Redox Biology 41 (2021) 101950

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Invited Review

The diverse functionality of NQO1 and its roles in redox control

David Ross *, David Siegel

Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045, USA

ARTICLE INFO

Keywords:
NQO1
DT-Diaphorase
Quinone
Redox switch
Nrf2
Oxidative stress

ABSTRACT

In this review, we summarize the multiple functions of NQO1, its established roles in redox processes and potential roles in redox control that are currently emerging. NQO1 has attracted interest due to its roles in cell defense and marked inducibility during cellular stress. Exogenous substrates for NQO1 include many xenobiotic quinones. Since NQO1 is highly expressed in many solid tumors, including via upregulation of Nrf2, the design of compounds activated by NQO1 and NQO1-targeted drug delivery have been active areas of research. Endogenous substrates have also been proposed and of relevance to redox stress are ubiquinone and vitamin E quinone, components of the plasma membrane redox system. Established roles for NQO1 include a superoxide reductase activity, NAD^+ generation, interaction with proteins and their stabilization against proteasomal degradation, binding and regulation of mRNA translation and binding to microtubules including the mitotic spindles. We also summarize potential roles for NQO1 in regulation of glucose and insulin metabolism with relevance to diabetes and the metabolic syndrome, in Alzheimer's disease and in aging. The conformation and molecular interactions of NQO1 can be modulated by changes in the pyridine nucleotide redox balance suggesting that NQO1 may function as a redox-dependent molecular switch.

1. Introduction

It has been more than sixty years since the discovery of DT-diaphorase now defined as NQO1 by Ernster and colleagues [1,2] and new roles for this enzyme are still being uncovered (see functions of NQO1 in Fig. 1). In this review, we will summarize the multiple functions of NQO1 but focus on the roles of NQO1 in redox processes that have been established and potential roles in redox control that are currently emerging. We will also highlight some disease areas where NQO1 has been shown to be protective and summarize literature regarding NQO1 in aging.

Subsequent to the discovery of DT-diaphorase (NQO1), its properties were more fully defined in the early 60's by Ernster and colleagues [3–5]. The enzyme had similarities to a protein investigated by Martius and colleagues as a vitamin K reductase [6,7] and as summarized in a historical perspective [8], these enzymes were probably identical.

Early work on NQO1 suggested it may play a role as a component of the electron transport chain but that was soon ruled out [3,9] Another early suggestion was that NQO1 played a role in vitamin K metabolism. While NQO1 efficiently reduces vitamin K3 or menadione and is inhibited by the anticoagulants warfarin and dicoumarol [6,10], more recent work has shown it is unlikely to play a major role in vitamin K metabolism with other enzyme systems catalyzing these reactions much more efficiently [11]. NQO1 knockout animals also do not have bleeding problems [12] and vitamin K protects against warfarin poisoning in both NQO1-deficient and wild type animals [13]. One of the significant and enduring early findings on NQO1 related to its inducibility by a wide variety of compounds and the ability of many of these compounds to protect against cancer [10,14–19]. This led to the emergence of the role of NQO1 primarily as a chemoprotective enzyme but as work over the years has shown, there are significant exceptions particularly with respect to anticancer compounds [20–24].

2. Detoxification of quinones

One of the most cited roles for NQO1 is its protective effects against the deleterious oxidative and arylating effects of quinones and many of these studies utilized menadione (2-methyl-1,4-naphthoquinone) in cellular and other model systems [25–30]. The mechanism of detoxification of quinones by NQO1 is based on the direct two electron mediated

* Corresponding author. Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, 12850 East Montview Blvd, Aurora, CO, 80045 USA.
E-mail address: david.ross@cuanschutz.edu (D. Ross).

https://doi.org/10.1016/j.redox.2021.101950
Received 1 March 2021; Received in revised form 15 March 2021; Accepted 16 March 2021
Available online 20 March 2021

reduction of quinones to hydroquinones by NQO1 [31,32] removing electrophilic quinones and bypassing semiquinone radical and reactive oxygen species generation via redox cycling reactions. The crystal structure and mechanism of two electron reduction catalyzed by NQO1 has been clearly delineated by Amzel and colleagues [33–36]. NQO1 has also been implicated in detoxification of benzene-derived quinones in bone marrow in a cell-specific manner [37–40]. Consistent with this suggestion, the null NQO1*2 polymorphism which results in a lack of NQO1 protein (see Section 5) and an inability to detoxify quinones has been associated with increased toxicity in individuals occupationally exposed to benzene [41–43]. However, mechanisms underlying benzene toxicity are complex including the generation of a multiplicity of electrophilic metabolites and have recently been summarized in an IARC monograph [44].

3. The other side of the chemoprotection story – activation of quinones by NQO1

Hydroquinone generation is not always a detoxification step depending on the ability of hydroquinone to redox cycle, to rearrange to generate reactive electrophiles and the ability of the specific biological system to eliminate the hydroquinone either before or after conjugation via glucuronidation or sulfation [20,45,46]. Even in the well-cited case of menadione, small changes in the structure of the naphthoquinone alter the stability of the hydroquinone generated and can modulate toxicity [47,48]. 2-Hydroxy and 2-amino 1,4-naphthoquinone derivatives can be activated by NQO1 but interestingly *in-vivo*, not only the extent of toxicity could be modified by minor changes in structure relative to menadione but also the target site [49–51]. Superoxide dismutase (SOD) can also influence the autoxidation rates of hydroquinones generated by NQO1 and can either inhibit or accelerate autoxidation dependent on the stability and redox chemistry of the hydroquinone [45]. Activation of quinones via bioreductive mechanisms is a well-known approach in anticancer drug design [46,52–54] and NQO1-catalyzed generation of reactive hydroquinones derived from compounds as diverse as mitomycin C [22], E09 [55,56], aziridinylbenzoquinones [23,57,58], streptonigrin [54], β-lapachone [59], deoxynyboquinone [60] and geldanamycin based Hsp90 inhibitors [24] have been utilized as an approach to kill tumor cells with high levels of NQO1 which includes many solid tumors [61,62]. The mechanisms underlying tumor cell killing vary depending on the hydroquinone generated but the production of electrophilic intermediates that arylate DNA (mitomycin C, aziridnylbenzoquinones), reactive oxygen species (β-lapachone, streptonigrin, deoxynyboquinone) or molecules that are more efficient at inhibiting the specific cellular target (Hsp90) have all been demonstrated (Fig. 1).

3.1. NQO1 targeted drug delivery

The efficient reduction of quinones by NQO1 to chemically reactive hydroquinones has been utilized in a number of innovative studies designed to target drug delivery to NQO1 rich tumors. Numerous quinone conjugates have been developed where following hydroquinone formation, the compound undergoes chemical rearrangement triggering the release of a cytotoxic molecule that is separate from the quinone component [63–70]. Similarly, the quinone/hydroquinone trigger has been used to catalyze the release of fluorescent dyes into NQO1-rich tumors as a mechanism to distinguish tumor cells from normal cells [71–74]. The NQO1-dependent quinone/hydroquinone trigger has also been employed to catalyze the release of encapsulated cargo from a carrier complex (liposome, nanoparticle) into tumor cells [75–77]. In these models, the quinone component of the carrier molecule undergoes reduction to a hydroquinone by NQO1 which results in either chemical modification or degradation of the carrier allowing for release of the encapsulated drug into the tumor. A highly novel method of self-triggered cascading amplification drug delivery to NQO1-rich cells has also been developed [78]. In this system, β-lapachone and doxorubicin are encapsulated in an oxygen sensitive carrier. Following uptake into the tumor, leakage of small amounts of β-lapachone or endogenous reactive oxygen species initiate the degradation of the oxygen sensitive carrier. This initial degradation induces the release of more β-lapachone from the carrier and increases the generation of ROS which further stimulates the degradation of the carrier and release of doxorubicin [78].

4. Are there endogenous quinone substrates for NQO1?

There are many examples of xenobiotic quinones and other exogenous compounds that are metabolized by NQO1 [8,10,79]. Endogenous quinones that are metabolized by NQO1 constitute a much smaller list. Early suggestions included vitamin K (above) but we will discuss other possibilities below.

4.1. Ubiquinone and CoQ derivatives

In an important observation for the potential role of NQO1 in oxidative stress, NQO1 was shown to reduce CoQ substrates with various chain lengths to their antioxidant hydroquinone forms [80]. Long chain

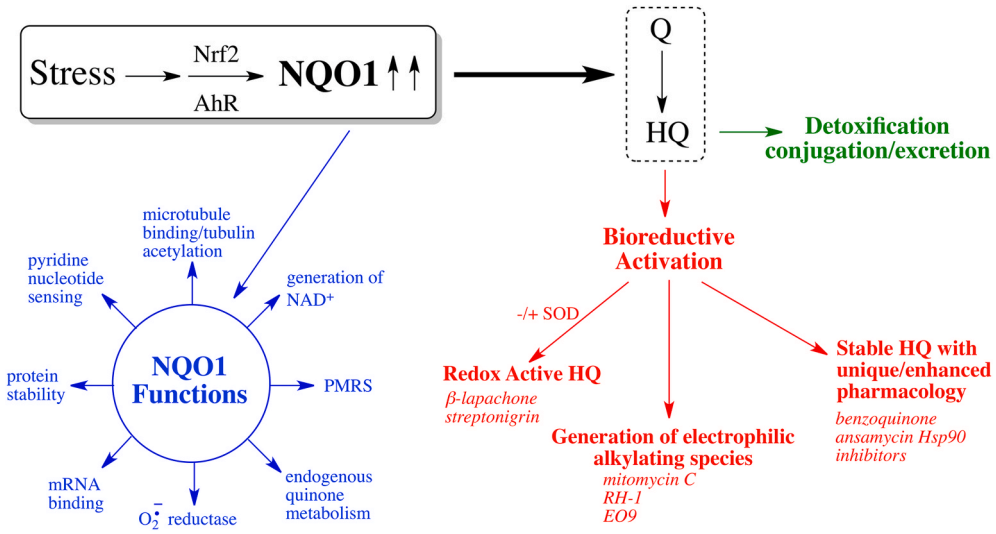

Fig. 1. Induction of NQO1 and the role of NQO1 in quinone metabolism and defense against oxidative stress.

derivatives of CoQ were approximately two orders of magnitude slower substrates for purified NQO1 as their shorter chain analogs but NQO1 was still able to efficiently reduce long chain ubiquinone derivatives (CoQ9 and CoQ10) that had been pre-incorporated into both artificial and natural membrane systems. Essentially all of the CoQ9 or CoQ10 pre-incorporated into lipid vesicles could be reduced to their quinol derivatives by the addition of NQO1 and NADH, a reaction inhibited by the NQO1 inhibitor dicoumarol. These observations were consistent with early work on NQO1 which showed activation of enzyme activity by lipids and the requirement of non-ionic detergents in assay systems for NQO1 for maximal activity [10] and provided support for a CoQ reductase role for NQO1. In lipid vesicles, CoQ10, NQO1 and NADH protected against lipid peroxidation and similarly CoQ10 prevented lipid peroxidation in isolated rat hepatocytes in reactions inhibited by the NQO1 inhibitor dicoumarol [80,81].

4.2. Vitamin E quinone

NQO1 can play a role in regenerating antioxidant forms of α-tocopherol (vitamin E) after free radical attack. Oxidation of α-tocopherol by hydroperoxyl radicals generates a tocopherone derivative which can either hydrolyze to α-tocopherol quinone (TQ) or can be reduced to regenerate α-tocopherol [82]. Recombinant NQO1 could reduce TQ, which is devoid of antioxidant protection, to α-tocopherol hydroquinone (THQ) which is an effective antioxidant [83] thus preserving antioxidant capacity. Cells stably transfected with human NQO1 exhibited greater reduction of TQ to THQ and greater protection against cumene hydroperoxide induced lipid peroxidation [83]. A role for NQO1 in regenerating α-tocopherol directly from its tocopherone derivative has been proposed [84] and the conversion of orally administered TQ to α-tocopherol has been verified in humans [85]. Although the enzyme systems responsible in conversion were not defined, a mechanism was proposed involving hydrolysis of THQ to α-tocopherol [85].

4.3. Catechol estrogen o-quinones

Metabolism of *o*-quinones derived from the endogenous estrogens estrone and estradiol by NQO1 has toxicological significance since the quinones are known to form depurinating adducts in DNA which have been suggested to contribute to the carcinogenic activity of estrogens [86,87]. However, there are conflicting reports of the ability of quinones derived from the oxidative metabolism of the estrogens estrone and estradiol to serve as substrates for NQO1. NQO1 has been reported to metabolize estrogen derived o-quinones [88] but the role of NQO1 in the detoxification of 4-hydroxyestrone o-quinone has been questioned [89] due to its relatively poor ability to undergo NQO1-mediated catalysis [90,91]. Estrogen derived ortho-quinones are also known to be better substrates for NQO2 than NQO1 [92]. Although estrogen derived o-quinones are relatively poor substrates for NQO1, expression of polymorphic variants of NQO1 (R139W and P187S) with diminished stability and metabolic capability resulted in increased estrogen DNA adducts in human mammary epithelial cells [93]. There is evidence that DNA adduct generation after treatment of human mammary epithelial cells with either estradiol or its oxidative metabolite 4-hydroxyestradiol was reduced by both pharmacological (sulforaphane) and genetic (siRNA for Kelch-like ECH-associated protein 1; Keap1) approaches to activate NF-E2 p45-related protein 2 (Nrf2) [94]. Although this finding is consistent with NQO1 mediated detoxification of estrogen-derived quinones limiting DNA adduct formation, results could also be explained via other Nrf2 upregulated systems or Nrf2 independent mechanisms [94]. Interestingly, antiestrogens have also been found to upregulate NQO1 via transcriptional mechanisms modulated at the level of the estrogen receptor resulting in decreased oxidative DNA damage in breast cancer cells [95,96].

4.4. Dopamine derived quinones

The metabolism of dopamine to neuromelanin is complex and involves a number of steps where quinoid metabolites can be generated [97–100]. The tyrosinase mediated generation of dopamine *ortho*-quinone is followed by cyclization at physiological pH to leukaminochrome, oxidation to the cyclized quinone aminochrome and eventual polymerization to melanins. Both NQO1 and NQO2 can metabolize dopamine derived ortho quinones [99,101,102]. Extensive work by Segura-Aguilar and colleagues have suggested a role for aminochrome in degeneration of dopaminergic neurons in the substantia nigra pars compacta in Parkinson's Disease and a protective role of NQO1 (for recent review see Ref. [100]). Aminochrome is a substrate for NQO1 [101] and despite generating a redox labile hydroquinone [99,101,102], NQO1 protects against many of the toxic effects induced by aminochrome. In dopaminergic cells, NQO1 has been found to be protective against aminochrome induced adverse effects including mitochondrial damage and ER stress [103], alpha synuclein oligomer formation [104], proteasomal dysfunction [99], lysosome dysfunction [105], microtubule and cytoskeletal damage [106,107] and autophagy [108]. NQO1 also protects dopaminergic cells against dopamine [109] and aminochrome induced cell death [110]. *In-vivo*, aminochrome was toxic to dopaminergic neurons located in the substantia nigra after intra-striatal injection into the brain but only after NQO1 was suppressed [111]. Since NQO1 has been found in rat substantia nigra [112] and in humans, in normal and Parkinsonian substantia nigra [113], it may play an endogenous detoxification role against dopamine-derived quinones in general and aminochrome in particular.

5. NQO1*2 polymorphism

The NQO1*2 polymorphism (rs1800566) is the result of a C to T base pair change at position 609 (cDNA) resulting in a proline to serine amino acid substitution at position 187 of the protein [114,115]. The mutant NQO1*2 protein has markedly decreased stability, FAD binding ability and a dramatically reduced half-life due to rapid polyubiquitination and proteasomal degradation [116,117]. The resultant phenotype of the NQO1*2 polymorphism is the near complete absence of a functional protein in individuals homozygous for the mutant allele while reduced levels of functional protein are seen in heterozygous individuals [117,118].

The mutant NQO1*2 protein has been thoroughly studied with respect to conformational dynamics and mobility. The substitution of the conformationally restricted proline 187 not only leads to local increased mobility close to the monomer interface but has destabilizing effects at distal sites including the FAD binding site in the N terminal domain and the C terminal regions [119–126]. Small molecules such as riboflavin and dicumarol have been shown to stabilize the NQO1*2 protein and prevent proteasomal degradation [123].

The frequency of NQO1*2 allele demonstrates wide ethnic diversity ranging from 0.18 in European populations to as high as 0.61 in the Hmong population of southeast Asia [127–129]. Over 100 studies have examined the association of the NQO1*2 allele either alone or in combination with other mutant alleles in human diseases. Recently, more in depth meta-analysis have been performed and the results from these studies suggests that the variant allele is associated with an increased risk of cancer in hepatocellular carcinoma as well as colorectal [130–132]; bladder [133,134]; and gastric [132,134,135] cancers.

6. Inducibility of NQO1 – Nrf2 and Ah receptor mediated induction

NQO1 is induced as a part of the Nrf2-directed adaptive response to cellular stress including electrophilic and oxidative stress and also activated as a component of the aromatic hydrocarbon receptor (AhR) directed response (Fig. 1), for reviews see Refs. [20,136]. In addition to

Nrf2 and AhR mediated induction of NQO1, the methylation status of the NQO1 promoter may also be an important factor controlling NQO1 expression [137–140]. Mechanisms have also been proposed for the transcriptional regulation of NQO1 by antiestrogen-liganded estrogen receptor [95,96].

One aspect of NQO1 induction that has been recently exploited is the activation of antitumor compounds by NQO1 in tumors that have aberrant and persistent Nrf2 upregulation as a result of activating mutations in the Keap1-Nrf2 pathway and other mechanisms [141]. Nrf2 is activated in many tumor types and such tumors often exhibit resistance to existing therapies resulting in poor patient outcomes [141]. This has led to the development of Keap1 knockout cell line screens for the identification of compounds that exhibit synthetic lethality with Nrf2 overexpression [142,143]. Compounds such as mitomycin C and quinone based Hsp90 inhibitors which are activated by NQO1 have been identified in screens for agents that induce selective toxicity to tumors with activated Nrf2 [142,143]. Nrf2 activation would increase tumor NQO1 levels leading to activation of either mitomycin C to reactive quinone methide metabolites capable of alkylating DNA and the generation of hydroquinone derivatives of geldanamycin quinones which are more active Hsp90 inhibitors [22,24]. It would be interesting to determine the selectivity profile of other NQO1-activated antitumor compounds in tumors with active Nrf2. β-Lapachone would be an interesting prospect given the innovative combination therapies developed by Boothman and colleagues with PARP inhibitors and with ionizing radiation [144–146]. However, additional molecules such as the aurora kinase inhibitor AT9283 have also been identified in these screens for selective killing of tumor cells with elevated Nrf2 levels [147] which do not have obvious links to NQO1-mediated bioreductive activation, although NQO1 has been reported to bind directly to aurora A [148]. A more complete analysis of compounds activated in cells with activated Nrf2 is detailed in the original references [142,143,147] and in a comprehensive recent review by Hayes and colleagues [141].

One of the common questions that arises is why is NQO1 so commonly activated as a component of the Nrf2 and Ah receptor induction systems in stress conditions and particularly in oxidative stress. In this short review, we will summarize the potential roles of NQO1 in protection against oxidative stress that have been described [20,79,84,149–151] and discuss other aspects of NQO1 biochemistry and function that are emerging which may indicate a role of NQO1 as a redox signaling system.

7. Catalytic functions of NQO1 in protection against oxidative stress

7.1. Generation of reduced CoQ9 and CoQ10 via NQO1 mediated reduction

The generation of hydroquinone forms of long chain CoQ derivatives CoQ9 and CoQ10 by NQO1 incorporated into lipid membranes and resultant protection from lipid peroxidation [80] was discussed in section 4.1. These authors suggested that NQO1 was selected during evolution as an endogenous CoQ reductase to maintain antioxidant protection [80].

7.2. Vitamin E quinone

Conversion of TQ to its antioxidant THQ by NQO1 was demonstrated using purified NQO1 and in cellular systems where it also provided antioxidant protection against lipid peroxidation [83]. Vitamin E quinone was discussed as a potential endogenous substrate for NQO1 in section 4.2.

7.3. The plasma membrane redox system (PMRS) system

Redox functions in the plasma membrane have been recognized for more than 75 years [152] and were extended to mitochondrial membrane redox systems with the concept of direct coupling of redox energy and ion transport (see Ref. [153] for a comprehensive review). The plasma membrane redox system (PMRS) is an important antioxidant system in cells and consists in its most basic form of antioxidants, enzymatic and chemical reductants and a source of reducing equivalents most commonly NAD(P)H [154]. Membrane antioxidant systems are complex but a useful schematic of the interrelationship of its components can be found in Ref. [155]. These components include CoQ10, α-tocopherol, ascorbate and a number of reducing enzymes capable of maintaining antioxidant forms of α-tocopherol and CoQ10. NADH-cytochrome b5 reductase can reduce CoQ via a one electron mechanism while as discussed above, NQO1 can reduce CoQ10 in lipid environments via a two-electron mechanism directly to ubiquinol. Other reductases capable of reducing CoQ have also been described [156–159]. Ubiquinol can also contribute to regeneration of α-tocopherol from the α-tocopherol radical [159] and mechanisms have also been proposed for the regeneration of α-tocopherol by ascorbate [160]. Enzymatic reductases are critical to the PMRS and NQO1 plays an important function in generating reduced forms of CoQ10 and TQ and protecting against lipid peroxidation as described in sections 4.1 and 4.2 [80,83,161].

7.4. Superoxide reductase activity

In biochemical experiments carried out to study oxidation and reduction reactions of free-flavins in solution, the addition of superoxide dismutase (SOD) prevented the oxidation of reduced flavin, suggesting that superoxide was responsible for the observed flavin oxidation [162,163]. Since the active site of NQO1 contains non-covalently bound flavin in the form of FAD and can generate and maintain reduced flavin (as $FADH_2$) via the oxidation of NAD(P)H, whether NQO1 could function as a NAD(P)H-dependent superoxide reductase was examined. Experiments using purified recombinant NQO1, and in cellular systems expressing NQO1, confirmed that NQO1 does possess superoxide reductase activity [164,165]. Kinetic studies, however, have shown that the rate of superoxide reduction by NQO1 was orders of magnitude slower than the rate reported for superoxide detoxification by SOD, suggesting a limited role for NQO1 in protection against superoxide [164]. However, the high levels of NQO1 found in many cell types either before or after induction via stress responses may help compensate for the slower rate of reduction of superoxide by NQO1. High levels of NQO1 protein expression have been detected in tissues from areas of the body with exposure to high levels of oxygen such as the cornea and lens of the eye [166,167], respiratory tract and blood vessels [167,168] and in cells sensitive to oxygen exposure including adipocytes where NQO1 may offer added protection against lipid peroxidation [167,169,170]. High levels of NQO1 can also be found in many types of cancers and may provide additional protection against oxidative damage [167,171].

8. Other potential roles of NQO1 during oxidative stress

8.1. Stabilization of target proteins against proteasomal degradation

One of the more intriguing features of NQO1 is its ability to bind to and protect a wide range of target proteins from proteasomal degradation. A growing list of proteins which have been shown to be protected against proteasomal degradation by NQO1 are shown in Table 1. For many of these proteins the protection afforded by NQO1 was shown to be NAD(P)H-dependent. In cell-free studies using purified proteins and mass spectrometry the NQO1 homodimer was shown to bind directly to the 20S proteasome [124]. In these studies, the association of NQO1 with the 20S proteasome was similar in the presence and absence of NADH suggesting that the interaction of NQO1 with the 20S proteasome, in contrast to interactions with target proteins, did not depend on the pyridine nucleotide redox balance.

Table 1
Proteins which have been shown to be protected against proteasomal degradation by NQO1.

Target Protein	Reference
p53, p63, p73	[265,266]
ODC1	[137,267]
p33(ING1b)	[268]
eIF4GI	[269]
PGC1-α	[270]
HIF-1α	[271]
HERP	[272]
Pol-β	[273]
SIRT6	[274]
TAT (HIV)	[172]
HBx	[173]

The ability of NQO1 to stabilize the viral HIV protein TAT and hepatitis B virus X protein (HBx) implicates NQO1 as a potential factor in viral replication. In cell studies the NQO1 inhibitor dicumarol was shown to reduce HIV viral replication by increasing proteasomal degradation of TAT which is required for the efficient transcription of HIV encoded genes. In a proposed feedback-loop one of these HIV genes encodes for the protein Rev, which was shown to down-regulate the expression of NQO1, resulting in increased TAT degradation. In this system, the authors describe NQO1 as a host protein which modulates the actions of two opposing HIV regulatory proteins [172]. Dicumarol also demonstrated antiviral activity against hepatitis B virus infection in hepatocytes and in animals. Treatment with dicumarol or NQO1 knock-down resulted in a decrease in amount of viral covalently closed circular DNA (cccDNA) by increasing the degradation of HBx, a viral protein required for cccDNA transcription [173].

8.2. *β-Lapachone and the generation of NAD$^+$*

Redox cycling quinones such as β-lapachone have potent anti-tumor activities due to their ability to generate reactive oxygen species and oxidative DNA damage [174]. Experiments have shown that NQO1 is the primary reductase responsible for the anti-tumor activity of β-lapachone [175]. NQO1 catalyzes the reduction of β-lapachone to an unstable hydroquinone which rapidly auto-oxidizes generating high levels of reactive oxygen species while at the same time also generating large amounts of NADP$^+$ and NAD$^+$ via the oxidation of NAD(P)H [175]. In experiments with β-lapachone, rapid NAD(P)H oxidation was observed but without a corresponding increase in NAD$^+$. The addition of PARP inhibitors restored NAD$^+$ levels indicating that PARP was responsible for the consumption of NAD$^+$ which was consistent with oxidative DNA damage induced by β-lapachone followed by PARP-mediated DNA repair [144,176,177]. NQO1-mediated futile redox cycling of β-lapachone leads to oxidative DNA damage, hyperactivation of PARP, depletion of NAD$^+$ and ATP and a specific type of programmed necrosis termed NAD$^+$-keresis [146,178–180]. These experiments exposed opposing roles for NQO1 in β-lapachone induced cytotoxicity where the enzyme is responsible for the generation of reactive metabolites, but at the same time produces NAD$^+$ to aid in DNA repair. To avoid oxidative DNA damage while retaining the ability to increase the NAD$^+$:NADH ratio, the use of low-dose β-lapachone has been examined for the treatment of a wide-range of disorders. In these studies with low dose β-lapachone, the generation of NAD$^+$ by NQO1 to enhance PARP and sirtuin-catalyzed reactions has been proposed in part to explain the therapeutic benefits observed [176,181–183].

8.3. *Association of NQO1 with microtubules*

The first reported association of NQO1 with microtubules came from studies using Xenopus egg extracts where experiments with inhibitors and immunodepletion showed that inhibition or loss of NQO1 resulted in a decrease in microtubule mitotic structures [184]. Later it was shown using immunostaining for NQO1 in cultured cells and archival tissues that NQO1 co-localized with α-tubulin to the centromere, mitotic spindles and midbody [177,185]. These microtubule structures contain high levels of acetylated α-tubulin (K40) and NQO1 was shown to co-localize with these acetylated structures in double-immunostaining studies [177]. Binding of NQO1 dimer to microtubules likely occurs via its positively charged C-terminal tails which are exposed when the enzyme is in the oxidized state [177,186]. A number of NAD$^+$-dependent enzymes including SIRT2 and PARP have also been observed to co-localize with these acetylated microtubule structures suggesting that NQO1 may be providing NAD$^+$ for these enzymes [187–189]. More recently it was demonstrated that mitotic progression was delayed when NQO1 was compromised [190]. In these studies, NQO1 and SIRT2 were shown to be bound together and co-localized to the mitotic spindle where it was proposed that NQO1 functions as a downstream modulator of SIRT2 deacetylase activity through its ability to bind to SIRT2 and provide NAD$^+$ [190].

We had previously suggested that binding of oxidized NQO1 to acetylated microtubules could act as a mechanism to retain the enzyme near microtubules where NQO1 could provide antioxidant protection [177]. Given more recent findings, it also seems probable that NQO1 localization on microtubules provides a mechanism to regulate the microtubule acetylome and acetylation/deacetylation balance (see Sec 10).

9. *NQO1 as a molecular switch responding to pyridine nucleotide redox ratios*

The flavoproteome consists of approximately 100 proteins and mutations in a surprisingly large proportion of flavoproteins (approximately 60%) are associated with human disease [191]. A role for flavin containing enzymes as cellular redox switches is well known and Becker et al. [192] have highlighted how the flavin redox state can mediate protein interactions with other proteins and macromolecules playing a role in transcriptional regulation, changes in localization, membrane binding and cell signaling. Conversion of the flavin from an oxidized to a reduced state or vice versa triggers a conformational change and functional output. Hydrogen bond networks linking the flavin to the surface of the protein are often found in these proteins [192]. Proteins highlighted by Becker et al. [192] included the fungal Vivid light sensor protein [193] and the transcriptional regulators of bacterial proline utilization A protein (PutA) [194,195] and nitrogen fixation (NifL) [196]. In addition, *E. coli* pyruvate oxidase switches from a cytosolic to a membrane bound protein after flavin reduction and release of the C terminal tail to allow the enzyme to efficiently catalyze ubiquinone reduction in the membrane [192,197,198].

Mammalian NQO2 has been proposed as a flavin redox switch with changes in FAD orientation on reduction in the presence of primaquine and chloroquine [199,200]. Reduced NQO2 has structural and electrostatic properties that result in preferential binding of certain DNA intercalating agents [201], thus demonstrating a separate pharmacological profile to the oxidized form of the enzyme.

Our own work has shown that NQO1 may also function as a redox sensing protein and redox switch. Local pyridine nucleotide ratios result in FAD reduction and altered conformation of the protein. The change in conformation results in loss of binding to antibodies that target multiple sites on NQO1 [177]. This conformational change is reversible depending on the levels of reduced pyridine nucleotides and flavin redox state. In many cases, protection against proteasome-mediated degradation of proteins by NQO1 (see above) was dependent upon pyridine nucleotide levels suggesting that the interaction of NQO1 with target proteins may be influenced directly by the NAD(P)H:NAD(P)$^+$ ratio and protein conformation. This has led us to consider the role of NQO1 as a potential reduced pyridine nucleotide redox sensor that can respond to changes in the pyridine nucleotide redox environment by altering its

conformation.

9.1. Biochemistry of the NQO1 redox switch

NAD(P)H was found to protect NQO1 against proteolytic digestion suggesting the protein underwent a protective conformational change in structure [202]. Under normal conditions where NAD(P)H levels are plentiful, NQO1 adopts a reduced conformation following hydride transfer from NAD(P)H to the FAD co-factor in NQO1. In the presence of efficient electron acceptors such as certain quinones, the reduced form of the flavin has a very short lifetime [203–205]. However, in the absence of efficient electron acceptors. there was only a slow rate of reaction between O_2 and reduced flavin [206] showing that the reduced form of the enzyme has appreciable stability under these conditions. X-ray crystallography, biochemical and computational studies performed by Amzel, and colleagues suggested that the stability of the reduced form of NQO1 occurred in part as a result of stabilization of charge separation in the reduced flavin by the protein [207,208]. The reduced and oxidized forms of NQO1 can be distinguished by using redox-dependent antibodies that bind to oxidized but not reduced NQO1 [177]. NQO1 undergoes a conformational change upon binding of reduced pyridine nucleotides, resulting in loss of immunoreactivity to antibodies that bind to helix 7 of the catalytic core domain or the C-terminus [177]. In the presence of NAD(P)H but in the absence of an efficient quinone electron acceptor, very little NQO1 could be immunoprecipitated demonstrating the presence of the reduced form of NQO1. As NAD(P)H levels are depleted, NQO1 can no longer maintain a reduced conformation and the protein reverts to its oxidized form enabling immunoprecipitation (Fig. 2). The distinct reduced and oxidized conformations of NQO1 have not been structurally characterized but non-denaturing gels clearly show different migratory properties for the reduced and oxidized conformations of the enzyme [177]. In subsequent studies [186], it was demonstrated that NQO1 can exist in at least three different conformational forms, a reduced conformation, an oxidized conformation and an inactivated conformation which have different reactivities with antibodies and therefore different implications for reacting with downstream proteins.

10. Implications of conformational changes in NQO1 on acetylation/deacetylation balance of microtubules

Acetylation and deacetylation of microtubules is a dynamic process and post translational modifications including acetylation balance at α-tubulin K40 have been suggested to affect microtubule stability and flexibility in turn minimizing microtubule aging and optimizing resilience [209–213]. Acetyl α-tubulin K40 is unique since it is the only lysine residue in the internal lumen of the microtubule. HDAC6 regulates the majority of microtubule deacetylation at K40 but SIRT2 also plays a significant K40 deacetylation role in the perinuclear region of the cell [214]. High intensity immunostaining for NQO1 in cells was reflective of an oxidized pyridine nucleotide environment in cells immunostaining and proximity ligation assays showed co-localization of NQO1 with acetylated microtubules and SIRT2 [177]. SIRT2 and NQO1 have also been found to co-immunoprecipitate [190]. The close proximity of NQO1, SIRT2 and acetyl K40 on microtubules led us to investigate the hypothesis that NQO1 may generate NAD^+ near microtubules to facilitate SIRT2 mediated deacetylation.

We initially utilized β-lapachone, which is an excellent substrate for NQO1 causing the generation of the oxidized form of NQO1, catalytic oxidation of NAD(P)H, the production of hydrogen peroxide and subsequent DNA damage and rapid NAD^+ depletion via PARP mediated DNA repair. In cells treated with β-lapachone a marked increase in the level of oxidized NQO1 was detected following immunoprecipitation with redox reactive *anti*-NQO1 antibodies concomitant with generation of the oxidized form of NQO1 [177]. This was consistent with the observation of high intensity cellular immunostaining for NQO1 under conditions where reduced pyridine nucleotide levels were decreased and the oxidized form of NQO1 was generated [177].

Oxidized and reduced NQO1 have different conformations but the addition of NQO1 inhibitors (dicoumarol or indolequinone mechanism based inhibitors) also induced a change in the conformation of NQO1 [177,186]. siRNA-mediated knockdown or CRISPR/Cas9 knockout of NQO1 in 16-HBE human lung epithelial cells or 3T3L1 mouse fibroblasts had little effect on acetyl α-tubulin K40 levels suggesting NQO1 was not providing NAD^+ for SIRT2 mediated deacetylation in this system. Altering the conformation of NQO1 using an indolequinone mechanism-based inhibitor, however, resulted in decreased binding of NQO1 to microtubules and, as observed when the oxidized conformation of NQO1 was generated intracellularly, an increase in the levels of acetyl α-tubulin K40 [186]. No changes in the cellular levels of reduced and oxidized pyridine nucleotides were detected as a result of treatment of cells with the indolequinone inhibitor of NQO1 suggesting the change in acetyl α-tubulin K40 levels was dependent on the conformational change in NQO1 and decreased microtubule binding [186]. Our interpretation of these results was that altered conformations of NQO1 regulate its binding to microtubules and disrupt the crowded protein environment in the lumen and the microtubule acetylome resulting in either increased acetylation or decreased deacetylation of α-tubulin K40 (Fig. 3).

NQO1 may modulate acetylation levels in cells via a number of

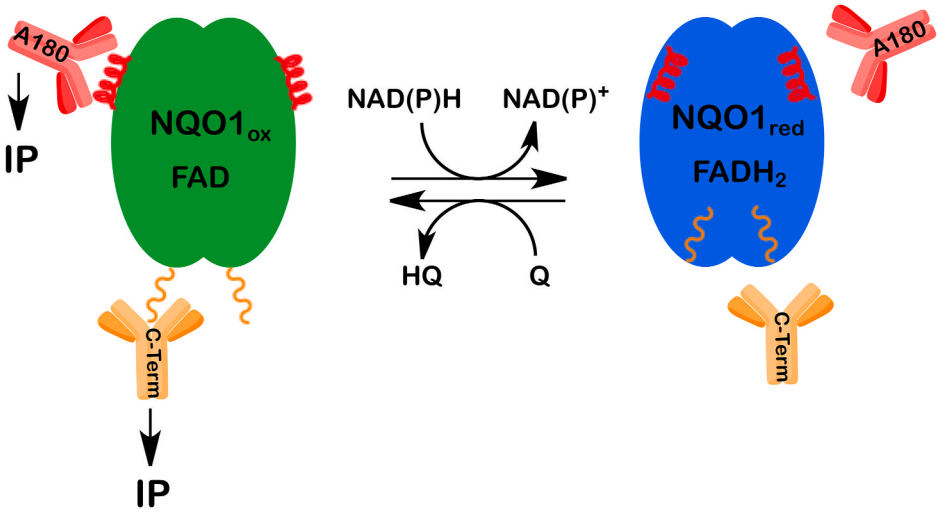

Fig. 2. Schematic representation of the redox-dependent immunoreactivity of NQO1. When NAD(P)H is readily available NQO1 adopts the reduced conformation (blue) preventing antibodies from binding to redox-dependent epitopes within helix 7 (A180) and to the C-terminal tails. When NAD(P)H levels drop the enzyme cannot maintain the reduced conformation and the redox-dependent epitopes are exposed allowing for immunoprecipitation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

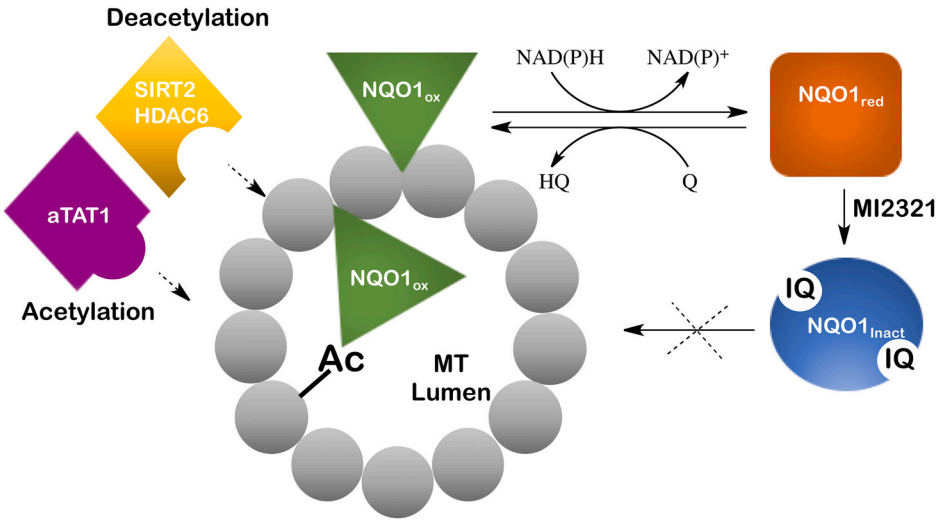

Fig. 3. Redox-dependent binding of NQO1 to microtubules. NAD(P)H levels direct the conformation of NQO1 and binding to microtubules. Inactivation of NQO1 by the inhibitor MI2321 alters the conformation of NQO1 preventing it from binding to microtubules disrupting the balance of acetylation/deacetylation (α-tubulin, K40) in the lumen of the microtubule leading to increased α-tubulin acetylation. Figure has been modified from Ref. [186].

mechanisms. The notion that NQO1 can generate NAD^+ during catalysis to provide NAD^+ for SIRT mediated deacetylation has been supported by a number of studies [183,190,215,216]. We did not find evidence for this mechanism in the cellular model systems that we used; however, we found that NQO1 conformation, which is primarily regulated by the redox environment, can result in modulation of acetyl α-tubulin K40 levels and microtubule structure. Therefore, in addition to providing NAD^+, NQO1 may also respond to the local pyridine nucleotide redox environment surrounding SIRT2 rich regions of microtubules and modulate the acetylation/deacetylation balance via conformation-dependent protein interactions.

Overall, this emphasizes the redox and conformational-dependent changes in NQO1 structure and how it may play an alternative redox sensing and/or redox-switching role. Changes in pyridine nucleotide redox status would result in altered NQO1 conformation which in turn could modulate downstream NQO1 interactions. Whether conformational changes in NQO1 result in altered location of the protein is intriguing and needs to be further investigated. NQO1 is known to be primarily cytosolic but has been reported to have significant nuclear, mitochondrial and membrane pools in different cell types [3,9,217–219].

11. Role for NQO1 in the regulation of mRNA translation

In experiments with proliferating HeLa cells, UV crosslinking was used to aid in the capture and characterization of novel mRNA binding proteins. Results from this study identified more than 800 mRNA binding proteins, one of which was NQO1 [220]. The binding of NQO1 to mRNA was hypothesized to occur via the di-nucleotide binding (Rossmann) fold [220]. The NQO1 active site contains a modified Rossmann fold where the third α/β pair is either missing or included in the crossover section located between two sections of the parallel β-sheet [221]. Since the active site of NQO1 undergoes a conformational change upon binding of NAD(P)H and transfer of the hydride to FAD it is reasonable to assume that the binding of NQO1 to mRNA could be regulated by the redox state of NQO1. Di Francesco et al., using ribonucleoprotein immunoprecipitation and microarray analysis identified a subset of NQO1 target mRNA's in human hepatoma HepG2 cells [222]. One of these mRNA targets was identified as SERPINA1 mRNA which encodes for the serine protease inhibitor α-1-antitrypsin (A1AT). Biotin pulldown experiments demonstrated that NQO1 can bind to both the 3′ untranslated region as well as the coding region of SERPINA1 mRNA. These studies also showed that NQO1 did not affect the levels of SERPINA1 mRNA, but instead, NQO1 binding enhanced the translation of SERPINA1 mRNA [222]. In another study, NQO1 was found to associate with polysomes isolated from mouse muscle tissue and in these experiments using co-immunoprecipitation NQO1 was shown to bind to the 60S ribosomal protein L13A [223]. The ability of NQO1 to bind to both mRNA transcripts and the 60S ribosome suggests that NQO1 may play multiple roles in mRNA translation.

12. Relevance of NQO1 to disease states

Oxidative stress is relevant to many disease states but we will focus on the potential roles of NQO1 in glucose and insulin response with relevance to type 2 diabetes and the metabolic syndrome and in Alzheimer's disease.

12.1. Nrf2 and NQO1 in glucose and insulin response

The Keap1-Nrf2 pathway is a potential target for the prevention of type 2 diabetes, obesity and metabolic syndrome [224]. Activation of Nrf2 in multiple murine diabetes models has led to improvements in insulin resistance [225]. Multiple biological mechanisms and pathways are likely responsible for the effects of Nrf2 including protection from oxidative stress, repression of hepatic gluconeogenesis, effects on lipid synthesis, mitochondrial function, inflammation, glycogen metabolism and crosstalk with other signaling systems [224–229]. A Nrf2 inducer reversed insulin resistance in obese mice, suppressed hepatic steatosis and reduced NASH and liver fibrosis via inhibition of endoplasmic reticulum, inflammatory and oxidative stress [230] However, these are complex diseases and there is conflicting experimental data regarding the effects of Nrf2 on insulin sensitivity, adipogenesis, inflammation and obesity [231,232] in part because of the multiplicity of Nrf2 mediated actions and context-dependent effects. A recent review focusing on redox biomarkers in obesity, metabolic syndrome and type 2 diabetes summarized conflicting data on the influence of Nrf2 in regulating obesity and metabolic health in response to HFD [233].

Interestingly, the downstream target of Nrf2, NQO1, has also been implicated in protection against diabetes and metabolic syndrome. Metabolic syndrome is associated with increased reactive oxygen generation leading to oxidative and pro-inflammatory processes that contribute to insulin insensitivity and disease progression [234,235]. The NQO1*2 null polymorphism in NQO1 has been associated with an

increased risk of adverse lipid profiles, coronary artery disease and Type 2 diabetes related to metabolic syndrome [236,237]. Gaikwad et al. reported that NQO1-null mice developed insulin resistance resulting in a type 2 diabetes-like phenotype [238]. However, in contrast, in a subsequent study, Diaz-Ruiz et al. found that NQO1-null mice exhibited reduced fasting insulin levels and improved glucose metabolism [239]. Pharmacological stimulation of NADH oxidation via NQO1 catalysis has also been associated with amelioration of obesity [176] and hypertension [240] in mice.

In recent collaborative work, we examined both the effects of overexpression of Nrf2 by deletion of Keap1 and NQO1 overexpression in transgenic mice fed high fat diets (HFD) [223]. While Nrf2 activation would be expected to activate more than 200 downstream genes [241], important similarities were observed between effects observed in systems where either Nrf2 was activated or the single gene NQO1 was overexpressed. Both Nrf2 activation and NQO1 overexpression in HFD-fed mice improved glucose and insulin metabolism, and improved lipid handling. Activation of Nrf2 however, unlike NQO1 overexpression, also protected against weight gain in animals on HFD so although NQO1 transgenic overexpressing (NQO1-Tg) mice developed obesity, they were still protected against liver steatosis and remained insulin sensitive. Mechanisms associated with the beneficial effects of NQO1 transgenesis were explored in more detail using integrated physiological data, histology and integrated metabolomics, proteomics and acetylomics. NQO1-Tg mice were protected from HFD-induced liver steatosis and macrophage infiltration in adipose tissues and metabolic signatures were consistent with improved glucose, NAD^+ and lipid metabolism and acetylation of a subset of SIRT3 targets in mitochondria [223]. NQO1 overexpression in skeletal muscle of mice fed HFD also led to decreased phosphorylation of the mTORC1 downstream target S6K1 and increased accumulation of 4EBP1, biochemical changes associated with protection against type 2 diabetes, obesity, diabetic nephropathy and insulin resistance [242–247]. A summary of the effects of NQO1 overexpression on nutritional excess as a result of high fat diet feeding is shown in Fig. 4. Interestingly, recent work has shown that the carotenoid astaxanthin reduces oxidative stress in a streptozotocin-induced diabetes model combined with high sugar and high fat. Of 120 targeted proteins and more than 13,000 diabetes mellitus targets, network analysis combined with transcriptional analysis identified NQO1 as one of the 3 key targets together with Col5A1 and Notch 2 responsible for the intersecting networks leading to astaxanthin-induced decreases in oxidative stress and reduced insulin resistance [248].

Much more work remains to be done regarding the mechanisms of protection of both Nrf2 and NQO1 against the many aspects of type 2 diabetes and the metabolic syndrome as well as elucidating both their similarities and differences.

12.2. NQO1 and Alzheimer's disease

NQO1 has long been associated with early pathological changes in Alzheimer's disease (AD) and its expression correlates with the progression and localization of AD pathology in human brains [249–251]. NQO1 levels are increased in AD brains relative to age matched controls and importantly, elevated NQO1 expression was limited to brain regions affected by AD pathology [249]. Increased NQO1 was found in neurofibrillary tangles and also in the cytoplasm of hippocampal neurons in post mortem samples from AD patients but not from young brains or in age matched controls from non-AD patients [251] and NQO1 immunostaining demonstrated localization of NQO1 surrounding senile plaques [249]. NQO1 is increased by oxidative stress as a part of the Nrf2 battery of stress response genes and the elevation of NQO1 associated with AD pathology is commonly viewed as a neuroprotective response to the oxidative stress that accompanies AD [249–251]. The NQO1*2 polymorphism is much more prevalent in Asian populations [127–129] and, a meta-analysis concluded that this polymorphism was significantly associated with AD in Chinese populations [252]. A recent review concluded that understanding links between NQO1 and AD pathology may contribute to an understanding of mechanisms of disease and could lead to new therapeutic approaches [253].

A novel observation of potential relevance to neurodegenerative diseases was obtained in studies using NQO1 and NQO1*2 as model flavoproteins and their potential to co-aggregate with β-amyloid ($A\beta_{1-42}$) known to form amyloid plaques in patients with Alzheimer's disease [254]. The NQO1*2 protein has a much lower affinity for FAD due to destabilizing effects in the FAD binding region distal from the position of the mutation resulting in rapid degradation of the protein via the proteasome [116,117,119–126]. The FAD-destabilized human recombinant NQO1*2 or wild type FAD-depleted apo NQO1 markedly stimulated co-aggregation with β-amyloid in cell-free systems relative to FAD-competent wild type NQO1 [254]. Riboflavin depletion also led to instability of NQO1 and other flavoproteins and enhanced amyloid aggregation in cells [254]. Thus, a deficiency in FAD led to misfolding of

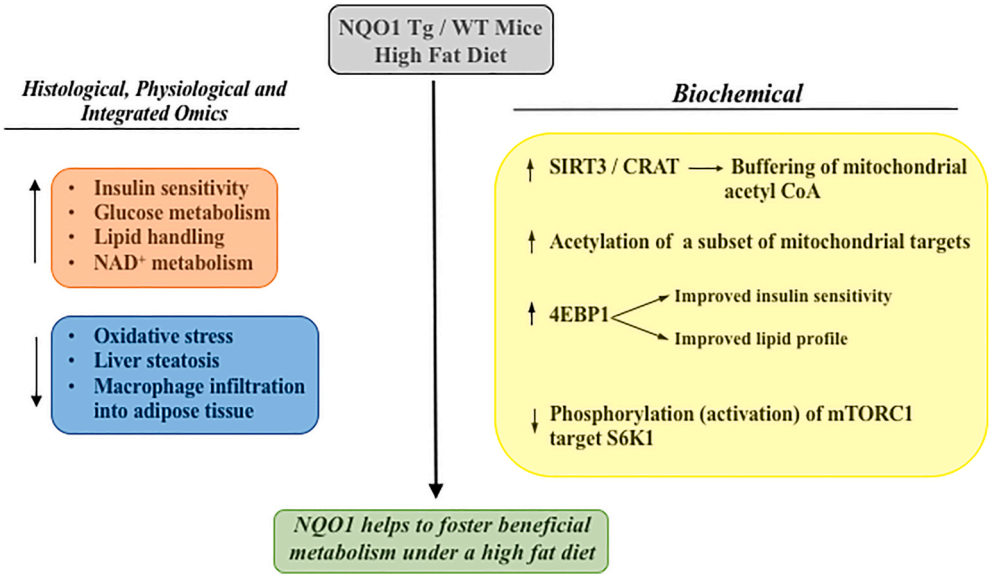

Fig. 4. The effects of NQO1 on markers of nutritional excess caused by feeding a high fat diet. For detailed discussion of histological, physiological, omic and biochemical changes associated with NQO1 overexpression in mice fed a high fat diet, see reference 223.

flavoproteins, overload of the proteasomal protein quality control system and the resultant co-aggregation of flavoproteins with β-amyloid potentially contributing to protein folding disorders.

13. NQO1 and aging

NQO1 declines with aging [255,256] providing less efficient protection against oxidative stress at many levels. Overexpression of a quinone reductase homolog in yeast extends both chronological and replicative lifespan [257]. One of the more robust approaches to manipulate the rate of aging in animal models is caloric restriction (CR) and CR upregulates levels of NQO1 and the PMRS in liver and brain thus conferring protection against oxidative stress [155,219,255]. Overexpression of NQO1 and cytochrome *b*5 reductase, two NAD^+ producing enzymes mimics aspects of CR in animals [258]. However, CR also resulted in improved survival of NQO1-knockout mice suggesting that although NQO1 may contribute to the effects of CR, it was not essential for the benefits of CR on lifespan [239]. A positive association of NQO1 with both maximal and median lifespan extension has been reported in a comprehensive analysis of gene expression changes of 17 known pharmacological, dietary and genetic lifespan-extending interventions applied to different strains, sexes and age groups of mice [259]. Feeding mice with the NQO1 substrate β-lapachone to mice in order to modulate the NAD^+/NADH ratio prevented age-dependent declines of motor and cognitive function in aged mice [182]. In the latter study, both β-lapachone and CR demonstrated similar effects on body weight, gene expression changes, behavioral function and increased longevity [182]. The use of NAD^+ precurors to increase cellular NAD^+ levels has resulted in improvement of cardiovascular and other age-related functional deficits [260–262], although many aspects of targeting NAD metabolism as a therapeutic approach in aging remain to be defined [263]. Interestingly, a recent high throughput anti-aging drug screen identified 2 compounds from more than 2600 screened, both of which affected pyridine nucleotide redox ratios and one of these compounds functioned via NQO1 catalysis [264]. Given the proposed roles of NQO1 to ameliorate oxidative stress via multiple mechanisms, its function as a redox switch and capacity to generate NAD^+ and influence proteostasis, the role of NQO1 in the aging phenotype is worthy of further examination.

14. Summary

In recent years we have gained more insights into the physiological roles of NQO1 and made significant advances in unveiling its complexities. NQO1 plays multiple physiological roles as a consequence of both its catalytic activity and its ability to directly interact with other proteins and RNA. Xenobiotic substrates for NQO1 have been well-characterized and some endogenous substrates have been proposed. However, the multiple roles of NQO1 across different cells and organ systems makes targeted inhibition of a single isolated function using pharmacological inhibitors a difficult challenge.

NQO1 is highly inducible in response to multiple forms of stress including oxidative stress and several protective mechanisms against oxidative damage have been characterized. Because NQO1 is expressed at high levels in many solid tumors, it has become a target for bioactivation of antitumor agents, and this may be particularly relevant if tumors have upregulated Nrf2 with a resultant increase in NQO1 levels. A role for NQO1 in disease states such as type 2 diabetes, the metabolic syndrome and Alzheimer's disease is beginning to emerge. Interestingly, in studies with mice fed a high fat diet, both Nrf2 upregulation and NQO1 overexpression led to improvements in glucose metabolism and insulin sensitivity although there were significant differences in phenotypes particulary in body weight trajectories. In aging, the potential involvement of NQO1 in lifespan extension is in need of further characterization and mechanistic insight.

The observation that the pyridine nucleotide ratio determines the conformation of NQO1 as demonstrated by the binding of redox specific antibodies suggests that NQO1 may also serve as a redox sensor, a role previously suggested for other flavoproteins. The implications of altered NQO1 functionality, particularly with respect to interactions with other proteins and RNA, as a function of pyridine nucleotide redox state raises interesting redox-dependent signaling possibilities.

Funding

DR and DS were supported in part by NIH grant R01-DK109964.

Declaration of competing interest

None.

Acknowledgments

We are indebted to our colleagues Drs. Michel Bernier, Rafael de Cabo, Andrea Di Francesco and Kris Fritz for advice and many helpful suggestions.

References

[1] L. Ernster, F. Navazio, Soluble diaphorase in animal tissues, Acta Chem. Scand. 12 (1958) 595–602.
[2] L. Ernster, Diaphorase activities in liver cytoplasmic fractions, Fed. Proc. 17 (1958) 216.
[3] L. Danielson, L. Ernster, Lack of relationship bewteen mitochondrial oxidative phosphorylation and the dicoumarol-sensitive flavoenzyme DT-diaphorase or vitamin K reductase, Nature 194 (1962) 155–157.
[4] L. Ernster, L. Danielson, M. Ljunggren, DT diaphorase. I. Purification from the soluble fraction of rat-liver cytoplasm, and properties, Biochim. Biophys. Acta 58 (1962) 171–188.
[5] L. Ernster, M. Ljunggren, L. Danielson, Purification and some properties of a highly dicoumarol-sensitive liver diaphorase, Biochem. Biophys. Res. Commun. 2 (1960) 88–92.
[6] F. Maerki, C. Martius, [Vitamin K reductase, preparation and properties], Biochem. Z. 333 (1960) 111–135.
[7] F. Maerki, C. Martius, [Vitamin K reductase, from cattle and ratliver], Biochem. Z. 334 (1961) 293–303.
[8] L. Ernster, DT-Diaphorase: a historical review, Chem. Scripta 27A (1987) 1–13.
[9] T.E. Conover, L. Ernster, DT-Diaphorase II. Relation to respiratory chain of intact mitochondria, Biochim. Biophys. Acta 58 (1962) 189–200.
[10] L. Ernster, DT-diaphorase. Meth, Enzymologia 10 (1967) 309–317.
[11] P.C. Preusch, D.M. Smalley, Vitamin K1 2,3-epoxide and quinone reduction: mechanism and inhibition, Free Radic. Res. Commun. 8 (1990) 401–415.
[12] X. Gong, R. Gutala, A.K. Jaiswal, Quinone oxidoreductases and vitamin K metabolism, Vitam. Horm. 78 (2008) 85–101.
[13] B.O. Ingram, J.L. Turbyfill, P.J. Bledsoe, A.K. Jaiswal, D.W. Stafford, Assessment of the contribution of NAD(P)H-dependent quinone oxidoreductase 1 (NQO1) to the reduction of vitamin K in wild-type and NQO1-deficient mice, Biochem. J. 456 (2013) 47–54.
[14] C. Huggins, R. Fukunishi, Induced protection of adrenal cortex against 7,12-dimethylbenz(a)anthracene. Influence of ethionine. Induction of menadione reductase. Incorporation of thymidine-H3, J. Exp. Med. 119 (1964) 923–942.
[15] A.M. Benson, M.J. Hunkeler, P. Talalay, Increase of NAD(P)H:quinone reductase by dietary antioxidants. Possible role in protection against carcinogenesis and toxicity, Proc. Natl. Acad. Sci. U.S.A. 77 (1980) 5216–5220.
[16] P. Talalay, A.M. Benson, Elevation of quinone reductase activity by anticarcinogenic antioxidants, Adv. Enzym. Regul. 20 (1981) 287–300.
[17] C. Huggins, E. Ford, R. Fukunishi, E.V. Jensen, Aromatic-induced prevention of fetal toxicity of 7,12-dimethylbenz(Alpha)Anthracene, J. Exp. Med. 119 (1964) 943–954.
[18] C.B. Huggins, E. Ford, E.V. Jensen, Carcinogenic aromatic hydrocarbons: special vulnerability of rats, Science 147 (1965) 1153–1154.
[19] H.G. Williams-Ashman, C. Huggins, Oxydation of reduced pyridine nucleotides in mammary gland and adipose tissue following treatment with polynuclear hydrocarbons, Med Exp Int J Exp Med 4 (1961) 223–226.
[20] D. Ross, J.K. Kepa, S.L. Winski, H.D. Beall, A. Anwar, D. Siegel, NAD(P)H:quinone oxidoreductase 1 (NQO1): chemoprotection, bioactivation, gene regulation and genetic polymorphisms, Chem. Biol. Interact. 129 (2000) 77–97.
[21] D. Siegel, C. Yan, D. Ross, NAD(P)H:quinone oxidoreductase 1 (NQO1) in the sensitivity and resistance to antitumor quinones, Biochem. Pharmacol. 83 (2012) 1033–1040.
[22] D. Siegel, N.W. Gibson, P.C. Preusch, D. Ross, Metabolism of mitomycin C by DT-diaphorase: role in mitomycin C- induced DNA damage and cytotoxicity in human colon carcinoma cells, Canc. Res. 50 (1990) 7483–7489.
[23] D. Siegel, N.W. Gibson, P.C. Preusch, D. Ross, Metabolism of diaziquone by NAD(P)H:(quinone acceptor) oxidoreductase (DT-diaphorase): role in diaziquone-

induced DNA damage and cytotoxicity in human colon carcinoma cells, Canc. Res. 50 (1990) 7293–7300.
[24] W. Guo, P. Reigan, D. Siegel, J. Zirrolli, D. Gustafson, D. Ross, Formation of 17-allylamino-demethoxygeldanamycin (17-AAG) hydroquinone by NAD(P)H: quinone oxidoreductase 1: role of 17-AAG hydroquinone in heat shock protein 90 inhibition, Canc. Res. 65 (2005) 10006–10015.
[25] P.L. Chesis, D.E. Levin, M.T. Smith, L. Ernster, B.N. Ames, Mutagenicity of quinones: pathways of metabolic activation and detoxification, Proc. Natl. Acad. Sci. U.S.A. 81 (1984) 1696–1700.
[26] C. Lind, P. Hochstein, L. Ernster, DT-Diaphorase as a quinone reductase: a cellular control device against semiquinone and superoxide radical formation, Arch. Biochem. Biophys. 216 (1982) 178–185.
[27] H. Thor, M.T. Smith, P. Hartzell, G. Bellomo, S.A. Jewell, S. Orrenius, The metabolism of menadione (2-methyl-1,4-naphthoquinone) by isolated hepatocytes. A study of the implication of oxidative stress in intact cells, J. Biol. Chem. 257 (1982) 12419–12425.
[28] H.J. Prochaska, P. Talalay, H. Sies, Direct protective effect of NAD(P)H:quinone reductaseagainst menadione-induced chemiluminescence of postmitochondrial fractions of mouse liver, J. Biol. Chem. 262 (1987) 1931–1934.
[29] H. Wefers, H. Sies, Hepatic low-level chemiluminescence during redox cycling of menadione and the menadione-glutathione conjugate: relation to glutathione and NAD(P)H:quinone reductase (DT-diaphorase) activity, Arch. Biochem. Biophys. 224 (1983) 568–578.
[30] A.S. Atallah, J.R. Landolph, L. Ernster, P. Hochstein, DT-diaphorase activity and the cytotoxicity of quinones in C3H/10T1/2 mouse embryo cells, Biochem. Pharmacol. 37 (1988) 2451–2459.
[31] T. Iyanagi, I. Yamazaki, Difference in the mechanism of quinone reduction by the NADH dehydrogenase and the NAD(P)H dehydrogenase (DT-diaphorase), Biochim. Biophys. Acta 216 (1970) 282–294.
[32] G. Tedeschi, S. Chen, V. Massey, DT-diaphorase. Redox potential, steady-state, and rapid reaction studies, J. Biol. Chem. 270 (1995) 1198–1204.
[33] M.A. Bianchet, M. Faig, L.M. Amzel, Structure and mechanism of NAD[P]H: quinone acceptor oxidoreductases (NQO), Methods Enzymol. 382 (2004) 144–174.
[34] R. Li, M. Bianchet, P. Talalay, L.M. Amzel, The three dimensional structure of NAD(P)H:(quinone acceptor) oxidoreductase, a chemoprotective flavoprotein, determined to 2.1A resolution, Faseb. J. 9 (1995) A1338.
[35] C.E. Foster, M.A. Bianchet, P. Talalay, M. Faig, L.M. Amzel, Structures of mammalian cytosolic quinone reductases, Free Radic. Biol. Med. 29 (2000) 241–245.
[36] M. Faig, M.A. Bianchet, P. Talalay, S. Chen, S. Winski, D. Ross, A.L. Mario, Structures of recombinant human and mouse NAD(P)H:quinone oxidoreductases: species comparison and structural changes with substrate binding and release, Proc. Natl. Acad. Sci. U. S. A 97 (2000) 3177–3182.
[37] D.J. Thomas, A. Sadler, V.V. Subrahmanyam, D. Siegel, M.J. Reasor, D. Wierda, D. Ross, Bone marrow stromal cell bioactivation and detoxification of the benzene metabolite hydroquinone: comparison of macrophages and fibroblastoid cells, Mol. Pharmacol. 37 (1990) 255–262.
[38] R.C. Smart, V.G. Zannoni, DT-Diaphorase and peroxidase influence the covalent binding of the metabolites of phenol, the major metabolite of benzene, Mol. Pharmacol. 26 (1984) 105–111.
[39] D. Ross, D. Siegel, D.G. Schattenberg, X.M.M. Sun, J.L. Moran, Cell-specific activation and detoxification of benzene metabolites in mouse and human bone marrow: identification of target cells and a potential role for modulation of apoptosis in benzene toxicity. *Environ. Health Perspect* 104, Supplement 6 (1996) 1177–1182.
[40] J.L. Moran, D. Siegel, D. Ross, A potential mechanism underlying the increased susceptibility of individuals with a polymorphism in NAD(P)H:quinone oxidoreductase 1 (NQO1) to benzene toxicity, Proc. Natl. Acad. Sci. U. S. A 96 (1999) 8150–8155.
[41] N. Rothman, M.T. Smith, R.B. Hayes, R.D. Traver, B. Hoener, S. Campleman, G. L. Li, M. Dosemeci, M. Linet, L. Zhang, L. Xi, S. Wacholder, W. Lu, K.B. Meyer, N. Titenko-Holland, J.T. Stewart, S. Yin, D. Ross, Benzene poisoning, a risk factor for hematological malignancy, is associated with the NQO1 609C–>T mutation and rapid fractional excretion of chlorzoxazone, Canc. Res. 57 (1997) 2839–2842.
[42] J. Wan, J. Shi, L. Hui, D. Wu, X. Jin, N. Zhao, W. Huang, Z. Xia, G. Hu, Association of genetic polymorphisms in CYP2E1, MPO, NQO1, GSTM1, and GSTT1 genes with benzene poisoning, Environ. Health Perspect. 110 (2002) 1213–1218.
[43] Y. Chen, G. Li, S. Yin, J. Xu, Z. Ji, X. Xiu, L. Liu, D. Ma, Genetic polymorphisms involved in toxicant-metabolizing enzymes and the risk of chronic benzene poisoning in Chinese occupationally exposed populations, Xenobiotica 37 (2007) 103–112.
[44] Iarc, Benzene. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 120, France, IARC, Lyon, 2020.
[45] E. Cadenas, Antioxidant and prooxidant functions of DT-diaphorase in quinone metabolism, Biochem. Pharmacol. 49 (1995) 127–140.
[46] D. Ross, D. Siegel, H. Beall, A.S. Prakash, R.T. Mulcahy, N.W. Gibson, DT-diaphorase in activation and detoxification of quinones. Bioreductive activation of mitomycin C, Canc. Metastasis Rev. 12 (1993) 83–101.
[47] D. Ross, H. Thor, M.D. Threadgill, M.S. Sandy, M.T. Smith, P. Moldeus, S. Orrenius, The role of oxidative processes in the cytotoxicity of substituted 1,4-naphthoquinones in isolated hepatocytes, Arch. Biochem. Biophys. 248 (1986) 460–466.
[48] G. Buffinton, K. Ollinger, A. Brunmark, E. Cadenas, DT-Diaphorase catalyzed reduction of 1,4-naphthoquinone derivatives and glutathionyl-quinone conjugates. Effects of substituents on autoxidation rates, Biochem. J. 256 (1989) 561–571.
[49] R. Munday, B.L. Smith, C.M. Munday, Effect of butylated hydroxyanisole on the toxicity of 2-hydroxy-1,4- naphthoquinone to rats, Chem. Biol. Interact. 117 (1999) 241–256.
[50] R. Munday, Activation and detoxification of naphthoquinones by NAD(P)H: quinone oxidoreductase, Methods Enzymol. 382 (2004) 364–380.
[51] R. Munday, B.L. Smith, C.M. Munday, Effect of inducers of DT-diaphorase on the haemolytic activity and nephrotoxicity of 2-amino-1,4-naphthoquinone in rats, Chem. Biol. Interact. 155 (2005) 140–147.
[52] G. Powis, Metabolism and reactions of quinoid anticancer agents, Pharmacol. Ther. 35 (1987) 57–162.
[53] D. Ross, H.D. Beall, D. Siegel, R.D. Traver, D.L. Gustafson, Enzymology of bioreductive drug activation, Br. J. Canc. 74 (Suppl. XXVII) (1996) S1–S8.
[54] H.D. Beall, R.T. Mulcahy, D. Siegel, R.D. Traver, N.W. Gibson, D. Ross, Metabolism of bioreductive antitumor compounds by purified rat and human DT-diaphorases, Canc. Res. 54 (1994) 3196–3201.
[55] S.M. Bailey, A.D. Lewis, R.J. Knox, L.H. Patterson, G.R. Fisher, P. Workman, Reduction of the indoloquinone anticancer drug EO9 by purified DT-diaphorase: a detailed kinetic study and analysis of metabolites, Biochem. Pharmacol. 56 (1998) 613–621.
[56] G.A. Choudry, P.A. Stewart, J.A. Double, M.R. Krul, B. Naylor, G.M. Flannigan, T. K. Shah, J.E. Brown, R.M. Phillips, A novel strategy for NQO1 (NAD(P)H:quinone oxidoreductase, EC 1.6.99.2) mediated therapy of bladder cancer based on the pharmacological properties of EO9, Br. J. Canc. 85 (2001) 1137–1146.
[57] D.L. Dehn, S.L. Winski, D. Ross, Development of a new isogenic cell-xenograft system for evaluation of NAD(P)H: quinone oxidoreductase-directed antitumor quinones: evaluation of the activity of RH1, Clin. Canc. Res. 10 (2004) 3147–3155.
[58] D.L. Dehn, S.H. Inayat-Hussain, D. Ross, RH1 induces cellular damage in an NAD (P)H: quinone oxidoreductase 1-dependent manner: relationship between DNA cross-linking, cell cycle perturbations, and apoptosis, J. Pharmacol. Exp. Therapeut. 313 (2005) 771–779.
[59] J.J. Pink, S.M. Planchon, C. Tagliarino, M.E. Varnes, D. Siegel, D.A. Boothman, NAD(P)H: quinone oxidoreductase activity is the principal determinant of beta-lapachone cytotoxicity, J. Biol. Chem. 275 (2000) 5416–5424.
[60] J.S. Bair, R. Palchaudhuri, P.J. Hergenrother, Chemistry and biology of deoxynyboquinone, a potent inducer of cancer cell death, J. Am. Chem. Soc. 132 (2010) 5469–5478.
[61] D. Siegel, D. Ross, Immunodetection of NAD(P)H:quinone oxidoreductase 1 (NQO1) in human tissues, Free Radic. Biol. Med. 29 (2000) 246–253.
[62] N.S. Awadallah, D. Dehn, R.J. Shah, S. Russell Nash, Y.K. Chen, D. Ross, J. S. Bentz, K.R. Shroyer, NQO1 expression in pancreatic cancer and its potential use as a biomarker, Appl. Immunohistochem. Mol. Morphol. 16 (2008) 24–31.
[63] M. Volpato, N. Abou-Zeid, R.W. Tanner, L.T. Glassbrook, J. Taylor, I. Stratford, P. M. Loadman, M. Jaffar, R.M. Phillips, Chemical synthesis and biological evaluation of a NAD(P)H:quinone oxidoreductase-1 targeted tripartite quinone drug delivery system, Mol. Canc. Therapeut. 6 (2007) 3122–3130.
[64] B. Huang, A. Desai, S. Tang, T.P. Thomas, J.R. Baker Jr., The synthesis of a c (RGDyK) targeted SN38 prodrug with an indolequinone structure for bioreductive drug release, Org. Lett. 12 (2010) 1384–1387.
[65] K. Sharma, A. Iyer, K. Sengupta, H. Chakrapani, INDQ/NO, a bioreductively activated nitric oxide prodrug, Org. Lett. 15 (2013) 2636–2639.
[66] P. Liu, J. Xu, D. Yan, P. Zhang, F. Zeng, B. Li, S. Wu, A DT-diaphorase responsive theranostic prodrug for diagnosis, drug release monitoring and therapy, Chem. Commun. 51 (2015) 9567–9570.
[67] W.S. Shin, J. Han, P. Verwilst, R. Kumar, J.H. Kim, J.S. Kim, Cancer targeted enzymatic theranostic prodrug: precise diagnosis and chemotherapy, Bioconjugate Chem. 27 (2016) 1419–1426.
[68] B. Li, P. Liu, D. Yan, F. Zeng, S. Wu, A self-immolative and DT-diaphorase-activatable prodrug for drug-release tracking and therapy, J. Mater. Chem. B 5 (2017) 2635–2643.
[69] S. Xu, H. Yao, L. Pei, M. Hu, D. Li, Y. Qiu, G. Wang, L. Wu, H. Yao, Z. Zhu, J. Xu, Design, synthesis, and biological evaluation of NAD(P)H: quinone oxidoreductase (NQO1)-targeted oridonin prodrugs possessing indolequinone moiety for hypoxia-selective activation, Eur. J. Med. Chem. 132 (2017) 310–321.
[70] X. Zhang, X. Li, Z. Li, X. Wu, Y. Wu, Q. You, X. Zhang, An NAD(P)H: quinone oxidoreductase 1 responsive and self-immolative prodrug of 5-fluorouracil for safe and effective cancer therapy, Org. Lett. 20 (2018) 3635–3638.
[71] S.T. Huang, Y.X. Peng, K.L. Wang, Synthesis of a new long-wavelength latent fluorimetric indicator for analytes determination in the DT-Diaphorase coupling dehydrogenase assay system, Biosens. Bioelectron. 23 (2008) 1793–1798.
[72] S.U. Hettiarachchi, B. Prasai, R.L. McCarley, Detection and cellular imaging of human cancer enzyme using a turn-on, wavelength-shiftable, self-immolative profluorophore, J. Am. Chem. Soc. 136 (2014) 7575–7578.
[73] B. Prasai, W.C. Silvers, R.L. McCarley, Oxidoreductase-facilitated visualization and detection of human cancer cells, Anal. Chem. 87 (2015) 6411–6418.
[74] Z. Shen, B. Prasai, Y. Nakamura, H. Kobayashi, M.S. Jackson, R.L. McCarley, A near-infrared, wavelength-shiftable, turn-on fluorescent probe for the detection and imaging of cancer tumor cells, ACS Chem. Biol. 12 (2017) 1121–1132.
[75] W. Ong, Y. Yang, A.C. Cruciano, R.L. McCarley, Redox-triggered contents release from liposomes, J. Am. Chem. Soc. 130 (2008) 14739–14744.
[76] S.R. Gayam, P. Venkatesan, Y.M. Sung, S.Y. Sung, S.H. Hu, H.Y. Hsu, S.P. Wu, An NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme responsive nanocarrier based on mesoporous silica nanoparticles for tumor targeted drug delivery in vitro and in vivo, Nanoscale 8 (2016) 12307–12317.

[77] J. Park, S. Jo, Y.M. Lee, G. Saravanakumar, J. Lee, D. Park, W.J. Kim, Enzyme-triggered disassembly of polymeric micelles by controlled depolymerization via cascade cyclization for anticancer drug delivery, ACS Appl. Mater. Interfaces 13 (7) (2021) 8060–8070.
[78] H. Li, Q. Li, W. Hou, J. Zhang, C. Yu, D. Zeng, G. Liu, F. Li, Enzyme-catalytic self-triggered release of drugs from a nanosystem for efficient delivery to nuclei of tumor cells, ACS Appl. Mater. Interfaces 11 (2019) 43581–43587.
[79] C. Lind, E. Cadenas, P. Hochstein, L. Ernster, DT-Diaphorase. Purification properties and function, Methods Enzymol. 186 (1990) 287–301.
[80] R.E. Beyer, J. Segura-Aguilar, S. Di Bernardo, M. Cavazzoni, R. Fato, D. Fiorentini, M. Galli, M. Setti, L. Landi, G. Lenaz, The role of DT-diaphorase in the maintenance of the reduced antioxidant form of coenzyme Q in membrane systems, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 2528–2532.
[81] L. Landi, D. Fiorentini, M.C. Galli, J. Segura-Aguilar, R.E. Beyer, DT-diaphorase maintains the reduced state of ubiquinones in lipid vesicles thereby promoting their antioxidant function, Free Radic. Biol. Med. 22 (1997) 329–335.
[82] D.C. Liebler, The role of metabolism in the antioxidant function of vitamin E, Crit. Rev. Toxicol. 23 (1993) 147–169.
[83] D. Siegel, E.M. Bolton, J.A. Burr, D.C. Liebler, D. Ross, The reduction of alpha-tocopherolquinone by human NAD(P)H: quinone oxidoreductase: the role of alpha-tocopherol hydroquinone as a cellular antioxidant, Mol. Pharmacol. 52 (1997) 300–305.
[84] E. Cadenas, P. Hochstein, L. Ernster, Pro-and antioxidant functions of quinones and quinone reductases in mammalian cells, Adv. Enzymol. Relat. Area Mol. Biol. 65 (1992) 97–146.
[85] A.N. Moore, K.U. Ingold, alpha-Tocopheryl quinone is converted into vitamin E in man, Free Radic. Biol. Med. 22 (1997) 931–934.
[86] E. Cavalieri, D. Chakravarti, J. Guttenplan, E. Hart, J. Ingle, R. Jankowiak, P. Muti, E. Rogan, J. Russo, R. Santen, T. Sutter, Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention, Biochim. Biophys. Acta 1766 (2006) 63–78.
[87] E. Cavalieri, K. Frenkel, J.G. Liehr, E. Rogan, D. Roy, Estrogens as endogenous genotoxic agents–DNA adducts and mutations, J. Natl. Cancer Inst. Monogr. (2000) 75–93.
[88] N.W. Gaikwad, E.G. Rogan, E.L. Cavalieri, Evidence from ESI-MS for NQO1-catalyzed reduction of estrogen ortho-quinones, Free Radic. Biol. Med. 43 (2007) 1289–1298.
[89] R.E. Chandrasena, P.D. Edirisinghe, J.L. Bolton, G.R. Thatcher, Problematic detoxification of estrogen quinones by NAD(P)H-dependent quinone oxidoreductase and glutathione-S-transferase, Chem. Res. Toxicol. 21 (2008) 1324–1329.
[90] L. Shen, E. Pisha, Z.W. Huang, J.M. Pezzuto, E. Krol, Z. Alam, Van Breemen, , R. B., J.L. Bolton, Bioreductive activation of catechol estrogen-*ortho*-quinones: aromatization of the B ring in 4-hydroxyequilenin markedly alters quinoid formation and reactivity, Carcinogenesis 18 (1997) 1093–1101.
[91] L.M. Nutter, B. Zhou, E.E. Sierra, Y.Y. Wu, M.M. Rummel, P. Gutierrez, Y. Abul-Hajj, Cellular biochemical determinants modulating the metabolism of estrone 3,4-quinone, Chem. Res. Toxicol. 7 (1994) 609–613.
[92] N.W. Gaikwad, L. Yang, E.G. Rogan, E.L. Cavalieri, Evidence for NQO2-mediated reduction of the carcinogenic estrogen ortho-quinones, Free Radic. Biol. Med. 46 (2009) 253–262.
[93] S. Singh, M. Zahid, M. Saeed, N.W. Gaikwad, J.L. Meza, E.L. Cavalieri, E. G. Rogan, D. Chakravarti, NAD(P)H:quinone oxidoreductase 1 Arg139Trp and Pro187Ser polymorphisms imbalance estrogen metabolism towards DNA adduct formation in human mammary epithelial cells, J. Steroid Biochem. Mol. Biol. 117 (2009) 56–66.
[94] L. Yang, M. Zahid, Y. Liao, E.G. Rogan, E.L. Cavalieri, N.E. Davidson, J.D. Yager, K. Visvanathan, J.D. Groopman, T.W. Kensler, Reduced formation of depurinating estrogen-DNA adducts by sulforaphane or KEAP1 disruption in human mammary epithelial MCF-10A cells, Carcinogenesis 34 (2013) 2587–2592.
[95] M.M. Montano, N.R. Bianco, H. Deng, B.M. Wittmann, L.C. Chaplin, B. S. Katzenellenbogen, Estrogen receptor regulation of quinone reductase in breast cancer: implications for estrogen-induced breast tumor growth and therapeutic uses of tamoxifen, Front. Biosci. 10 (2005) 1440–1461.
[96] M.M. Montano, A.K. Jaiswal, B.S. Katzenellenbogen, Transcriptional regulation of the human quinone reductase gene by antiestrogen-liganded estrogen receptor-alpha and estrogen receptor-beta, J. Biol. Chem. 273 (1998) 25443–25449.
[97] D.G. Graham, Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones, Mol. Pharmacol. 14 (1978) 633–643.
[98] D.G. Graham, S.M. Tiffany, W.R. Bell Jr., W.F. Gutknecht, Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related compounds toward C1300 neuroblastoma cells in vitro, Mol. Pharmacol. 14 (1978) 644–653.
[99] K.S. Zafar, D. Siegel, D. Ross, A potential role for cyclized quinones derived from dopamine, DOPA, and 3,4-dihydroxyphenylacetic acid in proteasomal inhibition, Mol. Pharmacol. 70 (2006) 1079–1086.
[100] A. Herrera, P. Munoz, H.W.M. Steinbusch, J. Segura-Aguilar, Are dopamine oxidation metabolites involved in the loss of dopaminergic neurone in the nigrstriatal system in Parkinson's Disease? ACS Chem. Neurosci. 8 (2017) 702–711.
[101] J. Segura-Aguilar, C. Lind, On the mechanism of the Mn-induced neurotoxicity of dopamine:Prevention of quinone derived oxygen toxicity by DT-diaphorase and superoxide dismutase, Chem. Biol. Interact. 72 (1989) 309–324.
[102] L.E. Cassagnes, P. Perio, G. Ferry, N. Moulharat, M. Antoine, R. Gayon, J. A. Boutin, F. Nepveu, K. Reybier, In cellulo monitoring of quinone reductase activity and reactive oxygen species production during the redox cycling of 1,2 and 1,4 quinones, Free Radic. Biol. Med. 89 (2015) 126–134.
[103] J. Segura-Aguilar, On the role of aminochrome in mitochondrial dysfunction and endoplasmic reticulum stress in Parkinson's disease, Front. Neurosci. 13 (2019) 271.
[104] P. Munoz, S. Cardenas, S. Huenchuguala, A. Briceno, E. Couve, I. Paris, J. Segura-Aguilar, DT-diaphorase prevents aminochrome-induced alpha-synuclein oligomer formation and neurotoxicity, Toxicol. Sci. 145 (2015) 37–47.
[105] C. Melendez, P. Munoz, J. Segura-Aguilar, DT-diaphorase prevents aminochrome-induced lysosome dysfunction in SH-SY5Y cells, Neurotox. Res. 35 (2019) 255–259.
[106] I. Paris, C. Perez-Pastene, S. Cardenas, P. Iturriaga-Vasquez, P. Munoz, E. Couve, P. Caviedes, J. Segura-Aguilar, Aminochrome induces disruption of actin, alpha-, and beta-tubulin cytoskeleton networks in substantia-nigra-derived cell line, Neurotox. Res. 18 (2010) 82–92.
[107] A. Briceno, P. Munoz, P. Brito, S. Huenchuguala, J. Segura-Aguilar, I.B. Paris, Aminochrome toxicity is mediated by inhibition of microtubules polymerization through the formation of adducts with tubulin, Neurotox. Res. 29 (2016) 381–393.
[108] P.S. Munoz, J. Segura-Aguilar, DT-diaphorase protects against autophagy induced by aminochrome-dependent alpha-synuclein oligomers, Neurotox. Res. 32 (2017) 362–367.
[109] K.S. Zafar, S.H. Inayat-Hussain, D. Siegel, A. Bao, B. Shieh, D. Ross, Overexpression of NQO1 protects human SK-N-MC neuroblastoma cells against dopamine-induced cell death, Toxicol. Lett. 166 (2006) 261–267.
[110] J. Lozano, P. Munoz, B.F. Nore, S. Ledoux, J. Segura-Aguilar, Stable expression of short interfering RNA for DT-diaphorase induces neurotoxicity, Chem. Res. Toxicol. 23 (2010) 1492–1496.
[111] A. Herrera-Soto, G. Diaz-Veliz, S. Mora, P. Munoz, P. Henny, H.W.M. Steinbusch, J. Segura-Aguilar, On the role of DT-diaphorase inhibition in aminochrome-induced neurotoxicity in, Vivo. Neurotox Res 32 (2017) 134–140.
[112] M. Schultzberg, J. Segura-Aguilar, C. Lind, Distribution of DT-diaphorase in the rat brain: biochemical and immunohistochemical studies, Neuroscience (1988) 763–776.
[113] F.L. van Muiswinkel, R.A. de Vos, J.G. Bol, G. Andringa, E.N. Jansen Steur, D. Ross, D. Siegel, B. Drukarch, Expression of NAD(P)H:quinone oxidoreductase in the normal and Parkinsonian substantia nigra, Neurobiol. Aging 25 (2004) 1253–1262.
[114] R.D. Traver, T. Horikoshi, K.D. Danenberg, T.H. Stadlbauer, P.V. Danenberg, D. Ross, N.W. Gibson, NAD(P)H:quinone oxidoreductase gene expression in human colon carcinoma cells: characterization of a mutation which modulates DT-diaphorase activity and mitomycin sensitivity, Canc. Res. 52 (1992) 797–802.
[115] R.D. Traver, D. Siegel, H.D. Beall, R.M. Phillips, N.W. Gibson, W.A. Franklin, D. Ross, Characterization of a polymorphism in NAD(P)H: quinone oxidoreductase (DT-diaphorase), Br. J. Canc. 75 (1997) 69–75.
[116] P. Tsvetkov, Y. Adamovich, E. Elliott, Y. Shaul, E3 ligase STUB1/CHIP regulates NAD(P)H:quinone oxidoreductase 1 (NQO1) accumulation in aged brain, a process impaired in certain Alzheimer disease patients, J. Biol. Chem. 286 (2011) 8839–8845.
[117] D. Siegel, A. Anwar, S.L. Winski, J.K. Kepa, K.L. Zolman, D. Ross, Rapid polyubiquitination and proteasomal degradation of a mutant form of NAD(P)H: quinone oxidoreductase 1, Mol. Pharmacol. 59 (2001) 263–268.
[118] D. Siegel, S.M. McGuinness, S.L. Winski, D. Ross, Genotype-phenotype relationships in studies of a polymorphism in NAD(P)H:quinone oxidoreductase 1, Pharmacogenetics 9 (1999) 113–121.
[119] K.D.P. Wu, S. Chen, Catalytic proerties of a naturally occurring mutant of human NAD(P)H:quinone oxidoreductase (DT-diaphorase) Pro-187 to Ser, K, Y., in: Pathophysiology of Lipids Peroxides and Related Free Radicals, Japan Scientific Societies Press, Tokyo, 1998, pp. 135–148.
[120] S. Chen, K. Wu, D. Zhang, M. Sherman, R. Knox, C.S. Yang, Molecular characterization of binding of substrates and inhibitors to DT-diaphorase: combined approach involving site-directed mutagenesis, inhibitor-binding analysis, and computer modeling, Mol. Pharmacol. 56 (1999) 272–278.
[121] A.L. Pey, C.F. Megarity, D.J. Timson, FAD binding overcomes defects in activity and stability displayed by cancer-associated variants of human NQO1, Biochim. Biophys. Acta 1842 (2014) 2163–2173.
[122] W.D. Lienhart, V. Gudipati, M.K. Uhl, A. Binter, S.A. Pulido, R. Saf, K. Zangger, K. Gruber, P. Macheroux, Collapse of the native structure caused by a single amino acid exchange in human NAD(P)H:quinone oxidoreductase(1.), FEBS J. 281 (2014) 4691–4704.
[123] E. Medina-Carmona, R.J. Palomino-Morales, J.E. Fuchs, E. Padin-Gonzalez, N. Mesa-Torres, E. Salido, D.J. Timson, A.L. Pey, Conformational dynamics is key to understanding loss-of-function of NQO1 cancer-associated polymorphisms and its correction by pharmacological ligands, Sci. Rep. 6 (2016) 20331.
[124] O. Moscovitz, P. Tsvetkov, N. Hazan, I. Michaelevski, H. Keisar, G. Ben-Nissan, Y. Shaul, M. Sharon, A mutually inhibitory feedback loop between the 20S proteasome and its regulator, NQO1, Mol. Cell. 47 (2012) 76–86.
[125] E. Medina-Carmona, J.L. Neira, E. Salido, J.E. Fuchs, R. Palomino-Morales, D. J. Timson, A.L. Pey, Site-to-site interdomain communication may mediate different loss-of-function mechanisms in a cancer-associated NQO1 polymorphism, Sci. Rep. 7 (2017) 44532.
[126] A.L. Pey, C.F. Megarity, D.J. Timson, NAD(P)H quinone oxidoreductase (NQO1): an enzyme which needs just enough mobility, in just the right places, Biosci. Rep. 39 (2019).
[127] A. Gaedigk, R.F. Tyndale, M. Jurima-Romet, E.M. Sellers, D.M. Grant, J.S. Leeder, NAD(P)H:quinone oxidoreductase: polymorphisms and allele frequencies in

Caucasian, Chinese and Canadian Native Indian and Inuit populations, Pharmacogenetics 8 (1998) 305–313.
[128] W.R. Kiffmeyer, E. Langer, S.M. Davies, J. Envall, L.L. Robison, J.A. Ross, Genetic polymorphisms in the Hmong population: implications for cancer etiology and survival, Cancer 100 (2004) 411–417.
[129] K.T. Kelsey, J.K. Wiencke, D.C. Christiani, Z. Zuo, M.R. Spitz, X. Xu, B.K. Lee, B. S. Schwartz, R.D. Traver, D. Ross, Ethnic variation in the prevalence of a common NAD(P)H:quinone oxidoreductase polymorphism and its implications for anticancer chemotherapy, Br. J. Canc. 76 (1997) 852–854.
[130] J. Chen, Y. Lin, R. Zhang, Z.J. Huang, X.G. Pan, Contribution of NAD(P)H quinone oxidoreductase 1 (NQO1) Pro187Ser polymorphism and risk of colorectal adenoma and colorectal cancer in Caucasians: a meta-analysis, Arch. Med. Res. 43 (2012) 58–66.
[131] R. Ding, S. Lin, D. Chen, Association of NQO1 rs1800566 polymorphism and the risk of colorectal cancer: a meta-analysis, Int. J. Colorectal Dis. 27 (2012) 885–892.
[132] U. Yadav, P. Kumar, V. Rai, NQO1 gene C609T polymorphism (dbSNP: rs1800566) and digestive tract cancer risk: a meta-analysis.", Nutr. Canc. 70 (2018) 557–568.
[133] Z.J. Guo, C.L. Feng, The NQO1 rs1800566 polymorphism and risk of bladder cancer: evidence from 6,169 subjects, Asian Pac. J. Cancer Prev. APJCP 13 (2012) 6343–6348.
[134] B. Lajin, A. Alachkar, The NQO1 polymorphism C609T (Pro187Ser) and cancer susceptibility: a comprehensive meta-analysis, Br. J. Canc. 109 (2013) 1325–1337.
[135] W.G. Hu, J.J. Hu, W. Cai, M.H. Zheng, L. Zang, Z.T. Wang, Z.G. Zhu, The NAD(P)H: quinine oxidoreductase 1 (NQO1) gene 609 C>T polymorphism is associated with gastric cancer risk: evidence from a case-control study and a meta-analysis, Asian Pac. J. Cancer Prev. APJCP 15 (2014) 2363–2367.
[136] D. Ross, D. Siegel, NQO1 in protection against oxidative stress, Current Opinion In Toxicology 7 (2018) 67–72.
[137] M. Sekiguchi, M. Seki, T. Kawai, K. Yoshida, M. Yoshida, T. Isobe, N. Hoshino, R. Shirai, M. Tanaka, R. Souzaki, K. Watanabe, Y. Arakawa, Y. Nannya, H. Suzuki, Y. Fujii, K. Kataoka, Y. Shiraishi, K. Chiba, H. Tanaka, T. Shimamura, Y. Sato, A. Sato-Otsubo, S. Kimura, Y. Kubota, M. Hiwatari, K. Koh, Y. Hayashi, Y. Kanamori, M. Kasahara, K. Kohashi, M. Kato, T. Yoshioka, K. Matsumoto, A. Oka, T. Taguchi, M. Sanada, Y. Tanaka, S. Miyano, K. Hata, S. Ogawa, J. Takita, Integrated multiomics analysis of hepatoblastoma unravels its heterogeneity and provides novel druggable targets, NPJ Precis Oncol 4 (2020) 20.
[138] Y.L. Wu, D. Wang, X.E. Peng, Y.L. Chen, D.L. Zheng, W.N. Chen, X. Lin, Epigenetic silencing of NAD(P)H:quinone oxidoreductase 1 by hepatitis B virus X protein increases mitochondrial injury and cellular susceptibility to oxidative stress in hepatoma cells, Free Radic. Biol. Med. 65 (2013) 632–644.
[139] M. Tada, O. Yokosuka, K. Fukai, T. Chiba, F. Imazeki, T. Tokuhisa, H. Saisho, Hypermethylation of NAD(P)H: quinone oxidoreductase 1 (NQO1) gene in human hepatocellular carcinoma, J. Hepatol. 42 (2005) 511–519.
[140] N. Huang, X. Pei, W. Lin, J.F. Chiu, T. Tao, G. Li, DNA methylation of a non-CpG island promoter represses NQO1 expression in rat arsenic-transformed lung epithelial cells, Acta Biochim. Biophys. Sin. 50 (2018) 733–739.
[141] H. Robertson, A.T. Dinkova-Kostova, J.D. Hayes, NRF2 and the ambiguous consequences of its activation during initiation and the subsequent stages of tumourigenesis, Cancers 12 (12) (2020).
[142] L. Baird, T. Suzuki, Y. Takahashi, E. Hishinuma, D. Saigusa, M. Yamamoto, Geldanamycin-derived HSP90 inhibitors are synthetic lethal with NRF2, Mol. Cell Biol. 40 (22) (2020).
[143] L. Baird, M. Yamamoto, NRF2-dependent bioactivation of mitomycin C as a novel strategy to target KEAP1-NRF2 pathway activation in human cancer, Mol. Cell Biol. 41 (2) (2020).
[144] X. Huang, E.A. Motea, Z.R. Moore, J. Yao, Y. Dong, G. Chakrabarti, J.A. Kilgore, M.A. Silvers, P.L. Patidar, A. Cholka, F. Fattah, Y. Cha, G.G. Anderson, R. Kusko, M. Peyton, J. Yan, X.J. Xie, V. Sarode, N.S. Williams, J.D. Minna, M. Beg, D. E. Gerber, E.A. Bey, D.A. Boothman, Leveraging an NQO1 bioactivatable drug for tumor-selective use of poly(ADP-ribose) polymerase inhibitors, Canc. Cell 30 (2016) 940–952.
[145] E.A. Motea, X. Huang, N. Singh, J.A. Kilgore, N.S. Williams, X.J. Xie, D.E. Gerber, M.S. Beg, E.A. Bey, D.A. Boothman, NQO1-dependent, tumor-selective radiosensitization of non-small cell lung cancers, Clin. Canc. Res. 25 (2019) 2601–2609.
[146] C.L. Starcher, S.L. Pay, N. Singh, I.J. Yeh, S.B. Bhandare, X. Su, X. Huang, E. A. Bey, E.A. Motea, D.A. Boothman, Targeting base excision repair in cancer: NQO1-bioactivatable drugs improve tumor selectivity and reduce treatment toxicity through radiosensitization of human cancer, Front Oncol 10 (2020) 1575.
[147] L. Torrente, G. Maan, A. Oumkaltoum Rezig, J. Quinn, A. Jackson, A. Grilli, L. Casares, Y. Zhang, E. Kulesskiy, J. Saarela, S. Bicciato, J. Edwards, A. T. Dinkova-Kostova, L. de la Vega, High NRF2 levels correlate with poor prognosis in colorectal cancer patients and with sensitivity to the kinase inhibitor AT9283, in: Vitro. Biomolecules, vol. 10, 2020.
[148] M.T. Park, E.T. Oh, M.J. Song, H. Lee, E.K. Choi, H.J. Park, NQO1 prevents radiation-induced aneuploidy by interacting with Aurora-A, Carcinogenesis 34 (2013) 2470–2485.
[149] D. Ross, Quinone reductases. Multitasking in the metabolic world, Drug Metabol. Rev. 36 (2004) 639–654.
[150] A.T. Dinkova-Kostova, P. Talalay, NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector, Arch. Biochem. Biophys. 501 (1) (2010) 116–123.
[151] D. Ross, D. Siegel, Functions of NQO1 in cellular protection and CoQ10 metabolism and its potential role as a redox sensitive molecular switch, Front. Physiol. 8 (2017) 595.
[152] H. Lundegardh, Absorption, transport and exudation of inorganic anions by plant roots, Arch. Bot. 32A (1945) 1–139.
[153] F.L. Crane, I.L. Sun, M.G. Clark, C. Grebing, H. Low, Transplasma-membrane redox systems in growth and development, Biochim. Biophys. Acta 811 (1985) 233–264.
[154] P. Navas, J.M. Villalba, G. Lenaz, Coenzyme Q-dependent functions of plasma membrane in the aging process, Age (Dordr) 27 (2005) 139–146.
[155] D.H. Hyun, J.O. Hernandez, M.P. Mattson, R. de Cabo, The plasma membrane redox system in aging, Ageing Res. Rev. 5 (2006) 209–220.
[156] T. Takahashi, T. Okamoto, T. Kishi, Characterization of NADPH-dependent ubiquinone reductase activity in rat liver cytosol: effect of various factors on ubiquinone-reducing activity and discrimination from other quinone reductases, J. Biochem. 119 (1996) 256–263.
[157] T. Takahashi, M. Shitashige, T. Okamoto, T. Kishi, K. Goshima, A novel ubiquinone reductase activity in rat cytosol, FEBS Lett. 314 (1992) 331–334.
[158] J.M. Villalba, F. Navarro, F. Cordoba, A. Serrano, A. Arroyo, F.L. Crane, P. Navas, Coenzyme Q reductase from liver plasma membrane: purification and role in trans-plasma-membrane electron transport, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 4887–4891.
[159] V.E. Kagan, A. Arroyo, V.A. Tyurin, Y.Y. Tyurina, J.M. Villalba, P. Navas, Plasma membrane NADH-coenzyme Q0 reductase generates semiquinone radicals and recycles vitamin E homologue in a superoxide-dependent reaction, FEBS Lett. 428 (1998) 43–46.
[160] M.K. Sharma, G.R. Buettner, Interaction of vitamin C and vitamin E during free radical stress in plasma: an ESR study, Free Radic. Biol. Med. 14 (1993) 649–653.
[161] G. Lopez-Lluch, M.P. Barroso, S.F. Martin, D.J. Fernandez-Ayala, C. Gomez-Diaz, J.M. Villalba, P. Navas, Role of plasma membrane coenzyme Q on the regulation of apoptosis, Biofactors 9 (1999) 171–177.
[162] V.P.G. Massey, Ballou, Ballou, in: V.P.G. Massey (Ed.), Oxidases and Related Redox Systems vol. I, Baltimore University Press, Baltimore, 1973, pp. 25–49.
[163] F. Muller, Flavin radicals: chemistry and biochemistry, Free Radic. Biol. Med. 3 (1987) 215–230.
[164] D. Siegel, D.L. Gustafson, D.L. Dehn, J.Y. Han, P. Boonchoong, L.J. Berliner, D. Ross, NAD(P)H:quinone oxidoreductase 1: role as a superoxide scavenger, Mol. Pharmacol. 65 (2004) 1238–1247.
[165] H. Zhu, Z. Jia, J.E. Mahaney, D. Ross, H.P. Misra, M.A. Trush, Y. Li, The highly expressed and inducible endogenous NAD(P)H:quinone oxidoreductase 1 in cardiovascular cells acts as a potential superoxide scavenger, Cardiovasc. Toxicol. 7 (2007) 202–211.
[166] L.P. Schelonka, D. Siegel, M.W. Wilson, A. Meininger, D. Ross, Immunohistochemical localization of NQO1 in epithelial dysplasia and neoplasia and in donor eyes, Invest. Ophthalmol. Vis. Sci. 41 (2000) 1617–1622.
[167] D. Siegel, D. Ross, Immunodetection of NAD(P)H:quinone oxidoreductase 1 (NQO1) in human tissues, Free Radic. Biol. Med. 29 (2000) 246–253.
[168] D. Siegel, W.A. Franklin, D. Ross, Immunohistochemical detection of NAD(P)H: quinone oxidoreductase in human lung and lung tumors, Clin. Canc. Res. 4 (1998) 2065–2070.
[169] D. Smith, L.F. Martin, R. Wallin, Human DT-diaphorase, a potential cancer protecting enzyme. Its purification from abdominal adipose tissue, Canc. Lett. 42 (1988) 103–112.
[170] J. Palming, K. Sjoholm, M. Jernas, T.C. Lystig, A. Gummesson, S. Romeo, L. Lonn, M. Lonn, B. Carlsson, L.M. Carlsson, The expression of NAD(P)H:quinone oxidoreductase 1 is high in human adipose tissue, reduced by weight loss, and correlates with adiposity, insulin sensitivity, and markers of liver dysfunction, J. Clin. Endocrinol. Metab. 92 (2007) 2346–2352.
[171] J.J. Schlager, G. Powis, Cytosolic NAD(P)H:(quinone-acceptor)oxidoreductase in human normal and tumor tissue: effects of cigarette smoking and alcohol, Int. J. Canc. 45 (1990) 403–409.
[172] S. Lata, A. Ali, V. Sood, R. Raja, A.C. Banerjea, HIV-1 Rev downregulates Tat expression and viral replication via modulation of NAD(P)H:quinine oxidoreductase 1 (NQO1), Nat. Commun. 6 (2015) 7244.
[173] S.T. Cheng, J.L. Hu, J.H. Ren, H.B. Yu, S. Zhong, V.K. Wai Wong, B.Y. Kwan Law, W.X. Chen, H.M. Xu, Z.Z. Zhang, X.F. Cai, Y. Hu, W.L. Zhang, Q.X. Long, F. Ren, H.Z. Zhou, A.L. Huang, J. Chen, Dicoumarol, an NQO1 inhibitor, blocks cccDNA transcription by promoting degradation of HBx, J. Hepatol. 74 (2020) 522–534.
[174] A. Vanni, M. Fiore, R. De Salvia, E. Cundari, R. Ricordy, R. Ceccarelli, F. Degrassi, DNA damage and cytotoxicity induced by beta-lapachone: relation to poly(ADP-ribose) polymerase inhibition, Mutat. Res. 401 (1998) 55–63.
[175] J.J. Pink, S. Wuerzberger-Davis, C. Tagliarino, S.M. Planchon, X. Yang, C. J. Froelich, D.A. Boothman, Activation of a cysteine protease in MCF-7 and T47D breast cancer cells during beta-lapachone-mediated apoptosis, Exp. Cell Res. 255 (2000) 144–155.
[176] J.H. Hwang, D.W. Kim, E.J. Jo, Y.K. Kim, Y.S. Jo, J.H. Park, S.K. Yoo, M.K. Park, T.H. Kwak, Y.L. Kho, J. Han, H.S. Choi, S.H. Lee, J.M. Kim, I. Lee, T. Kyung, C. Jang, J. Chung, G.R. Kweon, M. Shong, Pharmacological stimulation of NADH oxidation ameliorates obesity and related phenotypes in mice, Diabetes 58 (2009) 965–974.
[177] D. Siegel, D.D. Dehn, S.S. Bokatzian, K. Quinn, D.S. Backos, A. Di Francesco, M. Bernier, N. Reisdorph, R. de Cabo, D. Ross, Redox modulation of NQO1, PloS One 13 (2018) e0190717.
[178] L.S. Li, E.A. Bey, Y. Dong, J. Meng, B. Patra, J. Yan, X.J. Xie, R.A. Brekken, C. C. Barnett, W.G. Bornmann, J. Gao, D.A. Boothman, Modulating endogenous

NQO1 levels identifies key regulatory mechanisms of action of beta-lapachone for pancreatic cancer therapy, Clin. Canc. Res. 17 (2011) 275–285.
[179] E.A. Bey, K.E. Reinicke, M.C. Srougi, M. Varnes, V.E. Anderson, J.J. Pink, L.S. Li, M. Patel, L. Cao, Z. Moore, A. Rommel, M. Boatman, C. Lewis, D.M. Euhus, W. G. Bornmann, D.J. Buchsbaum, D.R. Spitz, J. Gao, D.A. Boothman, Catalase abrogates beta-lapachone-induced PARP1 hyperactivation-directed programmed necrosis in NQO1-positive breast cancers, Mol. Canc. Therapeut. 12 (2013) 2110–2120.
[180] G. Chakrabarti, M.A. Silvers, M. Ilcheva, Y. Liu, Z.R. Moore, X. Luo, J. Gao, G. Anderson, L. Liu, V. Sarode, D.E. Gerber, S. Burma, R.J. DeBerardinis, S. L. Gerson, D.A. Boothman, Tumor-selective use of DNA base excision repair inhibition in pancreatic cancer using the NQO1 bioactivatable drug, beta-lapachone, Sci. Rep. 5 (2015) 17066.
[181] Y.H. Kim, J.H. Hwang, J.R. Noh, G.T. Gang, D.H. Kim, H.Y. Son, T.H. Kwak, M. Shong, I.K. Lee, C.H. Lee, Activation of NAD(P)H:quinone oxidoreductase ameliorates spontaneous hypertension in an animal model via modulation of eNOS activity, Cardiovasc. Res. 91 (2011) 519–527.
[182] J.S. Lee, A.H. Park, S.H. Lee, S.H. Lee, J.H. Kim, S.J. Yang, Y.I. Yeom, T.H. Kwak, D. Lee, S.J. Lee, C.H. Lee, J.M. Kim, D. Kim, Beta-lapachone, a modulator of NAD metabolism, prevents health declines in aged mice, PloS One 7 (2012) e47122.
[183] H.J. Kim, G.S. Oh, A. Shen, S.B. Lee, S.K. Choe, K.B. Kwon, S. Lee, K.S. Seo, T. H. Kwak, R. Park, H.S. So, Augmentation of NAD(+) by NQO1 attenuates cisplatin-mediated hearing impairment, Cell Death Dis. 5 (2014) e1292.
[184] S.M. Wignall, N.S. Gray, Y.T. Chang, L. Juarez, R. Jacob, A. Burlingame, P. G. Schultz, R. Heald, Identification of a novel protein regulating microtubule stability through a chemical approach, Chem. Biol. 11 (2004) 135–146.
[185] D. Siegel, J.K. Kepa, D. Ross, NAD(P)H:quinone oxidoreductase 1 (NQO1) localizes to the mitotic spindle in human cells, PloS One 7 (2012) e44861.
[186] D. Siegel, S. Bersie, P. Harris, A. Di Francesco, M. Armstrong, N. Reisdorph, M. Bernier, R. de Cabo, K. Fritz, D. Ross, A redox-mediated conformational change in NQO1 controls binding to microtubules and alpha-tubulin acetylation, Redox Biol 39 (2021) 101840.
[187] B.J. North, E. Verdin, Interphase nucleo-cytoplasmic shuttling and localization of SIRT2 during mitosis, PloS One 2 (2007) e784.
[188] A. Saxena, L.H. Wong, P. Kalitsis, E. Earle, L.G. Shaffer, K.H. Choo, Poly(ADP-ribose) polymerase 2 localizes to mammalian active centromeres and interacts with PARP-1, Cenpa, Cenpb and Bub 3, but not Cenpc, Hum. Mol. Genet. 11 (2002) 2319–2329.
[189] P. Chang, M. Coughlin, T.J. Mitchison, Tankyrase-1 polymerization of poly(ADP-ribose) is required for spindle structure and function, Nat. Cell Biol. 7 (2005) 1133–1139.
[190] H.J. Kang, H.Y. Song, M.A. Ahmed, Y. Guo, M. Zhang, C. Chen, M. Cristofanilli, D. Horiuchi, A. Vassilopoulos, NQO1 regulates mitotic progression and response to mitotic stress through modulating SIRT2 activity, Free Radic. Biol. Med. 126 (2018) 358–371.
[191] W.D. Lienhart, V. Gudipati, P. Macheroux, The human flavoproteome, Arch. Biochem. Biophys. 535 (2013) 150–162.
[192] D.F. Becker, W. Zhu, M.A. Moxley, Flavin redox switching of protein functions, Antioxidants Redox Signal. 14 (2011) 1079–1091.
[193] B.D. Zoltowski, C. Schwerdtfeger, J. Widom, J.J. Loros, A.M. Bilwes, J.C. Dunlap, B.R. Crane, Conformational switching in the fungal light sensor Vivid, Science 316 (2007) 1054–1057.
[194] Y. Zhou, J.D. Larson, C.A. Bottoms, E.C. Arturo, M.T. Henzl, J.L. Jenkins, J.C. Nix, D.F. Becker, J.J. Tanner, Structural basis of the transcriptional regulation of the proline utilization regulon by multifunctional PutA, J. Mol. Biol. 381 (2008) 174–188.
[195] Y. Zhou, W. Zhu, P.S. Bellur, D. Rewinkel, D.F. Becker, Direct linking of metabolism and gene expression in the proline utilization A protein from Escherichia coli, Amino Acids 35 (2008) 711–718.
[196] S. Hill, S. Austin, T. Eydmann, T. Jones, R. Dixon, Azotobacter vinelandii NIFL is a flavoprotein that modulates transcriptional activation of nitrogen-fixation genes via a redox-sensitive switch, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 2143–2148.
[197] P. Neumann, A. Weidner, A. Pech, M.T. Stubbs, K. Tittmann, Structural basis for membrane binding and catalytic activation of the peripheral membrane enzyme pyruvate oxidase from Escherichia coli, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 17390–17395.
[198] P. Russell, H.L. Schrock, R.B. Gennis, Lipid activation and protease activation of pyruvate oxidase. Evidence suggesting a common site of interaction on the protein, J. Biol. Chem. 252 (1977) 7883–7887.
[199] K.K. Leung, B.H. Shilton, Chloroquine binding reveals flavin redox switch function of quinone reductase 2, J. Biol. Chem. 288 (2013) 11242–11251.
[200] E. Janda, F. Nepveu, B. Calamini, G. Ferry, J.A. Boutin, Molecular pharmacology of nrh: quinone oxidoreductase 2: a detoxifying enzyme acting as an undercover toxifying enzyme, Mol. Pharmacol. 98 (2020) 620–633.
[201] K.K. Leung, B.H. Shilton, Binding of DNA-intercalating agents to oxidized and reduced quinone reductase 2, Biochemistry 54 (2015) 7438–7448.
[202] S. Chen, P.S. Deng, J.M. Bailey, K.M. Swiderek, A two-domain structure for the two subunits of NAD(P)H:quinone acceptor oxidoreductase, Protein Sci. 3 (1994) 51–57.
[203] G. Tedeschi, S. Chen, V. Massey, DT-diaphorase. Redox potential, steady-state, and rapid reaction studies, J. Biol. Chem. 270 (1995) 1198–1204.
[204] S. Hosoda, W. Nakamura, K. Hayashi, Properties and reaction mechanism of DT diaphorase from rat liver, J. Biol. Chem. 249 (1974) 6416–6423.
[205] E. Anoz-Carbonell, D.J. Timson, A.L. Pey, M. Medina, The catalytic cycle of the antioxidant and cancer-associated human NQO1 enzyme: hydride transfer, conformational dynamics and functional cooperativity, Antioxidants 9 (2020).
[206] S. Hosoda, W. Nakamura, K. Hayashi, Properties and reaction mechanism of DT diaphorase from rat liver, J. Biol. Chem. 549 (1974) 6416–6423.
[207] G. Cavelier, L.M. Amzel, Mechanism of NAD(P)H:quinone reductase: ab initio studies of reduced flavin, Proteins 43 (2001) 420–432.
[208] M. Faig, M.A. Bianchet, P. Talalay, S. Chen, S. Winski, D. Ross, L.M. Amzel, Structures of recombinant human and mouse NAD(P)H:quinone oxidoreductases: species comparison and structural changes with substrate binding and release, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 3177–3182.
[209] C. Janke, G. Montagnac, Causes and consequences of microtubule acetylation, Curr. Biol. 27 (2017) R1287–R1292.
[210] L. Li, X.J. Yang, Tubulin acetylation: responsible enzymes, biological functions and human diseases, Cell. Mol. Life Sci. 72 (2015) 4237–4255.
[211] H. Maruta, K. Greer, J.L. Rosenbaum, The acetylation of alpha-tubulin and its relationship to the assembly and disassembly of microtubules, J. Cell Biol. 103 (1986) 571–579.
[212] D. Portran, L. Schaedel, Z. Xu, M. Thery, M.V. Nachury, Tubulin acetylation protects long-lived microtubules against mechanical ageing, Nat. Cell Biol. 19 (2017) 391–398.
[213] Z. Xu, L. Schaedel, D. Portran, A. Aguilar, J. Gaillard, M.P. Marinkovich, M. Thery, M.V. Nachury, Microtubules acquire resistance from mechanical breakage through intralumenal acetylation, Science 356 (2017) 328–332.
[214] R.H. Skoge, M. Ziegler, SIRT2 inactivation reveals a subset of hyperacetylated perinuclear microtubules inaccessible to HDAC6, J. Cell Sci. 129 (2016) 2972–2982.
[215] Y.H. Kim, J.H. Hwang, K.S. Kim, J.R. Noh, G.T. Gang, Y. Seo, K.H. Nam, T. H. Kwak, H.G. Lee, C.H. Lee, NAD(P)H:quinone oxidoreductase 1 activation reduces blood pressure through regulation of endothelial nitric oxide synthase acetylation in spontaneously hypertensive rats, Am. J. Hypertens. 28 (2015) 50–57.
[216] G.S. Oh, H.J. Kim, J.H. Choi, A. Shen, S.K. Choe, A. Karna, S.H. Lee, H.J. Jo, S. H. Yang, T.H. Kwak, C.H. Lee, R. Park, H.S. So, Pharmacological activation of NQO1 increases NAD(+) levels and attenuates cisplatin-mediated acute kidney injury in mice, Kidney Int. 85 (2014) 547–560.
[217] S.L. Winski, Y. Koutalos, D.L. Bentley, D. Ross, Subcellular localization of NAD(P)H:quinone oxidoreductase 1 in human cancer cells, Canc. Res. 62 (2002) 1420–1424.
[218] L. Milkovic, M. Tomljanovic, A. Cipak Gasparovic, R. Novak Kujundzic, D. Simunic, P. Konjevoda, A. Mojzes, N. Dakovic, N. Zarkovic, K. Gall Troselj, Nutritional stress in head and neck cancer originating cell lines: the sensitivity of the NRF2–NQO1 Axis, Cells 8 (2019).
[219] D.H. Hyun, S.S. Emerson, D.G. Jo, M.P. Mattson, R. de Cabo, Calorie restriction up-regulates the plasma membrane redox system in brain cells and suppresses oxidative stress during aging, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 19908–19912.
[220] A. Castello, B. Fischer, K. Eichelbaum, R. Horos, B.M. Beckmann, C. Strein, N. E. Davey, D.T. Humphreys, T. Preiss, L.M. Steinmetz, J. Krijgsveld, M.W. Hentze, Insights into RNA biology from an atlas of mammalian mRNA-binding proteins, Cell 149 (2012) 1393–1406.
[221] M.A. Bianchet, M. Faig, L.M. Amzel, Structure and mechanism of NAD[P]H: quinone acceptor oxidoreductases (NQO), Methods Enzymol. 382 (2004) 144–174.
[222] A. Di Francesco, C. Di Germanio, A.C. Panda, P. Huynh, R. Peaden, I. Navas-Enamorado, P. Bastian, E. Lehrmann, A. Diaz-Ruiz, D. Ross, D. Siegel, J. L. Martindale, M. Bernier, M. Gorospe, K. Abdelmohsen, R. de Cabo, Novel RNA-binding activity of NQO1 promotes SERPINA1 mRNA translation, Free Radic. Biol. Med. 99 (2016) 225–233.
[223] A. Di Francesco, Y. Choi, M. Bernier, Y. Zhang, A. Diaz-Ruiz, M.A. Aon, K. Kalafut, M.R. Ehrlich, K. Murt, A. Ali, K.J. Pearson, S. Levan, J.D. Preston, A. Martin-Montalvo, J.L. Martindale, K. Abdelmohsen, C.R. Michel, D.M. Willmes, C. Henke, P. Navas, J.M. Villalba, D. Siegel, M. Gorospe, K. Fritz, S. Biswal, D. Ross, R. de Cabo, NQO1 protects obese mice through improvements in glucose and lipid metabolism, NPJ Aging Mech Dis 6 (2020) 13.
[224] D.V. Chartoumpekis, T.W. Kensler, New player on an old field; the keap1/Nrf2 pathway as a target for treatment of type 2 diabetes and metabolic syndrome, Curr. Diabetes Rev. 9 (2013) 137–145.
[225] A. Uruno, Y. Furusawa, Y. Yagishita, T. Fukutomi, H. Muramatsu, T. Negishi, A. Sugawara, T.W. Kensler, M. Yamamoto, The Keap1-Nrf2 system prevents onset of diabetes mellitus, Mol. Cell Biol. 33 (2013) 2996–3010.
[226] D.V. Chartoumpekis, D.L. Palliyaguru, N. Wakabayashi, M. Fazzari, N.K.H. Khoo, F.J. Schopfer, I. Sipula, Y. Yagishita, G.K. Michalopoulos, R.M. O'Doherty, T. W. Kensler, Nrf2 deletion from adipocytes, but not hepatocytes, potentiates systemic metabolic dysfunction after long-term high-fat diet-induced obesity in mice, Am. J. Physiol. Endocrinol. Metab. 315 (2018) E180–E195.
[227] Y. Yagishita, A. Uruno, D.V. Chartoumpekis, T.W. Kensler, M. Yamamoto, Nrf2 represses the onset of type 1 diabetes in non-obese diabetic mice, J. Endocrinol. 240 (2019).
[228] M.H. Ludtmann, P.R. Angelova, Y. Zhang, A.Y. Abramov, A.T. Dinkova-Kostova, Nrf2 affects the efficiency of mitochondrial fatty acid oxidation, Biochem. J. 457 (2014) 415–424.
[229] P.J. Meakin, S. Chowdhry, R.S. Sharma, F.B. Ashford, S.V. Walsh, R. J. McCrimmon, A.T. Dinkova-Kostova, J.F. Dillon, J.D. Hayes, M.L. Ashford, Susceptibility of Nrf2-null mice to steatohepatitis and cirrhosis upon consumption of a high-fat diet is associated with oxidative stress, perturbation of the unfolded protein response, and disturbance in the expression of metabolic enzymes but not with insulin resistance, Mol. Cell Biol. 34 (2014) 3305–3320.

[230] R.S. Sharma, D.J. Harrison, D. Kisielewski, D.M. Cassidy, A.D. McNeilly, J. R. Gallagher, S.V. Walsh, T. Honda, R.J. McCrimmon, A.T. Dinkova-Kostova, M.L. J. Ashford, J.F. Dillon, J.D. Hayes, Experimental nonalcoholic steatohepatitis and liver fibrosis are ameliorated by pharmacologic activation of Nrf2 (NF-E2 p45-related factor 2), Cell Mol Gastroenterol Hepatol 5 (2018) 367–398.
[231] L.V. Vasileva, M.S. Savova, K.M. Amirova, A.T. Dinkova-Kostova, M.I. Georgiev, Obesity and NRF2-mediated cytoprotection: where is the missing link? Pharmacol. Res. 156 (2020) 104760.
[232] Z. Zhang, S. Zhou, X. Jiang, Y.H. Wang, F. Li, Y.G. Wang, Y. Zheng, L. Cai, The role of the Nrf2/Keap1 pathway in obesity and metabolic syndrome, Rev. Endocr. Metab. Disord. 16 (2015) 35–45.
[233] B. Korac, A. Kalezic, V. Pekovic-Vaughan, A. Korac, A. Jankovic, Redox changes in obesity, metabolic syndrome, and diabetes, Redox Biol (2021) 101887.
[234] A. Whaley-Connell, P.A. McCullough, J.R. Sowers, The role of oxidative stress in the metabolic syndrome, Rev. Cardiovasc. Med. 12 (2011) 21–29.
[235] J.F. Varghese, R. Patel, U.C.S. Yadav, Novel insights in the metabolic syndrome-induced oxidative stress and inflammation-mediated atherosclerosis, Curr. Cardiol. Rev. 14 (2018) 4–14.
[236] A. Martinez-Hernandez, E.J. Cordova, O. Rosillo-Salazar, H. Garcia-Ortiz, C. Contreras-Cubas, S. Islas-Andrade, C. Revilla-Monsalve, C. Salas-Labadia, L. Orozco, Association of HMOX1 and NQO1 polymorphisms with metabolic syndrome components, PloS One 10 (2015) e0123313.
[237] T. Ramprasath, P.S. Murugan, E. Kalaiarasan, P. Gomathi, A. Rathinavel, G. S. Selvam, Genetic association of Glutathione peroxidase-1 (GPx-1) and NAD(P)H: quinone Oxidoreductase 1(NQO1) variants and their association of CAD in patients with type-2 diabetes, Mol. Cell. Biochem. 361 (2012) 143–150.
[238] A. Gaikwad, D.J. Long, J.L. Stringer, A.K. Jaiswal, *In vivo* Role of NAD(P)H: quinone oxidoreductase 1 (NQO1) in the regulation of intracellular redox state and accumulation of abdominal adipose tissue, J. Biol. Chem. 276 (2001) 22559–22564.
[239] A. Diaz-Ruiz, A. Di Francesco, B.A. Carboneau, S.R. Levan, K.J. Pearson, N. L. Price, T.M. Ward, M. Bernier, R. de Cabo, E.M. Mercken, Benefits of caloric restriction in longevity and chemical-induced tumorigenesis are transmitted independent of NQO1, J Gerontol A Biol Sci Med Sci 74 (2018) 155–162.
[240] Y.H. Kim, J.H. Hwang, K.S. Kim, J.R. Noh, G.T. Gang, W.K. Oh, K.H. Jeong, T. H. Kwak, H.S. Choi, I.K. Lee, C.H. Lee, Enhanced activation of NAD(P)H: quinone oxidoreductase 1 attenuates spontaneous hypertension by improvement of endothelial nitric oxide synthase coupling via tumor suppressor kinase liver kinase B1/adenosine 5'-monophosphate-activated protein kinase-mediated guanosine 5'-triphosphate cyclohydrolase 1 preservation, J. Hypertens. 32 (2014) 306–317.
[241] J.D. Hayes, A.T. Dinkova-Kostova, The Nrf2 regulatory network provides an interface between redox and intermediary metabolism, Trends Biochem. Sci. 39 (2014) 199–218.
[242] M. Godel, B. Hartleben, N. Herbach, S. Liu, S. Zschiedrich, S. Lu, A. Debreczeni-Mor, M.T. Lindenmeyer, M.P. Rastaldi, G. Hartleben, T. Wiech, A. Fornoni, R. G. Nelson, M. Kretzler, R. Wanke, H. Pavenstadt, D. Kerjaschki, C.D. Cohen, M. N. Hall, M.A. Ruegg, K. Inoki, G. Walz, T.B. Huber, Role of mTOR in podocyte function and diabetic nephropathy in humans and mice, J. Clin. Invest. 121 (2011) 2197–2209.
[243] K. Inoki, H. Mori, J. Wang, T. Suzuki, S. Hong, S. Yoshida, S.M. Blattner, T. Ikenoue, M.A. Ruegg, M.N. Hall, D.J. Kwiatkowski, M.P. Rastaldi, T.B. Huber, M. Kretzler, L.B. Holzman, R.C. Wiggins, K.L. Guan, mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice, J. Clin. Invest. 121 (2011) 2181–2196.
[244] S.H. Um, F. Frigerio, M. Watanabe, F. Picard, M. Joaquin, M. Sticker, S. Fumagalli, P.R. Allegrini, S.C. Kozma, J. Auwerx, G. Thomas, Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity, Nature 431 (2004) 200–205.
[245] O. Le Bacquer, E. Petroulakis, S. Paglialunga, F. Poulin, D. Richard, K. Cianflone, N. Sonenberg, Elevated sensitivity to diet-induced obesity and insulin resistance in mice lacking 4E-BP1 and 4E-BP2, J. Clin. Invest. 117 (2007) 387–396.
[246] S.Y. Tsai, A.A. Rodriguez, S.G. Dastidar, E. Del Greco, K.L. Carr, J.M. Sitzmann, E. C. Academia, C.M. Viray, L.L. Martinez, B.S. Kaplowitz, T.D. Ashe, La Spada, , A. R., B.K. Kennedy, Increased 4E-BP1 expression protects against diet-induced obesity and insulin resistance in male mice, Cell Rep. 16 (2016) 1903–1914.
[247] P. Polak, N. Cybulski, J.N. Feige, J. Auwerx, M.A. Ruegg, M.N. Hall, Adipose-specific knockout of raptor results in lean mice with enhanced mitochondrial respiration, Cell Metabol. 8 (2008) 399–410.
[248] X. Sun, Y. Ji, A. Tahir, J. Kang, Network pharmacology combined with transcriptional analysis to unveil the biological basis of astaxanthin in reducing the oxidative stress induced by diabetes mellitus, Diabetes Metab Syndr Obes 13 (2020) 4281–4295.
[249] K.S. SantaCruz, E. Yazlovitskaya, J. Collins, J. Johnson, C. DeCarli, Regional NAD (P)H:quinone oxidoreductase activity in Alzheimer's disease, Neurobiol. Aging 25 (2004) 63–69.
[250] Y. Wang, K. Santa-Cruz, C. DeCarli, J.A. Johnson, NAD(P)H:quinone oxidoreductase activity is increased in hippocampal pyramidal neurons of patients with Aalzheimer's disease, Neurobiol. Aging 21 (2000) 525–531.
[251] A.K. Raina, D.J. Templeton, J.C. Deak, G. Perry, M.A. Smith, Quinone reductase (NQO1), a sensitive redox indicator, is increased in Alzheimer's disease, Redox Rep. 4 (1999) 23–27.
[252] J. Luo, S. Li, X. Qin, Q. Peng, Y. Liu, S. Yang, X. Qin, Y. Xiong, Z. Zeng, Association of the NQO1 C609T polymorphism with Alzheimer's disease in Chinese populations: a meta-analysis, Int. J. Neurosci. 126 (2016) 199–204.
[253] J. Chhetri, A.E. King, N. Gueven, Alzheimer's disease and NQO1: is there a link? Curr. Alzheimer Res. 15 (2018) 56–66.
[254] A. Martinez-Limon, M. Alriquet, W.H. Lang, G. Calloni, I. Wittig, R.M. Vabulas, Recognition of enzymes lacking bound cofactor by protein quality control, Proc. Natl. Acad. Sci. U. S. A 113 (2016) 12156–12161.
[255] R. De Cabo, R. Cabello, M. Rios, G. Lopez-Lluch, D.K. Ingram, M.A. Lane, P. Navas, Calorie restriction attenuates age-related alterations in the plasma membrane antioxidant system in rat liver, Exp. Gerontol. 39 (2004) 297–304.
[256] G.L. Zhang, W. Wang, Y.X. Kang, Y. Xue, H. Yang, C.M. Zhou, G.M. Shi, Chronic testosterone propionate supplement could activated the Nrf2-ARE pathway in the brain and ameliorated the behaviors of aged rats, Behav. Brain Res. 252 (2013) 388–395.
[257] M. Jimenez-Hidalgo, C. Santos-Ocana, S. Padilla, J.M. Villalba, G. Lopez-Lluch, A. Martin-Montalvo, R.K. Minor, D.A. Sinclair, R. de Cabo, P. Navas, NQR1 controls lifespan by regulating the promotion of respiratory metabolism in yeast, Aging Cell 8 (2009) 140–151.
[258] A. Diaz-Ruiz, M. Lanasa, J. Garcia, H. Mora, F. Fan, A. Martin-Montalvo, A. Di Francesco, M. Calvo-Rubio, A. Salvador-Pascual, M.A. Aon, K.W. Fishbein, K. J. Pearson, J.M. Villalba, P. Navas, M. Bernier, R. de Cabo, Overexpression of CYB5R3 and NQO1, two NAD(+) -producing enzymes, mimics aspects of caloric restriction, Aging Cell 17 (2018) e12767.
[259] A. Tyshkovskiy, P. Bozaykut, A.A. Borodinova, M.V. Gerashchenko, G.P. Ables, M. Garratt, P. Khaitovich, C.B. Clish, R.A. Miller, V.N. Gladyshev, Identification and application of gene expression signatures associated with lifespan extension, Cell Metabol. 30 (2019) 573–593, e578.
[260] S.I. Imai, L. Guarente, It takes two to tango: NAD(+) and sirtuins in aging/longevity control, NPJ Aging Mech Dis 2 (2016) 16017.
[261] C.R. Martens, B.A. Denman, M.R. Mazzo, M.L. Armstrong, N. Reisdorph, M. B. McQueen, M. Chonchol, D.R. Seals, Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults, Nat. Commun. 9 (2018) 1286.
[262] E. Verdin, NAD(+) in aging, metabolism, and neurodegeneration, Science 350 (2015) 1208–1213.
[263] A.J. Covarrubias, R. Perrone, A. Grozio, E. Verdin, NAD(+) metabolism and its roles in cellular processes during ageing, Nat. Rev. Mol. Cell Biol. 22 (2021) 119–141.
[264] S. Vatolin, T. Radivoyevitch, J.P. Maciejewski, New drugs for pharmacological extension of replicative life span in normal and progeroid cells, NPJ Aging Mech Dis 5 (2019) 2.
[265] G. Asher, P. Tsvetkov, C. Kahana, Y. Shaul, A mechanism of ubiquitin-independent proteasomal degradation of the tumor suppressors p53 and p73, Genes Dev. 19 (2005) 316–321.
[266] O. Hershkovitz Rokah, O. Shpilberg, G. Granot, NAD(P)H quinone oxidoreductase protects TAp63gamma from proteasomal degradation and regulates TAp63gamma-dependent growth arrest, PloS One 5 (2010) e11401.
[267] G. Asher, Z. Bercovich, P. Tsvetkov, Y. Shaul, C. Kahana, 20S proteasomal degradation of ornithine decarboxylase is regulated by NQO1, Mol. Cell. 17 (2005) 645–655.
[268] M. Garate, R.P. Wong, E.I. Campos, Y. Wang, G. Li, NAD(P)H quinone oxidoreductase 1 inhibits the proteasomal degradation of the tumour suppressor p33(ING1b), EMBO Rep. 9 (2008) 576–581.
[269] A. Alard, B. Fabre, R. Anesia, C. Marboeuf, P. Pierre, C. Susini, C. Bousquet, S. Pyronnet, NAD(P)H quinone-oxydoreductase 1 protects eukaryotic translation initiation factor 4GI from degradation by the proteasome, Mol. Cell Biol. 30 (2010) 1097–1105.
[270] Y. Adamovich, A. Shlomai, P. Tsvetkov, K.B. Umansky, N. Reuven, J.L. Estall, B. M. Spiegelman, Y. Shaul, The protein level of PGC-1alpha, a key metabolic regulator, is controlled by NADH-NQO1, Mol. Cell Biol. 33 (2013) 2603–2613.
[271] E.T. Oh, J.W. Kim, J.M. Kim, S.J. Kim, J.S. Lee, S.S. Hong, J. Goodwin, R. J. Ruthenborg, M.G. Jung, H.J. Lee, C.H. Lee, E.S. Park, C. Kim, H.J. Park, NQO1 inhibits proteasome-mediated degradation of HIF-1alpha, Nat. Commun. 7 (2016) 13593.
[272] T. Maeda, C. Tanabe-Fujimura, Y. Fujita, C. Abe, Y. Nanakida, K. Zou, J. Liu, S. Liu, T. Nakajima, H. Komano, NAD(P)H quinone oxidoreductase 1 inhibits the proteasomal degradation of homocysteine-induced endoplasmic reticulum protein, Biochem. Biophys. Res. Commun. 473 (2016) 1276–1280.
[273] Q. Fang, J. Andrews, N. Sharma, A. Wilk, J. Clark, J. Slyskova, C.A. Koczor, H. Lans, A. Prakash, R.W. Sobol, Stability and sub-cellular localization of DNA polymerase beta is regulated by interactions with NQO1 and XRCC1 in response to oxidative stress, Nucleic Acids Res. 47 (2019) 6269–6286.
[274] H.Z. Zhou, H.Q. Zeng, D. Yuan, J.H. Ren, S.T. Cheng, H.B. Yu, F. Ren, Q. Wang, Y. P. Qin, A.L. Huang, J. Chen, NQO1 potentiates apoptosis evasion and upregulates XIAP via inhibiting proteasome-mediated degradation SIRT6 in hepatocellular carcinoma, Cell Commun. Signal. 17 (2019) 168.