

NQO1, Role in Lung Cancer: A Review

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Abstract:

NAD(P)H: quinone oxidoreductase (NQO1), originally referred to as DT-diaphorase, is a flavoenzyme that plays an important role in protection against endogenous and exogenous quinones by catalyzing two- or four-electron reductions of these substrates. NQO1 has superoxide scavenging activity, stabilizes p53 and other tumor suppressor proteins which are otherwise degraded via the 20S proteasome. The role of NQO1 in pulmonary neoplasia, a diverse disease for which few biomarkers exist, is complicated and appears to depend on several factors like mutation and polymorphism of NQO1 gene. Therapeutic strategies for lung cancer targeting NQO1 have been observed. In this review the physiological, pathological and therapeutic values of NQO1 have been discussed.

Keywords:

Biomarker, NQO1, Nrf2, Lung cancer.

INTRODUCTION:

Lung cancer mortality rates are the highest among all cancers worldwide [1, 2]. Although smoking rates have decreased in the US, many countries have observed few changes in smoking habits, and 10–20% of lung cancer patients are nonsmokers [1,3,4]. Thus, understanding and identifying novel pathways for therapeutic targets is a primary goal in research on pulmonary neoplasms. Non-small-cell lung carcinoma (NSCLC) has the highest incidence rates and most studies focus on its specific subtypes, squamous cell carcinoma or adenocarcinoma (AC), although there are several other subtypes under the NSCLC heading [1, 2]. NSCLC is also the most common among smokers as well as the only lung cancer found in non smokers.

Quinones comprise a large class of aromatic compounds, found widely in plants, in the general (benzoyl) form of C₆H₄O₂, but also found in all organisms as flavonoids, electron-carrying coenzymes and metabolic end-products of oxidation. Quinones are potentially dangerous, in that they can be involved in a one-electron reduction to form semiquinones that will elicit oxidative stress in any cell; benzoquinones and naphthoquinones are among the most reactive in this category.

The NAD(P)H:quinone acceptor oxidoreductase (NQO) gene family is therefore believed to be ancient -- probably between 2 and more than 3 billion years old. Cytosolic NQO flavoenzymes catalyse the beneficial two-electron reduction of quinones to hydroquinones. The two-electron reaction prevents the reduction of quinones by one-electron reductases, which would result in the formation of reactive oxygen species (ROS) generated by redox cycling of semiquinones in the presence of molecular oxygen.

DISCOVERY OF DT DIAPHORASE:

Ernster and Navazioare credited with discovering (in the rat) the first member of the NQO family in the late 1950s. This enzyme is now officially named NQO1. It was later concluded that this enzyme is probably identical to a vitamin K reductase that had been isolated by Martius and colleagues [5]

NQO1 Enzyme And Gene:

NAD(P)H: quinone oxidoreductase (NQO1), originally referred to as DT-diaphorase, is a flavoenzyme that plays an important role in protection against endogenous and exogenous quinones by catalyzing two- or four-electron reductions of these substrates. Quinone compounds are present within our bodies (e.g., vitamin K) and in our natural environment (e.g., urushiol, the active chemical in poison ivy). The two- and four-electron reductions catalyzed by NQO1 are beneficial to the cell by preventing redox cycling, which leads to the generation of free radicals; therefore, NQO1 protects the cell from unwanted oxidative damage.

The human *NQO1* gene (formerly called *DIA4*) is located on chromosome 16q22, the gene spans approximately 17 kb and has six exons. 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. A distantly related *NQO2* gene has seven exons and resides on chromosome 6p25; its gene product uses dihydronicotinamide riboside (NRH) instead of NAD(P)H as its electron donor. Both NQO1 and NQO2 are induced by oxidative stress, dioxin, and polycyclic aromatic hydrocarbons such as those found in combustion processes (e.g., cigarette smoke, urban smog).⁵

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 NQO1 is 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). (The incidence of this variant differ widely by race and associations were reported between the existence of variant alleles in lung and urological cancers. The interethnic differences in this gene were reported to range from 16% 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 .

NQO 1 Catalytic Cycle :

NAD(P)H: quinone oxidoreductase 1 (NQO1), is a cytosolic flavoenzyme that catalyzes the two-electron reduction of quinones into hydroquinones. 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 therefore blocks 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).^[6]

Regulation of NQO1 by the NRF2-KEAP1/ARE pathway

The ability of a wide array of chemical inducers and of caloric restriction to upregulate NQO1 is mediated through the Keap1/Nrf2/ARE pathway. By controlling the expression of a battery of >100 cytoprotective genes, this pathway is essential for the adaptation of mammalian cells and organisms to various electrophilic and oxidative stressors.⁷ As the name of the pathway suggests, three cellular components are of central importance for the mechanisms by which the transcription of this gene battery

is regulated:

- (i) antioxidant response elements (ARE), DNA sequences that are present in the upstream regulatory regions of these genes and have the consensus: TGAG/CNNNGC.^[8] (ii) Nrf2 (nuclear factor-erythroid 2-related factor 2), a basic leucine zipper transcription factor of the "cap-'n collar" family that binds as a heterodimer with a small Maf protein, to the ARE, thereby signaling enhanced transcription^[9]
- (iii) Keap1 (Kelch-like ECH-associated protein 1), the protein sensor for inducers, a Kelch family multidomain repressor protein that binds Nrf2 and promotes its ubiquitination and proteasomal degradation by functioning as an adaptor for Cul3-based E3 ligase.^[10,11]

Several different models have been proposed for the mechanism of regulation of the Keap1/Nrf2/ARE pathway. The most widely accepted model postulates that inducers, all of which react with sulfhydryl groups, modify highly reactive cysteine residues of the sensor Keap1 which then loses its ability to target Nrf2 for degradation. Consequently, Nrf2 is stabilized and accumulates in the nucleus where it binds to AREs and triggers the expression of cytoprotective genes. Furthermore, in rodent and human cells and tissues, NQO1 is one of the most consistently and robustly inducible genes amongst the members of the family of cytoprotective proteins. This early finding has been repeatedly confirmed by global gene expression profiling in a number of systems that employed both pharmacological inducers of the Keap1/Nrf2/ARE pathway, and Keap1 knockdown or knockout genetic approaches. Although the protective effects of Nrf2 activators against cancer and other chronic diseases that have been observed in numerous animal models are undoubtedly due to the concerted action of many cytoprotective proteins whose gene expression is controlled by this transcription factor, the role of NQO1 is prominent, and it has been called a "quintessential" cytoprotective enzyme.¹²

The multiple cytoprotective functions of NQO1^[12]

1. NQO1 catalyzes the obligatory 2-electron reduction of various exogenous and endogenous quinones, quinoneimines, nitroaromatic compounds and azo dyes.
2. NQO1 has superoxide scavenging activity, which although much less efficient than superoxide dismutase (SOD), can be important in tissues or under conditions where expression of NQO1 is high and that of SOD is low.
3. NQO1 stabilizes p53 and other tumor suppressor proteins which are otherwise degraded via the 20S proteasome.
4. In *Xenopus* egg extracts, NQO1 stabilizes microtubules.
5. It has been proposed that NQO1 can modulate the ratios of reduced/oxidized nicotinamide nucleotide pools.

NQO1 ROLE IN LUNG CANCER

HUMAN NQO 1 STUDIES

The lung is an organ of high surface area that is intimately associated with the central compartment to facilitate gas diffusion. Therefore, it is a seminal point of exposure to environmental toxicants such as cigarette smoke, ozone, particulates, and exhaust emissions such as polyaromatic hydrocarbons and peroxyacetyl nitrate^[13]. Such toxicants have been implicated in the incidence of lung cancer and linked to increased burden of ROS in human tissues, as well as the upregulation of antioxidant-selective genes. The growing tumor and its microenvironment are an additional source of ROS from accelerated mitochondrial function required for rapid cell growth and division in the proliferative phase¹⁴. In addition, analyses of tumor tissue from a variety of cancers, including lung, display overexpression of the phase II antioxidant enzymes regulated by NRF2, such as glutathione-S-transferase (GST) and NAD(P)H: quinone oxidoreductase 1 (NQO1), which are both known to facilitate the elimination of reactive, oxidized metabolites^{13, 15}

Studies Of Genetic Variations Of Nqo1 And Effect On Lung Cancer:

Peluso ME et al showed that smokers carrying the EPHX1-139Arg and the NQO1-187Ser variants were significantly more likely to have higher DNA adduct levels of risk allele^[16]

Jin Hee Kim et al conducted a study on a total of 616 Korean patients that were newly diagnosed with lung cancer at Chungbuk National University Hospital in Cheongju, Dankook University Hospital in Cheonan, and Inha University Hospital in Incheon between 2001 and 2003, and 616 controls without lung cancer that were individually matched to cases by age and sex were recruited. The present study suggests that diplotypes of the *NQO1* gene play an important role in the development of lung cancer, and there is an additive interaction between smoking and polymorphisms in the *NQO1* gene for the risk of developing lung cancer. However, we need to clearly understand the function of the *NQO1* C-T haplotype in the development of lung cancer through further laboratory research.^[17]

Cui X et al showed that NQO1 plays an important role in the progression of SCLC, and it may potentially be used as a biomarker and therapeutic target of SCLC.^[18]

Jill M. kolesar et al conducted a prospective trial of adjuvant therapy in patients with resected stages II or IIIa NSCLC. In summary of the study, NQO1*2/*2 independently predicts poor survival in completely resected NSCLC stages II and III patients. In addition, NQO1*2 is associated with p53 wild-type. Prospective trials and determination of specific p53 mutations are needed to confirm and define the relationship of NQO1, p53 and NSCLC. The results of the current study demonstrate that evaluation of NQO1 polymorphisms may be an important consideration in individualizing the treatment of lung cancer.^[19]

Tian G1, Wang M, Xu X conducted a study with A total of 391 patients with inoperable advanced stage of NSCLC, namely, stage III (A + B) and IV NSCLC, and 663 age- and sex-matched healthy were enrolled. The effects of chemotherapy were evaluated. NQO1 C609T polymorphism was determined. The study showed that The NQO1 C609T polymorphism is an important molecular marker for advanced NSCLC, since it is associated with the NSCLC risk as well as the response status of platinum-based chemotherapy.^[20]

Saldivar SJ et al Case-control study, we genotyped the NQO1 variants successfully by PCR-RFLP in 826 lung cancer patients and 826 healthy control subjects matched for age, sex, ethnicity, and smoking status. These results suggest that the NQO1 variant genotype may modulate lung cancer risk, especially in younger individuals (age<62), women, and never smokers.^[21]

Sunaga N et al conducted a study in which, polymorphisms in five genes involved in the metabolism of carcinogens or in the repair of damaged DNA in lung cells, NQO1-Pro187Ser, GSTT1-positive/null, GSTM1-positive/null, CYP1A1-Ile462Val, and OGG1-Ser326Cys, were examined for association with lung adenocarcinoma risk in a case-control study of 198 patients and 152 control subjects. The results suggested that carcinogens in tobacco smoke, which are activated by NQO1 and detoxified by GSTT1, could have a role in lung adenocarcinoma development.^[22]

Lin P et al studied The possible association between NQO1 genetic polymorphism and lung cancer risk was examined among 95 male smokers without cancer and 100 male smokers with lung cancer in Taiwan. There was no significant difference in the proportion of wild-type NQO1 among all cancer cases and controls. The results suggest that NQO1 polymorphism is an important genetic risk factor for lung adenocarcinoma among smokers in Taiwan.^[23]

Eom SY et al performed a case-control study in 387 lung cancer patients and 387 age- and sex-matched cancer-free controls. Direct interview was conducted and the genotypes of NQO1, ALDH2, and CYP2E1 were investigated using PCR-RFLP or 5'-nuclease activity assay. result suggests that the risk of lung cancer is affected by smoking, alcohol drinking, and the genetic polymorphism of NQO1. In particular, genetic polymorphisms for NQO1, CYP2E1, and ALDH2 synergistically with cumulative smoking amounts and alcohol drinking levels interact in the carcinogenesis of lung cancer in Koreans.^[24]

Studies On Chemotherapeutic Strategies With Nqo1:

A high level of NQO1 protein expression was detected by immunohistochemistry in normal lung respiratory epithelium, with the highest levels of expression observed in ciliated columnar epithelial cells. Significant amounts of NQO1 protein were also detected in the vascular endothelium and adipocytes. These data demonstrate that NQO1 is overexpressed in NSCLC. Cells in normal lung also contain marked NQO1 protein and may be damaged by drugs activated by NQO1. These data validate NSCLC as a target for NQO1-directed agents and suggest that the

potential for lung toxicity be considered in the preclinical development of quinone-based antitumor drugs.

Fang Liu et al studied NQO1⁺ A549 cells and isogenically matched NQO1 transfected and negative H596 cells were used to test the properties and mechanisms of TSA induced cell death. The in vivo anti-tumor efficacy and the tissue distribution properties of TSA were tested in tumor xenografted nude mice. The results of these findings suggest that TSA is a highly specific NQO1 target agent and is promising in developing as an effective drug in the therapy of NQO1 positive NSCLC.^[25]

A proposed mechanism of cell death is via activation of a futile cycling of the drug by the cytoplasmic two-electron reductase NAD(P)H: quinone oxidoreductase, also known as NQO1, DT diaphorase and Xip3. Death of NQO1 expressing cells is prevented by the NQO1 inhibitor dicoumarol, and cells with low NQO1 are resistant. At higher drug concentrations the production of reactive oxygen species (ROS) appears to be responsible. Furthermore, this process is p53- and caspase- independent. Either apoptotic or necrotic cell death can result, as reported in various studies performed under differing conditions. β -Lapachone is one of a few novel anticancer drugs currently under active investigation, and it shows promise for chemotherapy alone and especially in combinations.^[26]

Potent mechanism-based inhibitors (suicide substrates) of NQO1 have also been developed. These indolequinones irreversibly alkylate the protein, preventing its function both in standard enzyme assays and also in cells. Some of these quinones are also potent inhibitors of growth of human pancreatic cancer cells, suggesting a potential role for such compounds as therapeutic agents.²⁷

Data indicate that the most efficacious strategy using β -lapachone in chemotherapy was to deliver the drug in short pulses, greatly reducing cytotoxicity to NQO1- "normal" cells. β -Lapachone killed cells in a tumor selective manner and is indicated for use against NQO1+ NSCLC cancers.^[28]

Fang Liu et al used Human NSCLC cell lines A549 (NQO1+) and NCI-H596 (NQO1-) to study the Anti-Tumor Effect of Tanshinone IIA against Non-Small Cell Lung Cancer. Evidence suggests that NQO1 is a promising therapeutic target for various tumors, especially for NSCLC, in which NQO1 is overexpressed compared with normal lung tissue. Although some anti-tumor drugs such as mitomycin can be bioactivated by NQO1, all of them lack sufficient selectivity and specificity to NQO1 and their anti-tumor effects are better explained by other mechanisms. Evidence collected from the studies of Lap indicates that the NQO1 activated futile redox cycle can induce a unique cell death pathway, inspiring the new idea of developing NQO1 target anti-tumor drugs. This study contributes to identify a specific NQO1 substrate TSA, which induces a unique p53 independent activation of mitochondrial apoptotic pathway upon NQO1 bioactivation.^[29]

CONCLUSION:

Based on the studies reviewed, NQO1 gene and its polymorphism have an important role in development of lung cancer. In addition NQO1 polymorphism have an additive effect along with smoking leading to increased cancer risk among smokers. NQO1 is also a potential biomarker and therapeutic target among lung cancer specially SCLC. The epidemiological studies reviewed suggests that NQO1 C609T polymorphism is an important genetic risk factor among smokers as well as non smokers in various ethnic groups. Chemotherapeutic studies reviewed on NQO1 suggests NQO1 is a promising therapeutic target for various tumors, especially for NSCLC, in which NQO1 is overexpressed compared with normal lung tissue. Various anticancer drugs are under trial and are in use as specific NQO1 inhibitors in NQO1 +ve NSCLC.

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