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A Review of NAD(P)H:Quinone Oxidoreductase 1 (NQO1); A Multifunctional Antioxidant Enzyme

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ABSTRACT

NAD(P)H:quinone-oxidoreductase-1 (NQO1) is a cytosolic enzyme that catalyses two- or four-electron reduction of many endogenous and environmental quinones using flavin adenine dinucleotide (FAD) as a cofactor. It is a cytosolic enzyme exists as a homodimer and is biochemically distinguished by its prominent ability to use either NADH or NADPH as reducing cofactors and by its suppression by the anticoagulant dicumarol. This enzyme generally considered as a detoxification enzyme due to of its ability to diminish reactive quinones and quinone-imines to its less reactive and less toxic hydroquinones forms. NQO1 is a substantially inducible enzyme that is controlled by the Nrf2-Keap1/ARE pathway. Evidence for the significance of the antioxidant functions of NQO1 in suppression of oxidative stress is provided by manifestations that induction of NQO1 levels or their reduction are associated with reduced and raised susceptibilities to oxidative stress, respectively. The gene coding for NQO1 has two common polymorphisms at nucleotide position 609(C-T) and 465 (C-T) of the human cDNA. C465T causes reduction in enzyme activity, whereas the C609T results in complete loss of enzymatic activity due to protein instability.In this review, we discuss the protective functions of NQO1 and present its possible transcriptional pathways regulating its induction by Nrf2-Keap1/ARE pathway.

INTRODUCTION

NAD(P)H:quinone oxidoreductase 1 (NQO1) is a cytosolic homodimeric flavoprotein that catalyses two-electron depletion and detoxification of quinones and its derivatives, protecting cells fromoxidative stress, redox cycling, and neoplastic lesion (Dinkova-Kostova and Talalay, 2000). NQO1 reduce quinones to hydroquinones in a two-electron step reduction. In addition to producing substrates for phase II conjugation reactions and enhancing excretion, this two -electron reduction process bypasses the possiblytoxic semiquinone radical intermediates. Hydroquinones are not redox-stable and in some situation metabolism by NQO1 produces a more active yield (Cadenas, 1995). NQO1 is expressed in many tissues, and its expression is regulated by the antioxidant response element (ARE) both in basal and during oxidative stress conditions (Nioi and Hayes, 2004). NQO1 contains ARE sequence in the promoter region and is known to be regulated by nuclear factor (erythroid-derived 2)-like 2 (Nrf2)(Kaspar and Jaiswal, 2010).Nrf2 belongs to the basic leucine zipper transcription factor family, a member of the Cap 'n' Collar family of transcriptional proteins that binds to ARE leading to induction of many cytoprotective and antioxidant genes.Nrf2 bind ARE and regulate expression and induction of NQO1 gene(Motohashi *et al.*, 2002). Meanwhile, Nrf2 knockout exhibited reduction in the constitutive expression of NQO1 and impairs its induction (Nioi and Hayes, 2004). NQO1 gene expression is induced together with other detoxifying enzyme genes in response to antioxidants, xenobiotics, electrophiles, heavy metals, and radiations (Venugopal and Jaiswal, 1998). A number of dietary compounds have been identified as prospective chemopreventive agents. Several vegetables and fruits including; broccoli, blueberries and cacao beans, are among the most protective specifically due to an excess of active molecules such as isothiocyanates, polyphenols, and flavonoids (Surh, 2003). Upon entering cells, these phytochemicals can directly scavenge free radicals and can also provoke electrophilic stress signals that trigger proteins linked to diverse cellular signalling pathways.

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This capability involves the activation of NQO1 gene and other phase II detoxification genes through the activation of Nrf2/Keap1complex system (Finley *et al.,* 2011).

NQO1 enzyme and gene

NAD(P)H:quinone oxidoreductase 1 (NQO1) (also referred to as DT-diaphorase, nicotinamide quinone oxidoreductase 1, quinone reductase type 1, or menadione reductase) is a flavoenzyme that plays a crucial role in protecting cells from endogenous and exogenous quinones by catalysing two- and four-electron reductions of these substrates to their hydroquinone forms (Ross *et al.,* 2000). The two- and four-electron reductions activity that catalysed by NQO1 are of benefit to the cell by preventing redox cycling, which results in generation of free radicals; thus, NQO1 help to protect the cell from oxidative stresses (Nebert *et al.,* 2000). According to toxicological classification, NQO1 is categorized as a phase I drug-metabolising enzyme, together with oxidases, reductases and hydrolases that serve to introduce functional groups into xenobiotics (Parkinson, 1995). NQO1 work as a homodimer with one flavin adenine dinucleotide (FAD) bound per monomer. This enzyme uses reduced pyridine nucleotide cofactors nicotinamide adenine dinucleotide (NADH) or NADPH to catalyse the direct two-electron reduction of many quinones (Nakamura *et al.,* 2000).

NQO1 is localized mostly in the cytosol but it also detected at low levels in the nucleus. In human tissues NQO1 is expressed at high levels in diverse epithelial cells, vascular endothelium and adipocytes (Siegel and Ross, 2000; Siegel, 1998). Unlike other mammals, humans do not express NQO1 in normal liver cells but its expression is manifestedin pre-neoplastic lesions and liver cancers (Strassburg *et al.,* 2002; Shen *et al.,* 2010; Cresteil and Jaiswal, 1991). NQO1 is highly expressed in many human solid tumours such as; colon, pancreas, lung and breast tumours (Schlager and Powis, 1990; Yang *et al.,* 2014). The human NQO1 gene (also referred as DIA4) is situated on chromosome 16q22.1; the gene spans around 17 kb and has six exons (Jaiswal et al., 1988). There are three of four polyadenylation sites in exon 6 can result in transcripts of 1.2 kb, 1.7 kb, and 2.7 kb in length (Jaiswal *et al.,* 1999). NQO1 are co-ordinately induced by cancer chemopreventive agents with certain phase II drug-conjugating enzymes including glutathione S-transferase (GST) and UDP-glucuronosyl transferase (UGT) isoenzymes (Prochaska *et al.,* 1985).

NQO1 catalytic cycle and substrate specificity

The catalytic activities of NQO1 were primarilystated by Ernster and Navazio in 1958 (Ernster and Navazio, 1958). NQO1 gene is an obligate two-electron reductase that catalyses reduction of a wide range of substrates by using either NADH or NADPH as reducing cofactors and by its effective inhibition by the anticoagulant dicumarol. It is mostly a cytosolic enzyme (around 90%) and exists as a homodimer with one molecule of FAD per monomer. Increased expression of NQO1, in response to oxidative stress, is frequently observed across various species and provides the cell with protection strategies, probably by its ability to reduce reactive quinones and quinone-imines to its less reactive and less toxic hydroquinones forms. Such a two-electron reduction also bypasses reactive and toxic semiquinone production and thereforeblocks the formation of reactive oxygen species derived from interaction of the semiquinone with molecular oxygen(Dinkova-Kostova and Talalay, 2010). The oxido-reductase functions via 'ping-pong' kinetics where the reduced pyridine nucleotide binds to the active site, reduces the flavin co-factor to FADH2, and is then the oxidized pyridine nucleotide is released before binding of the substrate and complete reduction by hydride transfer (Bianchet *et al.,* 2004). NQO1 shows activity towards many reactive species including quinones, quinone-imines, glutathionyl-substituted, methylene blue, dichlorophenolindolphenol, naphthoquinones, azo and nitro compounds, demonstrates its significance as a chemoprotective enzyme (Talalay and Dinkova-Kostova, 2004; Cenas *et al.,* 2004; Cavalieri *et al.,* 2004). In addition to a single two-electron reduction, NQO1 is also able of catalyse four-electron reduction of azo dyes and nitro substances (Boland *et al.,* 1991; Huang *et al.,* 1979). Using heterodimers of NQO1, it was recognized that the NQO1 subunits work independently in metabolizing two electron substrates and in a dependent way with four-electron substrates (Cui *et al.,* 1995).

Regulation of NQO1 by the NRF2-KEAP1/ARE pathway

The efficiency of many phytochemical inducers to up-regulate NQO1 is mediated through the Nrf2-Keap1/ARE system pathway, by controlling the expression of a diverse phase II enzyme genes. This pathway helps in protection of mammalian cells and organisms against several electrophilic and oxidative stressors. The Nrf2-Keap1/ARE pathway is the master regulator of cytoprotective responses to electrophilic and oxidative stresses(Li *et al.,* 2012).Three cellular components are of major significance for the mechanisms by which the transcription of the Nrf2-Keap1/ARE system pathway is regulated, that is; (i) Nrf2 (Nuclear factor (erythroid-derived 2)-like 2), a transcription factor belongs to the basic leucine zipper transcription factor family, a member of the cap 'n' Collar family of regulatory transcriptional proteins that also includes NF-E2, Nrf1, Nrf3, Bach1, and Bach2 (Zhang, 2006). Once stimulated, Nrf2 binds to ARE sites in the promoter sites of many cytoprotective and antioxidant genes, leading to the induction of various target cytoprotective genes that enhance cellular detoxification processes and antioxidant potential (Malloy *et al.,* 2013); (ii)as an adaptor for Cul3-based E3 ligase (Furukawa and Xiong, 2005;Stewart *et al.,* 2003; Nguyen et al., 2003); and (iii) ARE (Antioxidant response elements), a cis-acting enhancer element presented in the promoter region of various genes encoding phase II detoxification enzymes and have the consensus: TGAG/CNNNGC (Lee and Johnson, 2004;Dinkova-Kostova and Talalay, 2010). For NQO1gene, the precise sequence was reported by John Hayes et al. who revealed that particular nucleotides formerly thought to be redundant in the ARE function have important roles, while others that were formerly considered

crucial, were unnecessary (Nioi *et al.,* 2003). Several reports have been devoted to demonstrate molecular mechanisms responsible for activation of Nrf2-Keap1/ARE system pathway. Under normal physiological conditions, Keap1 physically entraps inactive Nrf2 in the cytoplasm, thereby suppressing its translocation to the nucleus. During oxidative status, Nrf2 moves into the nucleus, thus starting Nrf2-ARE transcriptional activation (Kensler *et al.,* 2007). Numerous models have been reported for the mechanism of regulation of the Keap1/Nrf2/ARE pathway (Itoh *et al.,* 1999). The most widely accepted model suggested that Nrf2 inducers modify highly reactive cysteine residues of the sensor Keap1. These cysteine residues form protein-protein cross links after exposure to electrophilic or oxidative insults, leading to disturbance of Nrf2/Keap1 stabilization and subsequent dissociation of Nrf2 (Wakabayashi *et al.,* 2004).

In human and rodent tissues, NQO1 is one of the main permanently and strongly inducible genes among the members of the family of cytoprotective genes. This early report has been frequently approved by inclusive gene expression profiling in many systems that utilized both pharmacological inducers of the Nrf2-Keap1/ARE pathway, and Keap1 knockdown genetic approaches (Benson *et al.,* 1980). NQO1 is significantly expressed in several tumour tissues including lung, liver, colon, breast and pancreatic tissues, and its expression induced in response to a variety of xenobiotics, antioxidants, oxidants, and heavy metals (Suh *et al.,* 2004). Mutations and deletions in the NQO1 gene promoter aided in recognizing the core ARE sequence. ARE is mainly required for expression and consistent induction of NQO1 and other phase II enzyme genes (Jaiswal, 2000). Nrf2 bind ARE and regulate expression and initiation of NQO1 gene. While, Nrf2 knockout exhibited reduction in the constitutive expression of NQO1 and impairs its induction (Nioi and Hayes, 2004). In addition, treatment with BHA, known Nrf2 activator, increases hepatic and intestinal NQO1 levels in wild type, but not in Nrf2 knockout mice (Ishii *et al.,* 2002). All of these data confirm a role for Nrf2 in the expression of NQO1 in various tissues.

NQO1 as an antioxidant enzyme

Numerous reports have suggested that NQO1 may play an antioxidant role, possibly by the reduction of endogenous quinones which subsequently help protect cellular membranes against oxidative damage. NQO1 is thought to help preserve certain endogenous antioxidants in their reduced and active forms. Particularly, both ubiquinone (co-enzyme Q) and α- tocopherol-quinone, two essential lipid-soluble antioxidants, are substrates for NQO1 in vitro Beyer *et al.,* 1996; Landi *et al.,* 1997). In addition to its catalytic role in reduction of quinones, NQO1 has been found to scavenge superoxide directly, and this activity could provide extra protection and could be particularly efficient in tissues with low level of SOD enzyme expression. Therefore, in cardiovascular cells, where expression of SOD is relatively low and that of NQO1 is high, induction of NQO1 was revealed to correlate with enhancing superoxide scavenging activity, while its suppression result in a decrease in superoxide scavenging activity (Zhu *et al.,* 2007). Experiments have reported that rat liver NQO1 can stimulate the reduction of ubiquinone analogues (coenzyme Q) to their ubiquinol forms in liposomes and rat hepatocytes [50,48]. The reduction rate of coenzyme Q derivatives was dependent upon chain length, with molecules containing longer chains being less efficiently reduced. In these studies it was demonstrated that the ubiquinol formed following reduction by NQO1 was an efficient antioxidant protecting membrane phospholipids from lipid peroxidation. Unlike its role in the electron transport chain, co-enzymeQalso serves as an antioxidant and is distributed in most of cell membranes in its reduced (ubiquinol) form (Zhang, 2006).

Furthermore, NQO1 elaborated in the metabolism of vitamin E (α-tocopherol) derivatives. α-tocopherol-quinone, a product of α-tocopherol oxidation has been demonstrated to have antioxidant activities following reduction to α-tocopherolhydroquinone (Kohar *et al.,* 1995). In human NQO1 experiment, it was shown that this enzyme is active towards α-tocopherol-quinone, stimulating its reduction to α-tocopherol-hydroquinone, and this property protects against damage to the cell membrane. Moreover, another experiments have also revealed that Chinese hamster ovary cells transfected with human NQO1 produced higher levels of α-tocopherol hydroquinone and were more resistant to lipid peroxidation than cells lacking NQO1 (Siegel *et al.,* 1997).

The role of NQO1 as an antioxidant enzyme is also confirmed by studies in humans that have demonstrated that NQO1 protein is expressed in various tissues such as; epithelial cells of lung, breast and colon, providing a high level of antioxidant protection. The high levels of NQO1 indicate that NQO1 may serve mainly in an antioxidant capacity in these cells. However, immunological and biochemical-based assays have not succeeded to detect significant levels of NQO1 expression in human liver (Siegel and Ross, 2000; Schlager and Powis, 1990). This suggests that in human, distinct from other species, NQO1 does not evolve in a master role in hepatic xenobiotic metabolism.

NQO1 gene variants

There have been two types of single nucleotide polymorphisms (SNPs) described in the human NQO1 gene. The most prominent and frequent variant of NQO1is a C to T substitution at nucleotide position 609 of the NQO1 cDNA (rs1800566), also known as NQO1*2.This nucleotide alteration results in a proline to serine amino acid change at position 187 (P187S) that is accompanied with a reduction of enzyme activity due to instability of the protein product (Dunna *et al.,* 2011). The variant NQO1*2 protein is extremely unstable, and is promptly ubiquitinated by the proteasome (Siegel *et al.,* 2001). Thus, the activity of the homozygous variant genotype (NQO1*2/*2) enzyme is substantially undetectable, whereas NQO1*1/*2 heterozygotes exhibit activities intermediate between the homozygous SNP genotype and wild type (NQO1*1/*1) (Ross and Siegel, 2004). The incidence of this variant differ widely by race and associations were reported between the existence of variant alleles in lung and urological cancers (Kelsey, 1997;Rosvold,

1995). The interethnic differences in this gene were reported to range from16% in Caucasians to 49% in Chinese populations, and the frequency of NQO1*2/*2 homozygosity is reported to range between 1.5% and 20.3% in several ethnic (Nebert *et al.*, 2002).

Another genetic variant of NQO1 is a single nucleotide substitution from C to T at codon 465 (rs4986998), also referred to as NQO1*3, which alters the amino acid at codon 139 from arginine to tryptophan (R139W). This polymorphism results in substitutional messenger RNA splice sites that can lead to a deletion of exon 4 and produce a protein lacking the quinone binding site for which enzyme activity varies according to the substrate (Gasdaska *et al.*, 1995; Pan *et al.*, 1995; Gaedigk *et al.*, 1998). The NQO1*3 SNP frequency is generally low and ranges from 0% to 5% among various ethnic populations (Gaedigk et al., 1998).

CONFLICT OF INTEREST STATEMENT

No potential conflicts of interest were disclosed.

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