETO).ETO-induced apoptosis was suppressed during niacin deficiency and enhanced by its supplementation [171]. Increased B vitamins may negatively regulate the enzymatic activities of Sir2/SIRT1, as a feedback mechanism. In this regard, caloric restriction-mediated activation of Sir2/SIRT1 may at least partly relate to the nutrient availability of B vitamins, including biotin and niacin. Although niacin restriction might increase cancer incidence, it might also improve outcome of cancer once the disease is formed by lowering the concentration of NAD^+ and poly(ADP-ribose), by altering p53 expression, increasing genomic instability and impairing the cellular responses to DNA damage, as observed in different animal studies [165,172-173]. However, opposite effect was observed in nicotinamide-restricted HaCaT keratinocytes, which were able to proliferate indefinitely despite increased production of ROS and significant DNA damage - conditions that cause instability in the genome, genetic alterations and might ultimately lead to progression of carcinogenesis [5].

Controversial roles of NAD^+ in promoting versus suppressing cancer

Neoplasms can be generated if damaged cells survive and evade apoptosis. Loss of apoptosis capability and increased genomic instability leads to greater cell survival and increased mutation frequency, respectively, putting an advantage to cancer cells, due to the growth stimulation. Mutant cells with growth advantage will undergo natural selection, clonal expansion which can end in cancer formation [174].

The function of nicotinamide adenine dinucleotide (NAD^+) mediated reactions on the mechanism of apoptotic cell death is controversial [175] since it could act both, pro - and anti-tumorogenic. The tumor promoting or inhibiting properties of the NAD^+ may thus depend mainly on a) the stages of cancer development b) concentration of NAD^+ and /or NAD^+ / NADH ratio and c) (de) activation of PARPs and sirtuins. Evidence will be presented that PARPs and sirtuins can have beneficial or detrimental effects on cell survival, depending on the intensity of their activation (Figure 4).

PARPs, sirtuins and the adequate availability of NAD^+

PARPs: With the adequate availability of NAD^+ and when PARPs and sirtuins are moderately activated, the genome is maintained by sufficient activation of cellular repair mechanisms and appropriate cell cycle velocity which “buys” time for efficient damage repair. It was observed that PARP-1 activity levels are lower in families predisposed to cancer and some cancers are found to have reduced PARP activities [176]. Additionally, it seems that longevity is associated with a higher poly-ADP-ribosylation capacity, as PARP is increased by 1.6-fold in centenarians [177] and PARP activity of 13 mammalian species correlates with a species-specific life span [178]. On the other hand, overexpression of PARPs is not always beneficial. Higher PARP-1 activity might be detrimental for SIRT1 function and global metabolism as observed in mice expressing an additional copy of the human PARP-1 which had reduced median lifespan, impaired glucose homeostasis, and higher susceptibility to age-related diseases [179].

Cellular responses according to PARP activation intensity may vary (Figure 4), e.g. upon DNA damage, PARP activity in the cell is highly enhanced. Excessive activation of PARP after genotoxic stress leads to rapid NAD^+ depletion, limited DNA repair, reduced cell survival and increased programmed cell death caused by the depletion intracellular ATP and bioenergetic collapse [145,180] (Figure 3). Severe PARP activation leads to depletion of intracellular ATP, Additionally, (NAD / poly(ADP-ribose) synthesis is involved in the regulation of p53 and its dependent pathways [181] and the release of apoptosis-inducing factor (AIF) [153]. Specifically, Parp1 is involved in modulating DNA repair, DNA replication, transcription, DNA methylation and chromatin remodeling through PARylation of downstream proteins. However, high expression level and activity of Parp1 are correlated with pluripotent status, reprogramming, and cancer [182]. On the other hand, PARP1 plays significant role in repairing single-strand breaks and the replication of unrepaired SSBs can cause the formation of double strand breaks. However, PARP1 mediated microhomology-mediated end joining (MMEJ)

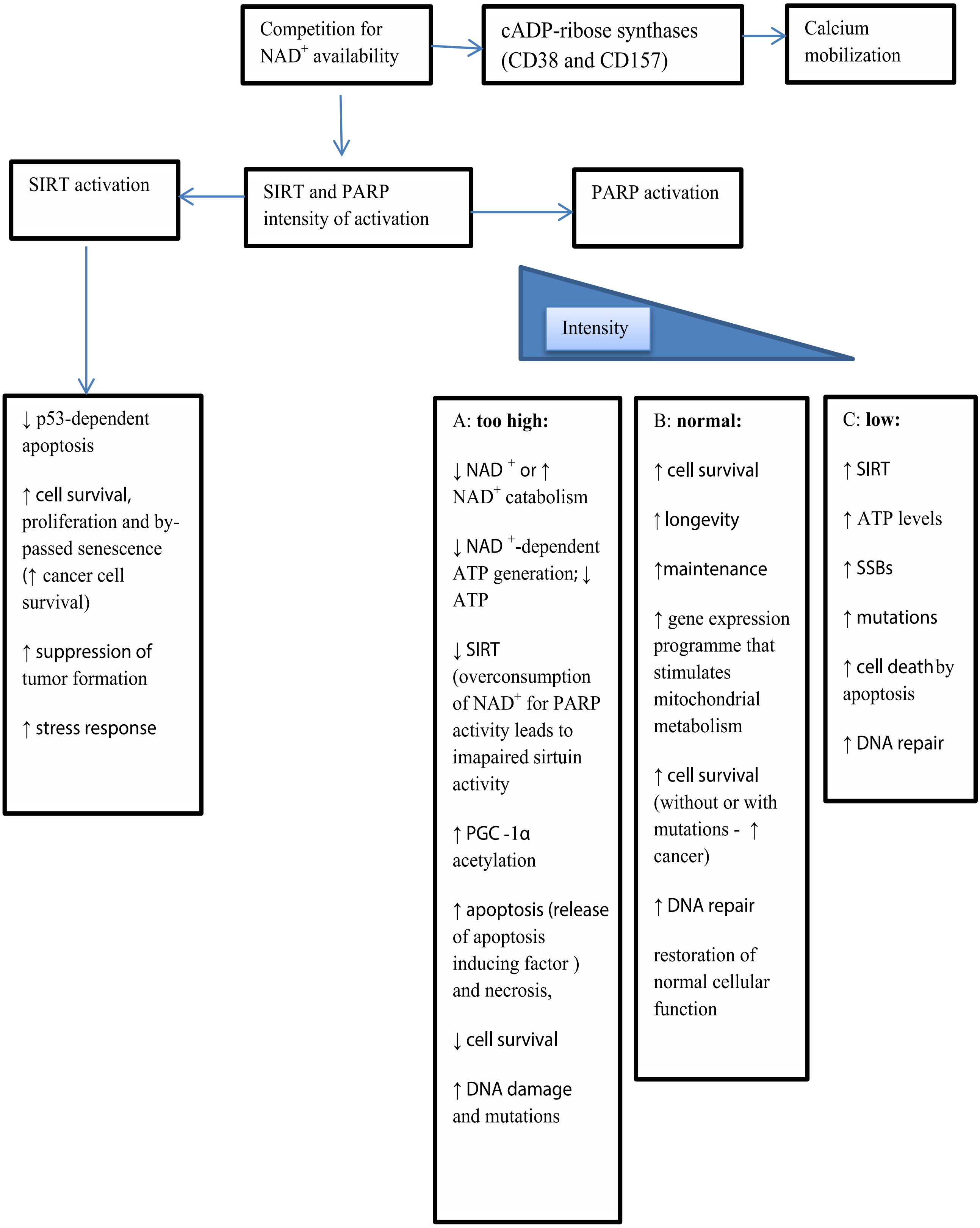

Figure 4: PARP-family ADP-ribosyltransferases and sirtuin deacetylases all compete for NAD^+ as substrate for ADP-ribosyl transfer. Sirtuins, PARPs and $CD38^+$ are all NAD^+ consumers and degrade NAD^+ back to NAM. Availability of NAD^+ influences the intensity of PARPs $CD38^+$ and sirtuin activation.

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repair is highly inaccurate when it is over-expressed, rather than under-expressed, and might stimulate formation of cancer due to the growth advantages [174]. It was reported that several forms of cancer are more dependent on PARP than regular cells and over-expresseion of PARP1 was observed in tyrosine kinase-activated leukemias [183] in neuroblastoma [184] in testicular and other germ cell tumors [185] and in Ewing's sarcoma [186]. Additionally, it was recently reported that PARP6, novel member of PARPs family, may act as a tumor suppressor via suppressing cell cycle progression [187].

SIRTs: Sirtuins also play a significant role in tumorigenesis, but there are conflicting results regarding siruins role before and during tumorigenesis. For example, SIRT1 has been observed to both promote and suppress tumour growth [188]. It seems that sirtuins may have a cell protective role under stress and may give cancer cells a growth advantage [189] as well; by preventing apoptotic death, stimulating proliferation, facilitating acquired resistance through genetic mutations, promoting survival of cancer stem cells, and changing the tumor microenvironment for resistance [190]. Overexpression or activation of SIRT1 promotes cellular proliferation, increases growth rate and impairs cellular senescence via the activation of ERK/ S6K1 signaling [191], thus increasing the risk of cancer since the cell loss from apoptosis and senescence-like growth arrest may be important anti-cancer regulators. For example, NAD^+ amount influences SIRT1 activity which can modulate cell death by increasing cell survival and proliferation. NAD/NADH ratio may regulate the tumour suppressor p53 via Sir2p/SIRT1 [192,193]. Sirt1 could be oncogenic and in several types of human tumours Sirt1 is upregulated [194]. For example, Herranz et al., [195] revealed that SIRT1 over-expression increased incidence of thyroid carcinomas and their lung metastasis and promotes both tumor initiation and progression in transgenic mice. Namely, by SIRT1 produced deacetylation of p53 its degradation is increased and p53-mediated cell death can be prevented [192,196,197].

Both human and mouse SIRT1 are thought to promote cell survival by deacetylating and thus deactivating p53 tumour suppressor gene hence enhancing p53 degradation [59,60]. Deacetylation by Sir2/SIRT1 is dependent on high concentrations of NAD^+ and also inhibited by increased PARP activity and by physiologic levels of nicotinamide [198,199]. Additionally, deacetylation of the DNA repair protein KU70 which blocks mitochondrial translocation of BAX and results in decreased apoptosis is another pro-cancerogenic effect where SIRT1 is involved [50]. To sum up, cellular apoptotic responses may vary, according to sirtuin activation intensity. As already mentioned moderate SIRT1 activation can prevent apoptosis while on the other hand, SIRT1 can increase the cell death by accelerating NAD^+ depletion [200]. Additionally, SIRT1 inhibits the expression of DNA repair enzymes (e.g. p53, BRCA1 and 2) and the expression of apoptosis-associated genes and can thus contribute to the cancer formation [201].

SIRT1 overexpression can epigenetically repress the activity or expression of DNA repair genes and tumor suppressors including FOXO family members (FOXO1, FOXO3a, and FOXO4) [202], p73 [203], Rb [204], MLH1 [205], and Ku70 [206].

Although SIRT1 can promote cell survival of malignant cells, many *in vivo* studies indicate that Sirt1 is a tumour suppressor [21,207-209] and SIRT1 expression is reduced in different human cancers, like glioblastoma, bladder carcinoma, prostate carcinoma, and ovarian cancer [209]. Tumor suppressor promotion by SIRT1 is involved in its DNA repair processes and genome stability maintenance [208,209]. Additionally, SIRT1 deacetylation of β-catenin leads to its inactivation and reduced cell proliferation [210]. What is more, SIRT1 might have a beneficial role in hormonal carcinogenesis by the deacetylation of androgen and estrogen receptors [211].

SIRT2 was reported to be downregulated in gliomas, breast cancer, head and neck squamous cell carcinoma, and esophagus adenocarcinoma [212-215]. Due to the ability of SIRT2 to induce the gene expression of both the proapoptotic enzymes as well as the antioxidation enzymes its dual effect on cell survival should be stressed [94]. SIRT3 is downregulated in breast cancer, hepatocellular carcinoma, and head and neck squamous cell carcinoma [216]. SIRT4 is downregulated in lung cancer [217]. The SIRT6 chromosomal locus was found to be deleted in pancreatic, colon, and liver cancers [218,219]. On the other hand, some studies reported cancer promotion and overexpression of SIRT2 and SIRT6 in acute myeloid leukemia, neuroblastoma, pancreatic cancer [220,221]. SIRT2 is upregulated in acute myeloid leukemia, neuroblastoma, pancreatic cancer, HCC, and regulates the Myc oncogenic pathway [222].

It can be concluded that the role for SIRT1 in p53-mediated tumor suppression still remains to be fully elucidated. The Sirt1 tumour suppressive activity is mainly ascribed to the ability of Sirt1 to preserve genomic integrity in the face of p53 deficiency [208,209]. SIRT1 deacetylates and inactivates p53, leading to down regulation of p53-mediated growth arrest and apoptosis which may result in increased risk of cancer [194]. On the other hand, increased SIRT1 inhibits expression and/or activity of several oncogenes, leading to reduced cell proliferation, increased apoptosis, and tumor suppression [194]. Although SIRT1 represses apoptosis, it also enhances DNA repair, thus SIRT1 might stimulate the priority to repair over apoptosis [223]. It should be stressed, however, that according to Herranz and Serrano, [224] there is no direct link between p53 and SIRT1 activities suggesting that SIRT1 inhibition could lead to tumor suppression and SIRT1 activation would promote tumor formation. Data from SIRT1 transgenic models challenge this hypothesis and point out that SIRT1 activation actually suppresses tumor formation [63,224].

Many other mechanisms of Sirt1 cancer protection were reported, including protection from DNA damage, protection from diet-induced inflammation, and inhibition of the oncogenic activity of β-catenin [224]. For example, SIRT1 deacetylates and inactivates hypoxia-inducible factor 1α, thus inhibits the expression of genes targeted by hypoxia-inducible factor 1α in certain tumors [132]. SIRT1 inhibits proliferation of pancreatic cancer cells expressing oncogenic pancreatic adenocarcinoma upregulated factor, by suppression of β-catenin and cyclin-D1 [225]. SIRT1 can influence also inflammatory responses, mainly through the regulation of NFκB and FOXO transcription factors (Figure 2) [226-228].To sum up, SIRT1 might differentially regulate genomic stability and apoptosis in normal versus cancer cells. Sirtuins role in cancer is complex and it seems that a specific sirtuin is crucial for a specific type of cancer. Besides, SIRT1, SIRT2 and SIRT3 appear to have both pro and anti-cancer roles [189].

Similarly, PARPs intensity influences cell death response. On the one hand activation of PARP-1 might preserve death of moderate damaged cells, while severe DNA damage leads to depletion of NAD^+ and severe consume of ATP resulting in increased cell death. Exposure to PARP-1 inhibitors can again stimulate or prevent cell death due to regeneration of NAD^+ and ATP [229,230] and activation of sirtuins.

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Deactivation of SIRT1 activity due to PARP-1-mediated NAD^+ depletion contrary stimulates the activity of several apoptotic effectors such as p53 [231], therefore, sensitizing cells to apoptosis. Adequate NAD^+ levels are critical to maintaining SIRT1 activity, which can delay apoptosis and provide vulnerable cells with additional time to repair even after the repeated oxidative stress insult – what is good for normal (although damaged) cells but detrimental for neoplastic cells due to pro-survival programme activation. Namely, increased PARP-1 and sirtuins expression in a cancer cells might exert a protective effect on the cancer cell's genome and decrease the efficacy of chemo or radiotherapy.

By increasing maintenance and repair systems with PARPs and sirtuins, different out-come in normal and cancer cells could evolve. On one hand cancer cell survival and proliferation by avoiding deleterious impact of DNA damage on key oncogenes could be stimulated with increased activity of sirtuins and PARPs, while increased DNA repair could lead to more selective mutations in cancer cells important for cancer evolution on the other hand. For example, increased PARP over-activation stimulates low fidelity DNA repair in cancer cells that might enable cancer cells to accumulate non-fatal lesions and mutations and evolve towards high grade malignancy leading to chemo and radiotherapy resistance. Contrary, moderate PARP and sirtuin activity in normal cells results in genome stability and tumor suppression. Increased PARPs and sirtuins can enable cells to survive in the face of stress that would normally trigger their programmed suicide. For example, Sirt1 does this by regulating the activity of several key cellular proteins, such as p53, FoxO and Ku70 – all of them are involved in cellular survival under stress. What is important to emphasise at the end, different effects of NAD^+ on the before mentioned processes could have opposite results in normal cells and in malignant transformation process (Figure 3).

To sum up, SIRT1 has both pro-cancer and anticancer effects and small molecule activators or repressors of SIRT1 could be used as cancer therapeutics [50].

It could be concluded that there are conflicting literature reports on the effect of NAD^+ on cell proliferation, cycle arrest, necrosis and apoptosis as well as on p53 dysregulation [181,192,232-235], and on PARP and sirtuin activation.

Sufficient supply of niacin and other NAD^+ precursors maintain sufficient amount of intracellular NAD^+ pool that plays important role in genomic stability due to PARP-1 and sirtuin activators [94].

Conclusion

NAD^+ has multiple and diverse cellular functions. Changes in NAD^+ metabolism have been associated with several pathologies, including cancer. In the hypothesis presented NAD^+ is shown as an important factor related to cancer formation and prevention. It is not only the NAD^+ as the cofactor in redox reactions that has important role in cancer biology, but also the NAD^+ as the substrate for sirtuins and PARP signaling. How exactly NAD^+ metabolism is regulated in the human cancer cells still remains to be fully elucidated as well as different metabolic changes that can take place following pharmacological supplementation with NAD^+ precursors and NAD^+ inhibitors. NAD^+ levels can be influenced with sport activity, caloric restriction and ingestion of NAD^+ precursors. PARP and sirtuin inhibitors are used also as anti-cancer agents. Namely, by decreasing intracellular PARP and sirtuin's level apoptosis can be influenced. Additionally, cancer preventive strategies presented could have dichotomous roles in the later stages of the disease (once tumor has developed and progressed), namely they could be tumor preventive for healthy (non-mutated cells) or tumor suppressing at early stages of tumorigenesis and could be tumor promoting later on. Increased amounts of NAD^+ may contribute to the development and/or progression of cancer once the cells already have cancer-like properties.

Due to controversial role of NAD^+ depletion on induction of cell death and its role in p53 activation and due to limited human trials, it is necessary to further elucidate mechanisms underlying the effects of NAD^+in the process of cancer and the role of NAD^+ on cancer prevention, initiation, promotion and progression phases. To devise better and different therapeutic strategies for cancer prevention and management in-depth understanding of how NAD^+ metabolism affects cellular defenses, repair, energy production and programmed cell death in different phases of the malignant process and in a particular type of cancer is necessary. Prolonged human studies are required to exclude potential adverse effects of NAD^+ administration and to establish optimal NAD concentrations for responding to DNA damage in non-cancerous cells and to find the optimal NAD^+ concentrations in cancerous cells in order to stimulate their apoptosis.

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