Regulatory function of peroxiredoxin I on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung cancer development (Review)

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Abstract. Smoking is a major cause of lung cancer, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is one of the most important carcinogens in cigarette smoke. NNK modulates the expression of peroxiredoxin (Prdx) I in lung cancer. Prdx1 is upregulated in lung squamous cell carcinoma and lung adenocarcinoma, and considered a potential biomarker for lung cancer. The current article reviewed the role and regulatory mechanisms of Prdx1 in NNK-induced lung cancer cells. Prdx1 protects erythrocytes and DNA from NNK-induced oxidative damage, prevents malignant transformation of cells and promotes cytotoxicity of natural killer cells, hence suppressing tumor formation. In addition, Prdx1 has the ability to prevent NNK-induced lung tumor metabolic activity and generation of large amount of reactive oxygen species (ROS) and ROS-induced apoptosis, thus promoting tumor cell survival. In contrast to this, Prdx1, together with NNK, can promote the epithelial-mesenchymal transition and migration of lung tumor cells. The signaling pathways associated with NNK and Prdx1 in lung cancer cells have been discussed in present review; however, numerous potential pathways are yet to be studied. To develop novel methods for treating NNK-induced lung cancer, and improve the survival rate of patients with lung cancer, further research is needed to understand the complete mechanism associated with NNK.

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Abbreviations: NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; Prdx1, peroxiredoxin I; ROS, reactive oxygen species; Prdx, peroxiredoxins; NK cells, natural killer cells; NSCLC, non-small cell lung cancer; TGF-β1, transforming growth factor-β1; EMT, epithelial mesenchymal transition; Nrf2, nucleosome 2-related factor 2; SOD, superoxide dismutase; H_2O_2, hydrogen peroxide; AM, alveolar macrophages; IL-12, interleukin-12; TNF, tumor necrosis factor; IL-10, interleukin 10; COX-2, cyclooxygenase 2; PGE2, prostaglandin E2; nAChRs, nicotinic acetylcholine receptors; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; TxA2, thromboxane A2; PTEN, phosphatase and tensin homolog

Key words: EMT, lung cancer, NNK, oxidative damage, Peroxiredoxin I

Contents

1. Introduction

Environmental risk factors, such as cigarette smoking and asbestos, lead to increased risk of lung cancer. Before the 20th century, incidences of lung cancer were very rare, up to 1898, only 140 cases of lung cancer were reported in the world medical literature (1). Since the start of tobacco usage, the morbidity and mortality rates of lung cancer have been gradually rising (2,3), and according to WHO statistics, lung cancer has the highest incidence and mortality rate among the 36 most common cancers in the world in 2018 (3). Studies have shown that smoking is directly related to lung cancer (4). According to the statistical data from the World Health Organization, lung cancer was the leading cause of cancer-associated death in 2018; currently there are 300 million tobacco users worldwide, and there are 8 million deaths every year (3).

Multiple studies have shown that 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is the most potent carcinogen

in tobacco that causes lung cancer (5,6). NNK can induce DNA strand breaks and DNA adduct formation, while its metabolism results in the generation of hydroxyl and other reactive oxygen radica9 ls, which in turn causes lung cancer (7). A study by Yeh *et al* (8) demonstrated that the incubation of A549 lung cancer cells with NNK results in increased levels of reactive oxygen species (ROS) formation (8). Furthermore, it has been shown that NNK induces oxidative stress by increasing ROS level in cells and promotes lung cancer progression, which may be associated with the changes in the expression of the genes related to ROS metabolism (9).

The antioxidant defense system in mammalian cells prevents excessive ROS accumulation (10) and maintains the intracellular redox balance. The peroxiredoxin (Prdx) family of proteins function in the cellular oxidative defense system, which eliminates ROS (11) and affects various cellular activities, such as cell proliferation, differentiation (12), apoptosis (13) and gene expression (14). Prdx1 inhibits NNK-induced DNA damage and prevents the development of lung tumors (15-17). NNK-induced changes in the expression of peroxide redox proteins in lung cancer cells indicates that Prdx1 may be involved in the detoxification of ROS during NNK-induced oxidative stress (17). Hence, Prdx1 protects the cells, DNA and proteins from NNK-induced damage, and thus development of lung cancer. The interplay between NNK and Prdx1 has recently gained attention (12,16-18), and an improved understanding of the role of Prdx1 in the development of NNK-induced lung cancer may shed new light towards the development of therapeutic strategies against lung cancer.

2. NNK

NNK, an aromatic compound, is the most potent carcinogen in tobacco smoke (19). In multiple organs, the nicotine in tobacco is rapidly metabolized by cytochrome (CY) P450. In the liver, it is hydroxylated by CYP2A26 at the 2'position to form an amino ketone intermediate, which is subsequently nitrosated to produce NNK (20).

In vivo experiments show that NNK is metabolized by three methods: Carbonyl reduction, pyridine oxidation and α-hydroxylation (21). In the carbonyl reduction process, NNK is carbonylated by 11β-hydroxysteroid dehydrogenase to form 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which is then metabolized by glucuronidation to produce NNAL-glucuronic acid (22). During oxidation of pyridine nitrogen, CYP450 2B1 and CYP3A4 metabolize NNK to NNK-N-oxide (23). The α-hydroxylation process includes two modes: A-hydroxylation of the methyl carbon adjacent to the N-nitroso nitrogen and α-hydroxylation of the methylene carbon adjacent to the N-nitroso nitrogen. NNK is hydroxylated at the methyl group adjacent to N-nitroso to form α-hydroxymethyl-NNK, which then decomposes to form formaldehyde and 4-(3-pyridyl)-4-oxobutane-1-diazohydroxide. Finally, the latter reacts with water to form ketone alcohol. The methylene carbon of NNK can also be hydroxylated to generate an unstable α-methylene hydroxyl-NNK, which quickly decomposes to methane diazohydroxide and keto aldehyde, and finally keto aldehyde oxidizes to form keto acid (19) (Fig. 1).

Using Syrian golden hamster tissue sections, it has been shown that lung tissue has a lower NNK total metabolic rate compared with that of kidney and liver tissues (24). The oxidative metabolism of NNK to DNA-reactive intermediates by α-hydroxylation accounts for 13-31%, pyridine nitrogen oxidation accounts for 5-22%, while carbonyl group reduction of NNK to NNAL accounts for 47-81% of the total metabolism of NNK in the lung. The total metabolism of NNAL in all the tissues is ~10 times lower compared with that of NNK (24). The difference in the metabolic rate of various NNK metabolites is one of the reasons that the lung is more susceptible to the NNK carcinogen (24).

3. Prdx1

Prdxs, a class of antioxidant protective proteins, play an important role in the elimination of ROS and cancer development (25). Prdx1 is a member of the Prdxs family of proteins, which is primarily localized in the cytosol, as well as found in the nucleus, plasma, membrane and centrosome (11). Prdx1 is considered to be an important antioxidant protein (15), and exerts an antioxidant effect by forming a homodimer. The Cys^{52} sulfhydryl group on one peptide chain and the Cys^{172} sulfhydryl group on the other peptide chain are dehydrogenated to form an intermolecular disulfide bond, Cys^{52}S-SCys^{172}, which reduces peroxides by providing hydrogen ions, thereby detoxifying them (26). Prdx1 is highly sensitive to hydrogen peroxide (H_2O_2), among various peroxides (11).

In most cancer cells, such as breast, esophageal and lung cancer, Prdx1 can removes excess intracellular ROS, maintains ROS balance and protects the cells from oxidative stress-induced DNA damage (27). Furthermore, by eliminating ROS, Prdx1 prevents oxidative stress-induced mutations in the *P53* and *K-Ras* genes, thereby inhibiting tumor formation, suppressing lung cancer cell proliferation, invasion and migration, and increasing radiation sensitivity of the cancer cells (15,28). Cys^{52} is the active center of Prdx1 (29), which either reacts with H_2O_2 (30) or combines with heme; hence, Prdx1 is also called as heme-binding protein 23 (31). Prdx1 acts as a scavenger for the cytoplasmic heme and has an important inhibitory effect on heme toxicity (32). Furthermore, Prdx1 enhances the immune activity of natural killer (NK) cells against tumor cells, and is also known as natural killer enhancement factor (11). It has been shown that Prdx1 can effectively prevent lung cancer progression by enhancing the tumor killing effects of NK cells (33,34). Prdx1 is overexpressed in non-small cell lung cancer (NSCLC) cells, which has been demonstrated to promote transforming growth factor-β1 (TGF-β1)-induced epithelial mesenchymal transition (EMT) and A549 cell migration (35). In addition, the interaction between Prdx1 and nuclear erythroid 2-related factor 2 (Nrf2) can significantly affect the proliferation of lung cancer cells (28,36). In a rat acute lung injury model, overexpression of Prdx1 increased the expression of proinflammatory cytokines interleukin-6 (IL-6), IL-8 and tumor necrosis factor-α (37). Inflammatory factors play an important role in the development of lung cancer. In addition, Prdx I affects the proliferation, migration and invasion of lung cancer cells by regulating various cytokines, in turn modulating different cell signaling pathways (38,39).

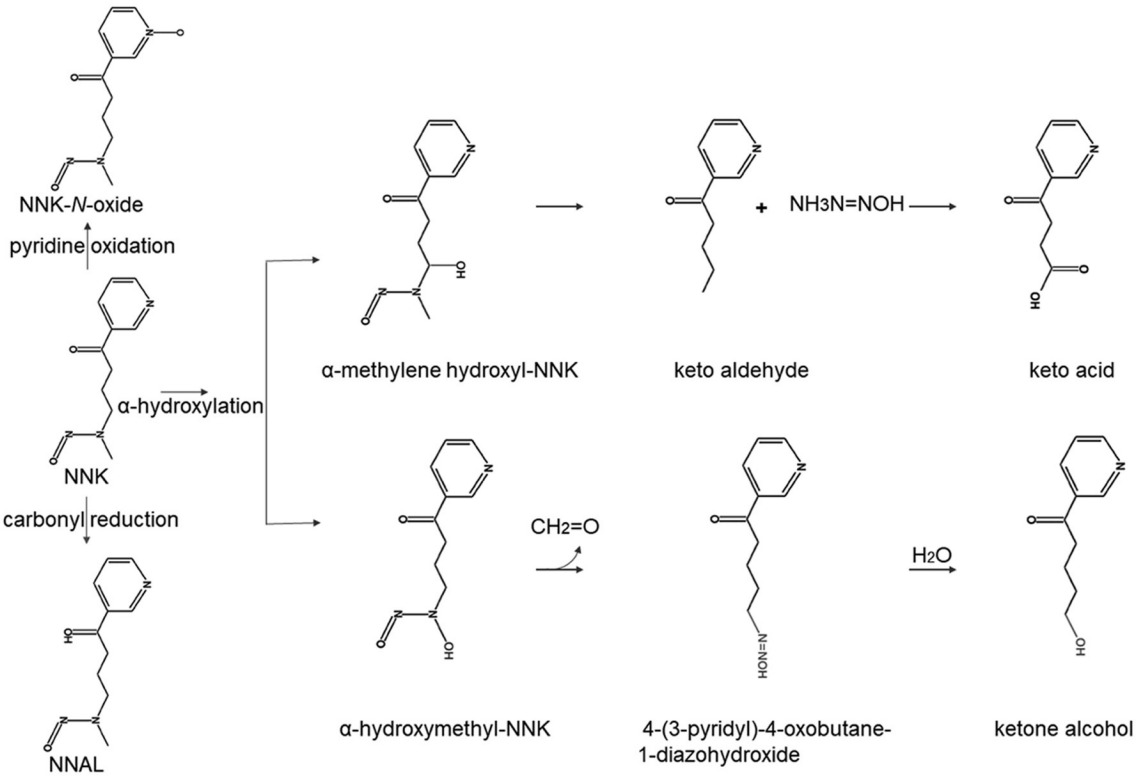

Figure 1. Metabolic process of NNK, including three major metabolic methods of NNK: Carbonyl reduction, pyridine oxidation and α-hydroxylation. Modified a previous study (7). NNK, NNK(4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone); NNAL, NNAL(4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol).

On one hand, Prdx1 protects macromolecules, such as proteins and DNA, from oxidative damage and suppresses malignant transformation of normal cells, thus preventing tumor development. On the other hand, Prdx1 inhibits ROS-induced apoptosis of cancer cells and promotes tumor cell survival (27). Hence, understanding its mechanism of action may provide novel insights into the development of better therapeutic strategies for lung cancer.

Prdx1 and NNK affect the growth and development of lung cancer by acting on P53 and K-Ras genes. NNK mainly undergoes metabolic activation through α-methyl and α-methylene hydroxylation, thereby producing DNA adducts and promoting cancer development. α-methyl hydroxylated metabolites of NNK can pyridyloxobutylate DNA and produce DNA pyridyloxobutyl adducts, whereas α-methylene hydroxylation generates α-methylenehydroxy-NNK, methane diazohydroxide and methyldiazonium ions. These react with DNA and yield 7-methyl guanine, O^6-methyl guanine and O^4-methyl thymine adducts (7). NNK induces oxidative stress by increasing the level of intracellular ROS, which in turn leads to the mutation of *K-Ras* and *P53* oncogenes. In addition, the NNK metabolites have been shown to result in the mutation of *K-Ras* and *P53* oncogenes in the lung. Thus, these deleterious effects of NNK on DNA may promote the development of lung cancer.

Prdx1 is considered a potential marker for NSCLC, and the interaction between Prdx1 and ROS plays an important role in the development of tumors (40). ROS plays a role in cell growth, differentiation, immune response and apoptosis (41,42). Increase in intracellular levels of ROS activates the expression of *P53* (15), which in turn induces the expression of apoptotic factors, such as Bak and Bax, under oxidative stress, promotes the activation of caspases and finally activates the mitochondrial apoptotic signaling pathway (27). P53 in its active form suppresses the proliferation of abnormal cells, thereby exerting a tumor suppressor effect (43). In addition, P53 plays an important role in detecting DNA damage. P53 status after reducing the expression of Prdx1 is the major determinant of tumor growth and response of lung cancer cells to treatment (15). *K-Ras* mutations are known to cause uncontrolled division of human lung adenocarcinoma cells (44-46). Furthermore, *K-Ras* mutations and ROS-induced oxidative stress are the major causes of NSCLC development. Prdx1 inhibits the activation of ROS/ERK/cyclin D1 pathway, thus results in *Nrf2*-dependent inhibition of K-Ras-driven lung tumorigenesis (28).

NNK may promote lung cancer development by increasing the intracellular ROS level and inducing mutations in important oncogenes. Prdx1 effectively eliminates excess ROS and prevents gene mutations caused by oxidative damage of DNA. Prdx1 prevents the occurrence of mutations in the *P53* gene, enabling it to detect and repair damaged DNA. Furthermore, activation of the Nrf2 pathway results in upregulation of Prdx1. Prdx1 inhibits the ROS/ERK/cyclin D1 signaling pathway and suppresses the development of lung tumors (Fig. 2) (42,43,47,48).

Prdx1 and NNK affect the growth and development of lung cancer by reacting with heme and hemoglobin. It has been demonstrated that NNK-induced DNA damage is significantly reduced by antioxidants (BHT), catalase and

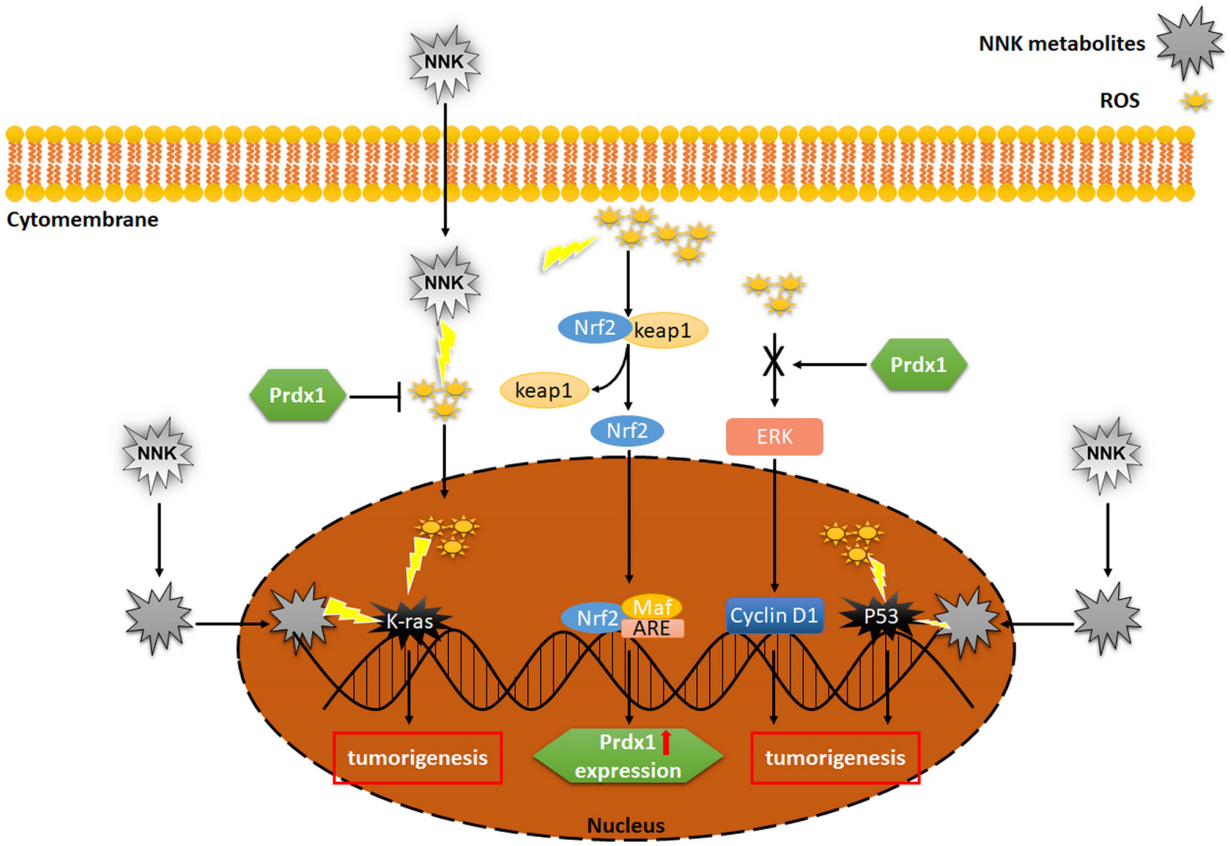

Figure 2. Effects of Prdx1 and NNK on *P53* and *K-Ras* genes in lung cancer cells. NNK stimulates the production of ROS and Prdx1 scavenges ROS, which affects the development of lung cancer through DNA damage. Prdx1, peroxiredoxin I); NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; Nrf2, nucleosome 2-related factor 2; ARE, antioxidant response element; ROS, reactive oxygen species; keap1, kelch-like ECH-associated protein-1.

superoxide dismutase (SOD) in A549 cells. The order of the effectiveness has been indicated to be BHT > catalase > SOD (8). Thus, it is speculated that NNK mainly induces generation of H_2O_2 (8,49,50). The α-methyl hydroxylation of NNK results in the formation of unstable α-hydroxymethyl NNK. The decomposition of a-hydroxymethyl NNK results in the formation of electrophilic 4-(3-pyridyl)-4-oxybutyl diazoxide, which can react with hemoglobin to form hemoglobin adduct (7,51). NNK α-methyl hydroxylation results in globulin methylation and pyridyloxybutylation (15), and the hemoglobin adduct formed by pyridyloxybutylation releases 4-hydroxy-1-(3-pyridyl)-1-butanone by alkaline hydrolysis (51). Studies have shown that keto alcohol-releasing adducts were formed by treatment of hemoglobin with NNK (51-53). Phenylethyl isothiocyanate treatment can significantly inhibit NNK-mediated lung tumorigenesis by reducing the release of ketone alcohol products (54).

Prdx1 can bind to heme (53), which is abundant in red blood cells. Furthermore, heme is widely distributed in organelles, such as the nucleus, endoplasmic reticulum and plasma membrane (55,56), and it is involved in a processes in mammalian cells, including respiration, metabolism, transcription, DNA binding and protein degradation (55,57). Heme is synthesized in mitochondria and loosely bound to Prdx1 (31), which is proposed to facilitate the transport of heme to other organelles (55,56,58). Heme is insoluble in aqueous solutions and is toxic to the cells (59), and the toxicity is further manifested by the generation of ROS (57). However, binding of heme to Prdx1 reduces heme toxicity and promotes H_2O_2-mediated heme degradation (60). Thus, Prdx1 protects free heme from peroxidation but loses its peroxidase activity when bound to heme (31). NNK induces the generation H_2O_2 and Prdx1 is more sensitive to H_2O_2. H_2O_2 causes erythrocyte lysis, leading to the release of large amounts of heme and hemoglobin (61). Heme interacts with oxygen to produce ROS (62), which further destroys red blood cells. The binding of heme and Prdx1 reduces heme cytotoxicity; however, Prdx1 loses its ROS scavenging ability. NNK metabolites produce adducts with hemoglobin, thereby promoting the development of lung tumors, and Prdx1 plays a role in ROS scavenging, which in turn protects red blood cells from oxidative damage and inhibits lung tumorigenesis (Fig. 3).

Prdx1 and NNK affect the growth and development of lung cancer by acting on alveolar macrophages (AMs) and NK cells. NNK metabolites inhibit AM-mediated production of interleukin-12 (IL-12), nitric oxide and TNF; however, they also induce the production of IL-10 (63), which may promote the growth and development of lung tumors (64). Additionally, NNK has an inhibitory effect on TNF-dependent cytotoxicity of AMs (49). Furthermore, metabolites produced by NNK α-methyl hydroxylation may be involved in the regulation of AM function. For example, keto acid inhibits IL-12 production by AMs, while keto alcohol may inhibit the AM production of TNF and IL-12 (65). NNK may induce the expression of cyclooxygenase 2 (*COX-2*) and upregulate prostaglandin E2

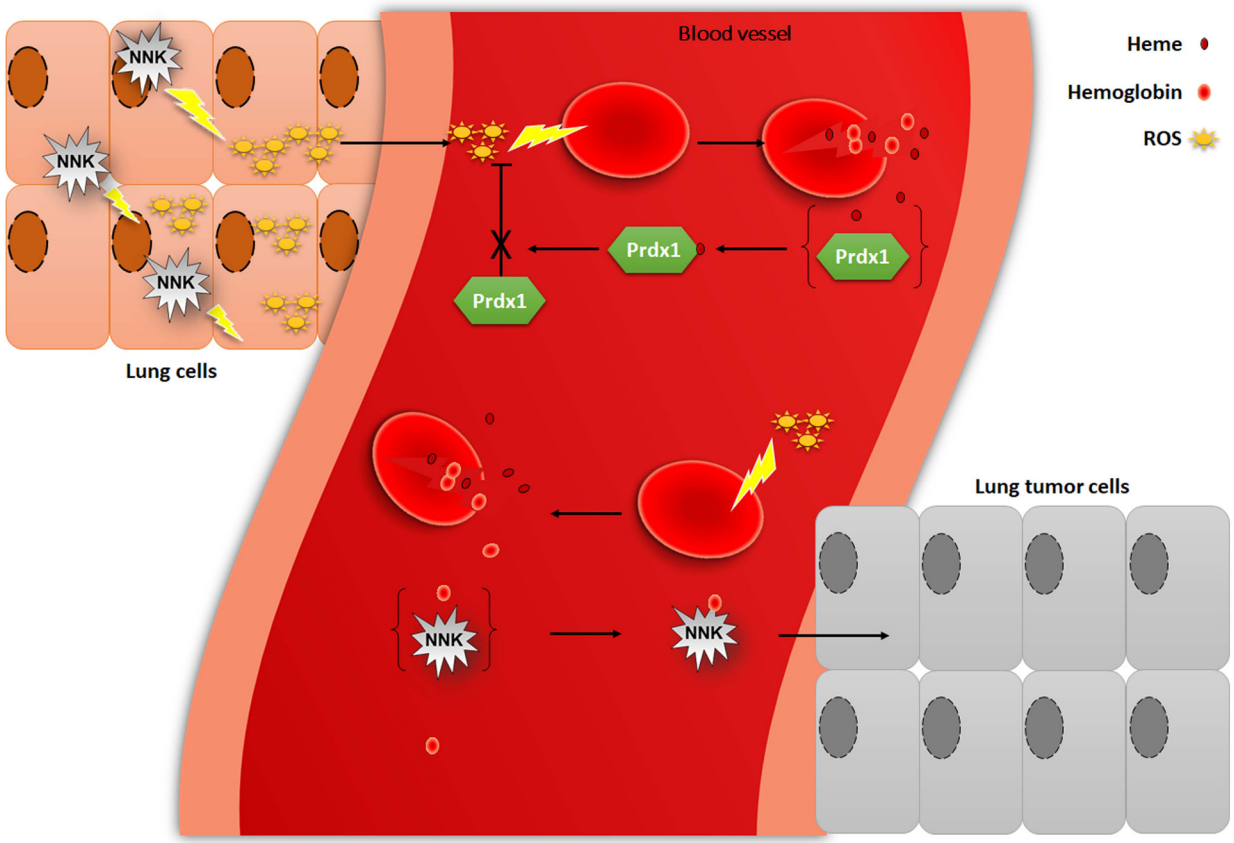

Figure 3. Effects of Prdx1 and NNK on heme and hemoglobin in lung cancer cells. In the blood, NNK interacts with hemoglobin, Prdx1 interacts with heme and they jointly affect the occurrence and development of lung cancer. Prdx1, peroxiredoxin I; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; ROS, reactive oxygen species.

(*PGE2*); PGE2 in turn upregulates IL-10 (63,66). Nicotinic acetylcholine receptors (nAChRs) are present in immune cells (67), and NNK has high affinity towards nAChRs. Thus, interaction of NNK and nAChRs may activate the production of IL-10 (68). Moreover, IL-10 suppresses the production of IL-12 (69), and inhibition of IL-12 leads to decreased expression of interferon-γ (70,71). Furthermore, IL-12 is mainly produced by phagocytes (monocytes/macrophages and neutrophils) and dendritic cells (72) and enhances the cytotoxicity of AM and NK cells (73). NK cells are a group of lymphocytes that can kill tumor cells (74). Therefore, it can be speculated that NNK attenuates the toxic effects of NK cells on tumor cells and further promotes the development of lung cancer.

All six Prdxs are expressed by human lung cells; however, AMs mainly express Prdx1 and III (75). Prdx1 may affect the production of pro-inflammatory cytokines in macrophages (76) and has the ability to enhance NK cell toxicity *in vitro*. Furthermore, it has been reported that free thiol groups are required to maintain NK cell toxicity against tumor cells (42). The alkylation of free sulfhydryl groups in Prdx1 upon reduction decreases its ability to enhance NK cell toxicity, further indicating the requirement of free thiol groups for enhanced cytotoxicity of NK cells (16). Therefore, Prdx1 not only protects the cells from oxidative damage, but also selectively promotes the killing effect of AM and NK cells in certain tumors.

NNK may activate AMs to produce H_2O_2. NNK inhibits the production of IL-12 and TNF by AMs, thereby reducing the cytotoxicity of AMs and NKs against the tumor cells. Prdx1 is expressed mainly in AMs and may play a role in immune regulation by affecting inflammatory factors. Prdx1 may inhibit lung tumors by enhancing the killing effect of NK cells. However, the exact role of NNK and Prdx1 in AM-mediated killing of tumor cells is still unclear (Fig. 4) (64,70,74-76).

Prdx1 and NNK affect EMT. Long-term exposure of lung alveolar cells to NNK results in their proliferation and eventually malignant transformation (77). After the cells are exposed to NNK, the expression of intracellular β-catenin and F-actin decrease, whereas that of fibronectin, vimentin and matrix metalloproteinase-2 increase. This in turn promotes EMT (77). EMT is a process by which epithelial cells are transformed into the mesenchymal phenotype, which increases their invasion and migration capabilities. Morphologically, the epithelial cells are loosely connected and the cytoskeleton structure is reorganized. The EMT process is accompanied by various changes in protein expression, including a decrease in E-cadherin and an increase in fibronectin expression levels (77). Low E-cadherin expression decreases cell adhesion, and downregulation of E-cadherin is also considered as a sign of EMT (78). NNK and ROS induce EMT through different signaling pathways (79). In cancer cells, NNK may promote the production of ROS, such as H_2O_2, which in turn

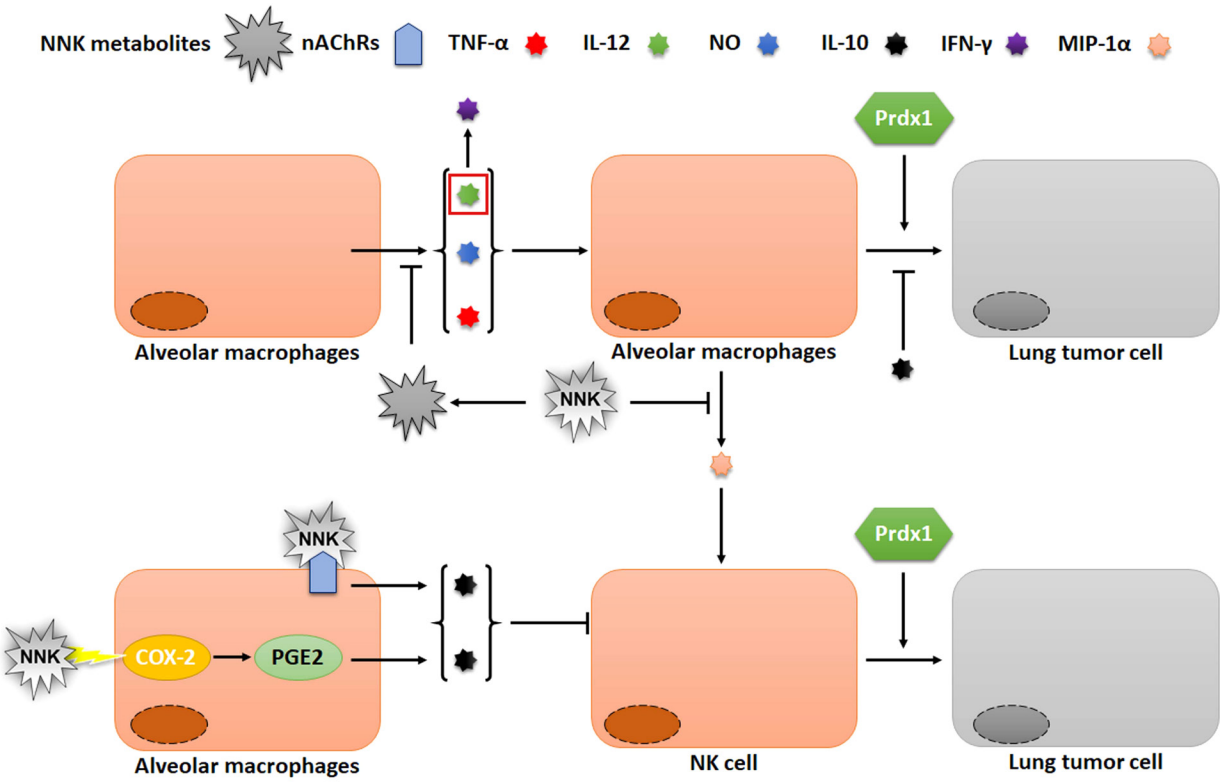

Figure 4. Effects of Prdx1 and NNK on AM and NK cells. NNK can reduce the toxicity of AM and NK cells to lung cancer cells, while Prdx1 can stimulate NK cells to kill lung cancer cells. Prdx1, peroxiredoxin I; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; AM, alveolar macrophages; NK, natural killer cells; IL, interleukin; nAChRs, nicotinic acetylcholine receptors; MIP, macrophage inflammatory protein; PGE2, prostaglandin E2; COX, cyclooxygenase.

activates c-Src (80,81), leading to cytoskeletal modifications (79) and initiation of EMT (82). Most tissues usually do not express *COX-2* or express it at a low level (83). The induced expression of *COX-2* inhibits apoptosis and increases the migration potential of cancer cells (84). The combination of NNK and a7-nAChR can induce the expression of *COX-2*, which upregulates fibronectin and promotes EMT (79).

Furthermore, Prdx1 is a type of peroxidase reductase, which can play the role of scavenging ROS, thus inhibiting the EMT process. It has been observed that Prdx 1 can promote EMT in breast (85), pancreatic (86) and colon cancer (87). Furthermore, high expression levels of Prdx1 downregulates E-cadherin, whereas, at lower levels it upregulates E-cadherin in A549 lung adenocarcinoma cells (88). TGF-β1 is a pleiotropic cytokine that is involved in apoptosis, differentiation and proliferation of cells and is the primary inducer of EMT (83,89-91). It has been shown that the overexpression of Prdx1 in lung cancer cells significantly enhances TGF-β1-mediated EMT and cell migration (92).

In A549 lung cancer cells, NNK treatment results in a significant increase in Prdx1 expression. NNK not only results in ROS production, but also upregulates the expression of fibronectin via COX-2 and promotes EMT. Prdx1 can play a role in scavenging ROS, and Prdx1 can also inhibit EMT process by scavenging ROS caused by NNK. Additionally, high levels of Prdx1 results in upregulation of E-cadherin, which promotes EMT (Fig. 5) (77-82,84,85).

Signaling pathways associated with Prdx1 and NNK in lung cancer cells. NADPH oxidase of Nox family is expressed in both normal and cancer cells, and is related to ROS production and tumorigenicity in various cancer cells. For example, Nox1 is highly expressed in human colon cancer and prostate cancer, and lung cancer A549 cells also express Nox1, 2 and 4 (16,93). NNK induces the expression of NOX protein and results in the production of large amount of ROS, which causes damage to protein and DNA through oxidative stress. In A549 lung cancer cells, NNK-mediated generation of ROS through NOX activates phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) and Wnt signaling pathways, which leads to the development of drug resistance in lung cancer cells (16) and is associated with lower survival rate of patients with stage 1 lung tumors in Tumor-Node-Metastasis staging system (94). NNK increases the expression of thromboxane A2 (TxA2) and Tx receptor in lung cancer cells by elevating COX and Tx synthase expression (95). NNK has been shown to promote adhesion and invasion of CL1.0 cells through α7-nAChR/ERK/Contactin 1 signaling (96). Furthermore, NNK prevents PH domain leucine-rich repeat-containing protein phosphatase 2-mediated AKT dephosphorylation, activates AKT to inhibit E-cadherin expression and promotes lung cancer cell migration (97). The combination of NNK and α7-nAChRs activates c-Src and protein kinase C, and promotes the dissociation of phosphorylated Bad from Bcl-xl, which in turn inhibits apoptosis (98).

In tumor cells, Prdx1 has been reported to eliminate large quantities of ROS produced by tumor cell metabolism and thus, suppresses tumor cell death. Additionally, Prdx1 inhibits the oxidative stress-induced PI3K/AKT signaling pathway by eliminating ROS. It is known that the ROS-induced activation

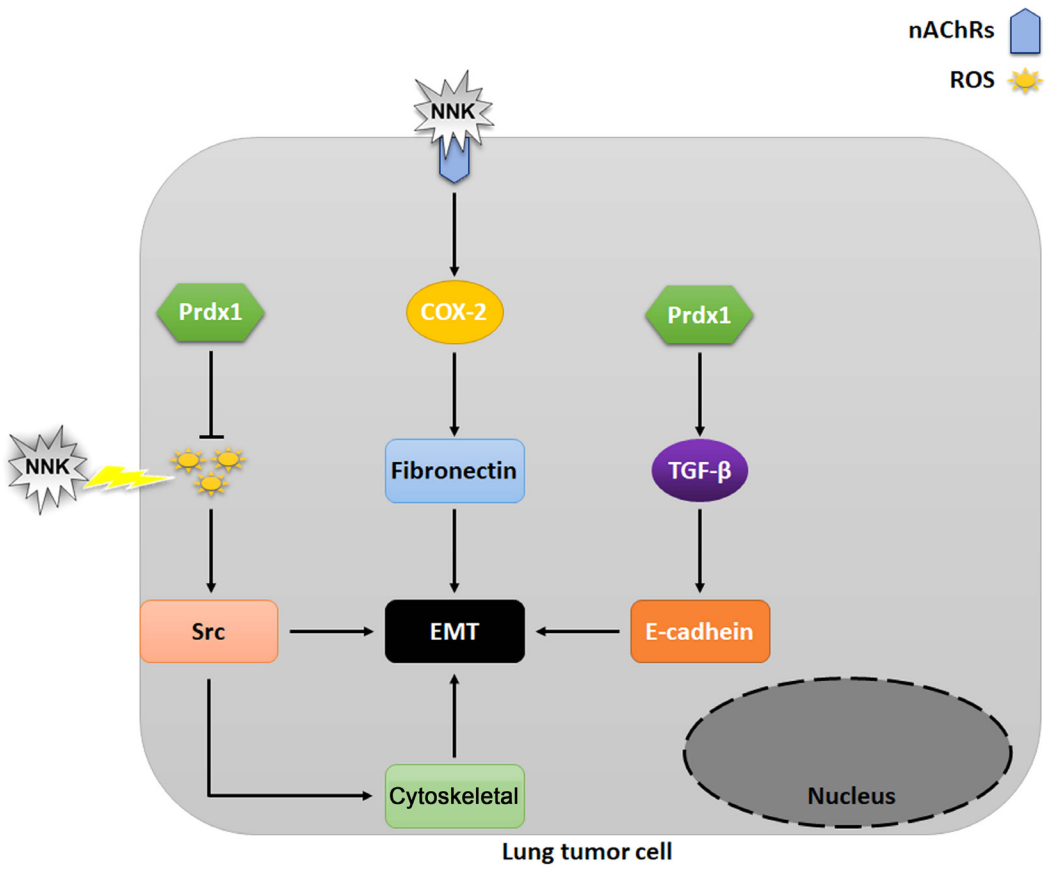

Figure 5. Effects of Prdx1 and NNK on EMT of A549 lung cancer cells. In lung cancer cells, NNK can promote EMT process, Prdx1 can inhibit EMT process by scavenging ROS, but high level of Prdx1 can promote EMT process. Prdx1, peroxiredoxin I; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; EMT, epithelial-mesenchymal transition; nAChRs, nicotinic acetylcholine receptors; ROS, reactive oxygen species; COX, cyclo-oxygenase.

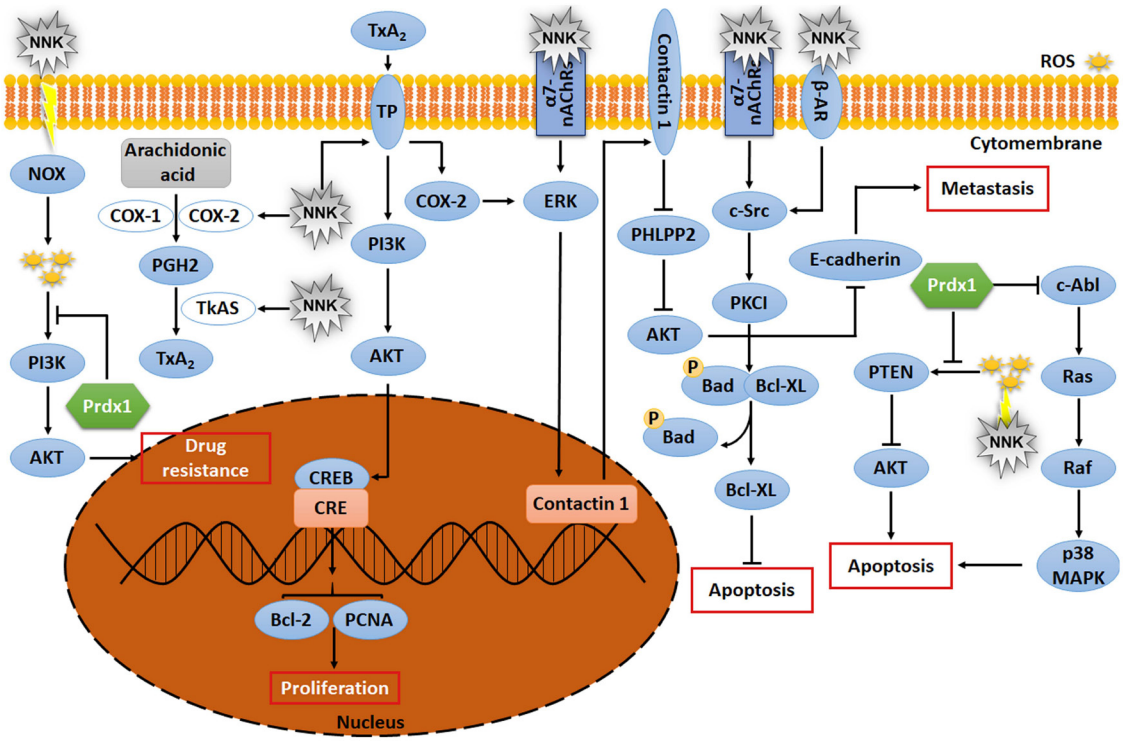

Figure 6. Signaling pathway of Prdx1 and NNK. NNK and Prdx1 are involved in the regulation of signaling pathways in the development of lung cancer cells. NOX, NADPH oxidase; TxA_2, thromboxane A2; PGH2, prostaglandin H2; COX, cyclooxygenase; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; TP, thromboxane receptor; PCNA, proliferating cell nuclear antigen; CREB, cyclic AMP response element-binding protein; CRE, cyclic AMP response element; ROS, reactive oxygen species; PHLPP2, pleckstrin homology domain leucine-rich repeat protein phosphatase 2; PKCI, protein kinase C interacting protein.

of PI3K/AKT is due to the oxidative inactivation of phosphatase and tensin homolog (PTEN) protein (99). Furthermore, Prdx1 protects PTEN lipid phosphatase activity from oxidative inactivation, thereby preventing AKT from driving tumor cell proliferation and inducing apoptosis (26). C-Abl plays a vital role in oxidative stress-induced cell death (100). Prdx1 can be used as a physiological inhibitor of C-Abl (18) to inhibit apoptosis induced by the C-Abl/P38/MAPK signaling pathway.

NNK induces Nox protein to produce ROS, and activates the PI3K/Akt signaling pathway; however, NNK inhibits the same pathway by removing ROS or preventing oxidative inactivation of phosphatase and PTEN. In addition, NNK activates α7-nAChRs and downstream signaling pathways, and hence promotes apoptosis and migration of lung cancer cells. Furthermore, both NNK and Prdx1 can regulate apoptosis-related proteins and thus, control the apoptosis of lung cancer cells (99,101-103) (Fig. 6).

4. Conclusions

In conclusion, on the one hand, Prdx1 has the ability to protect erythrocytes and DNA from NNK-induced oxidative damage, prevent malignant transformation of cells and promote cytotoxicity of NK cells, suppressing tumor formation. In addition, Prdx1 prevents NNK-induced generation of large amount of ROS and hence, ROS-induced apoptosis, and promotes tumor cell survival. On the other hand, together with NNK, Prdx1 promotes EMT and migration of lung tumor cells. The signaling pathways of NNK and Prdx1 in lung cancer cells are intricate, and the associated mechanisms are yet to be explored.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

HNS, CXR, YXG and TK conceived and designed the review. HNS, CXR, YXG, DPX and TK wrote the manuscript and prepared the figures. HNS and TK reviewed and edited the manuscript. TK acquired the funding. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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