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Nicotine and lung cancer

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Abstract

Tobacco use in cancer patients is associated with increased cancer treatment failure and decreased survival. Nicotine is one of over 7,000 compounds in tobacco smoke and nicotine is the principal chemical associated with addiction. The purpose of this article is to review the tumor promoting activities of nicotine. Nicotine and its metabolites can promote tumor growth through increased proliferation, angiogenesis, migration, invasion, epithelial to mesenchymal transition, and stimulation of autocrine loops associated with tumor growth. Furthermore, nicotine can decrease the biologic effectiveness of conventional cancer treatments such as chemotherapy and radiotherapy. Common mechanisms appear to involve activation of nicotinic acetylcholine receptors and beta-adrenergic receptors leading to downstream activation of parallel signal transduction pathways that facilitate tumor progression and resistance to treatment. Data suggest that nicotine may be an important mechanism by which tobacco promotes tumor development, progression, and resistance to cancer treatment.

Keywords: Cancer, lung, nicotine, smoking, tobacco

BACKGROUND

Tobacco use is the largest preventable cause of cancer with an estimated 30% of all cancer deaths attributed to tobacco use.[1-4] Cigarette smoke is the predominant form of tobacco consumption consisting of approximately 95% of tobacco use. There are an estimated 7,000 compounds in cigarette smoke including at least 60 known carcinogens.[4] Though there is tremendous literature supporting the role of tobacco in carcinogenesis, there are proportionately few studies that report on the effects of tobacco on cancer treatment outcomes. Several studies demonstrate that tobacco decreases survival, decreases quality of life, impairs wound healing, increases recurrence, and decreases survival in patients with well-established tobacco-related cancers such as head and neck or lung cancer.[5-11] In traditionally non-tobacco-related cancers, tobacco use is also associated with a more advanced stage at diagnosis, younger age at cancer presentation, decreased compliance to cancer treatment, decreased quality of life, increased risk of treatment toxicity, increased risk of developing second primary cancers, increased surgical risk, increased recurrence, and increased risk of cancer-related and non-cancer-related mortality.[12-37] Importantly, tobacco use may dominate overall mortality in some non-tobacco-related cancers (such as prostate cancer) due to significantly increased risks of cardiovascular mortality.[14,15,38] There are limited data evaluating the effects of smoking cessation on outcome, but data suggest that tobacco cessation improves outcomes in cancer patients.[39-41] In more structured evaluations, patients who did not smoke a median of 32 days after completion of radiotherapy have improved survival as compared with

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patients who smoked during radiotherapy.[42] Collectively, these data support tobacco assessment and cessation as important to improve cancer treatment outcomes.

With the given adverse effects of tobacco on health, recommendations for tobacco cessation are supported by several national cancer organizations including the American Society for Clinical Oncology,[43] American Association for Cancer Research,[44] and National Comprehensive Care Network.[45] Public Health Service Guidelines are the mainstay for tobacco cessation that recommends providing behavioral counseling and pharmacotherapy to help support effective tobacco cessation.[46] Nicotine, varenicline (Chantix), and bupropion (Zyban) are the most commonly used and well-supported pharmacotherapies used in tobacco cessation. Nicotine is a component of tobacco and cigarette smoke that is the primary component associated with addiction.[2,46,47] Nicotine is a systemically available agent that exerts many of its biological effects through the binding and activation of nicotinic acetylcholine receptors (nAChRs) that are known to be expressed on both normal and cancerous tissues.[48-51] Though once associated primarily with neuronal signaling, nAChRs are increasingly implicated in the pathogenesis and progression of cancer.[52,53] The purpose of this review is to introduce the cellular and physiological activities of nicotine as related to the biological development, progression, and treatment of lung cancer.

NICOTINE CHEMISTRY AND METABOLISM

Nicotine is a product of tobacco that undergoes several pathways of chemical conversion and metabolism.[48,49] During the tobacco curing and smoking process, nicotine can be converted to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, and N'-nitrosonornicotine (NNN) through nitrosation. After entering the body, nicotine is rapidly absorbed and distributed throughout the body. Approximately 75% of nicotine is metabolized to cotinine primarily by cytochrome P450 (CYP) 2A6, CYP2B6, and aldehyde oxidase. Further metabolism of cotinine involves additional hydroxylation primarily to 3-OH cotinine, glucuronidation, and excretion primarily in urine. Approximately 50-60% of nicotine is metabolized and excreted as glucuronidated 3-OH cotinine. The remaining nicotine can be converted to other metabolites such as nicotine-N-oxide. Glucuronidated nicotine and its metabolites are also excreted in the urine.[48,49] Nicotine and its principal metabolites involved in tumor promotion are shown in Figure 1.

Tumorigenesis

Nicotine alone is generally accepted as a tumor promoter, but not a tumor initiator in carcinogenesis. However, NNK

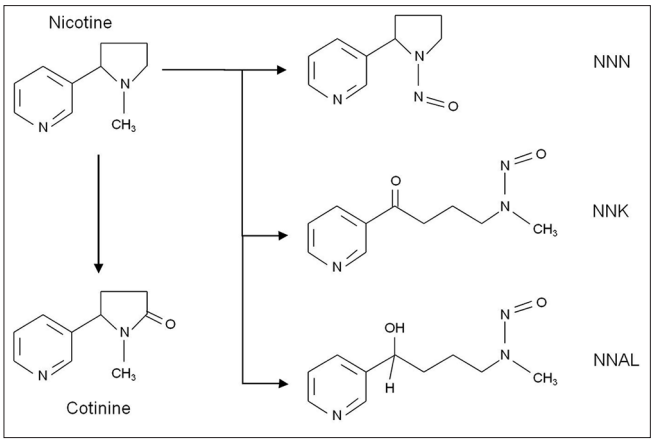

Figure 1: Nicotine and metabolites associated with tumor promotion [NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, NNN: N'-nitrosonornicotine, NNO: Nicotine-N-oxide]

is a well-established initiating carcinogen that can lead to tumor development. NNK tumorigenesis is enhanced with beta-adrenergic receptor (β-AdrR) stimulation and reduced with inhibition of β-AdrRs.[54] Similar studies demonstrate that inhibition of 5-lipoxygenase or cyclooxygenase-2 (COX-2) decreases tumorigenesis by NNK.[55,56] Beyond initiation, NNK can promote tumor development through activation of nAChRs and β-AdrRs leading to increased proliferation.[57] NNK or NNN can increase transformation of immortalized cells, though these effects of NNK appear to be related primarily to activation of the α7nAChR, whereas the effects of NNN may be preferentially modulated through the α3nAChR.[58] The potential importance of nAChRs in regulating tumor growth is demonstrated by recent data showing that inhibition of nAChRs *in vivo* decreases tumor growth by approximately 90%.[59] In this latter study, preferential inhibition of the α7nAChR results in significant apoptosis in tumor xenografts associated with significant decreases in angiogenesis.

Nicotine and its metabolites may facilitate tumorigenesis by other carcinogens. Nicotine administration in human bronchial epithelial cells significantly upregulates several genes particularly associated with activation of mitogen activated protein kinase (MAPK).[60] Nicotine increases methylation of the fragile histidine triad (FHIT) gene resulting in decreased FHIT and increased deoxyribonucleic acid (DNA) methyltransferase (DNMT) 3a expression.[61] Notably, removal of nicotine restores normal methylation patterns and expression suggesting the effect of nicotine is reversible. Cotinine may also increase the tumor forming effects of NNK.[62] However, other studies suggest that nicotine has no appreciable effects on tumor number, size, or metastasis by NNK.[63,64]

Recent evidence suggests that variations in the tumor-promoting effects of nicotine are mediated in part by p53 expression. In cells without p53 function, nicotine has a more pronounced pro-survival effect in cells treated with cytotoxic agents or serum starvation.[65,66] Translocation of nuclear factor kappa-B (NFκB) to the nucleus in cells without functional p53 also occurs at lower doses of nicotine, thereby promoting tumor growth.[67] Data suggest that nicotine decreases G1 arrest following DNA damage by several cytotoxic agents, thereby promoting cellular transformation and tumor formation.[65,68] A more pronounced effect of nicotine in cells without functional p53 supports a cellular alteration in cell cycle checkpoint, thereby promoting tumorigenesis through dysregulation of proliferation, DNA repair, and apoptosis. However, the removal of nicotine from combustible products does not appear to reduce DNA damage[69] and nicotine replacement therapy has no appreciable effect on the development of lung cancer in clinical cohorts.[70]

Proliferation

Nicotine and activation of nAChRs appear to be important in the proliferative effects of cigarette smoke. In C57BL/6J mice engrafted with Lewis lung cancer cells, smoke increases cotinine levels and increases tumor size, weight, capillary density, and circulating serum vascular endothelial growth factor (VEGF).[71] Inhibition of nAChRs with mecamylamine partially prevents the effects of second-hand smoke on tumor growth and VEGF levels. Further examination of nAChRs suggests that they are important in tumor proliferation. Evaluation of small-cell lung cancer (SCLC) cell lines demonstrates that acetylcholine increases proliferation and SCLC has broad nAChR subunit expression as well as the ability to synthesize, secrete, and metabolize acetylcholine.[72] Treatment of H69 SCLC cells with nicotinic agonists (nicotine or cytisine) increases proliferation through activation of nAChRs,[73] but inhibition of muscarinic AChRs does not prevent the proliferative effects of nicotine.[74] Nicotine increases proliferation of SCLC cells in a manner prevented with inhibition of the α7nAChR, but higher doses of nicotine result in the loss of proliferative stimulus.[75] In this study, nicotine does not appear to increase proliferation in non-malignant cells. The proliferative effects of nicotine and its metabolites may vary by cell type. Studies in BEP2D bronchial epithelial cells demonstrate broad nAChR expression and increased proliferation with NNK or NNN through activation of nAChRs.[76] Nicotine or NNK increases proliferation in neuroendocrine cells (H727) with no effect in type II alveolar cells; however although NNK increases Clara cell proliferation, nicotine has no effect.[77]

Data also suggest that nicotine and other agonists of the nAChR can stimulate an autocrine loop to promote proliferation. Nicotine or cytosine (a nAChR agonist) increases proliferation and serotonin production through activation of nAChRs; however, serotonin increases proliferation independently of nAChR.[78] Furthermore, serotonergic-induced proliferation is not enhanced in the presence of nicotine.[79] Nicotine can increase proliferation or secretion of noradrenaline and adrenaline in pancreatic cancer cells through activation of nAChR and β-AdrR.[80] Collectively, these data suggest that nicotine and its metabolites increase proliferation of malignant and non-malignant cells through modulation of nAChRs, β-AdrRs, and potential activation of proliferative autocrine loops.

Nicotine and its metabolites increase proliferation through activation of several downstream pathways. Nicotine increases proliferation associated with increased activation of MAPK and DNA synthesis in a α7nAChR-dependent manner.[81] Further examination *in vivo* suggests that nicotine activates MAPK kinase (MEK) leading to downstream activation of extracellular signal related kinase (ERK) 1/2, COX-2 expression, prostaglandin production, VEGF expression, and proliferation.[82,83] Nicotine-induced proliferation in colon cancer cells is partially and synergistically prevented with inhibition of epidermal growth factor receptor tyrosine kinase (EGFR-TK) and Src.[84] Similar activation of proliferation through Src, cyclin dependent kinase (CDK), Raf-1, beta-arrestin, and EGFR-TK is also observed in lung cancer cells and endothelial cells[66,85] The molecular pathways activated by nicotine are presented in Figure 2.

NNK and NNN are also activators of proliferation and tumor promotion through activation of the nAChRs and β-AdrRs.

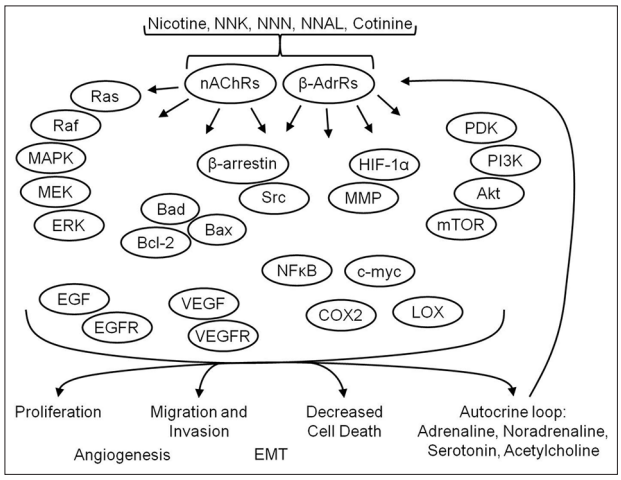

Figure 2: Principal mechanisms of tumor promotion by nicotine and its metabolites. Nicotine and its metabolites primarily promote tumor growth, angiogenesis, migration, invasion, epithelial to mesenchymal transition, and resistance to cancer treatment. Shown are downstream proteins and signal transduction pathways associated with activation of β-AdrRs and nAChRs by nicotine and its metabolites

Whereas the effects of NNK preferentially modulate α7nAChRs, NNN may preferentially modulate proliferation through α3nAChRs.[57,58,86,87] In non-small-cell lung cancer and SCLC lines, nicotine or NNK activates nAChRs and Akt leading to increased Cyclin D1 expression and proliferation.[88] Notably, NNK induces proliferation at markedly lower doses than proliferation induced by nicotine. Proliferation induced by NNK in immortalized human pancreatic cells appears to be dependent upon β-AdrRs, adenylyl cyclase, ERK, and EGFR-TK.[89] In SCLC, NNK-induced proliferation appears to involve activation of the α7nAChRs, MEK, protein kinase C (PKC), and c-myc.[90] The common downstream signals following nAChR or β-AdrR activation appear to suggest that activation of MAPK, MEK, and ERK 1/2 are important in the proliferative effects of nicotine and its metabolites.

Angiogenesis

Several studies demonstrate that nicotine increases angiogenesis in tumor models as well as with endothelial cells in models of limb ischemia.[52] Nicotine increases proliferation and decreases hypoxia-induced apoptosis in endothelial cells.[91] Further examination demonstrates that nicotine increases tumor growth associated with increased VEGF secretion in mice inoculated with Lewis lung cancer cells.[91] Broad nAChR expression is noted in endothelial cells and nicotine or hypoxia increases expression of the α7nAChR.[92] In this latter study, inhibition of the nAChR prevents endothelial network formation and agonists of the α7nAChR increase endothelial network formation with concomitant increases in VEGF production. The effects of nicotine or nAChR agonists are prevented with inhibition of MAPK, MEK, phosphatidylinositol-3-kinase (PI3K), or NFκB. Notably, angiogenesis is reduced in α7nAChR knockout mice and non-specific inhibition of nAChRs decreases vascular diameter without decreasing the number of vascular collaterals.[92] Separate studies also demonstrate that nicotine-induced angiogenesis can be prevented with inhibition of the α7nAChR in mice containing SCLC xenografts.[93] Data also suggest that inhibition of COX-2 may prevent the angiogenic effects of nicotine.[82] NNK also increases angiogenesis and VEGF production.[94] and co-administration of nicotine with estradiol results in synergistic increase in tumor growth, angiogenesis, and VEGF production.[95] The diverse pathways and effects of nicotine on angiogenesis are extensively reviewed by others discussing the role of the α7nAChR leading to activation of β-arrestin, Src, Raf-1, and Rb.[96]

Migration, invasion, and epithelial to mesenchymal transition

One of the most deadly consequences of lung cancer is the inherent ability for lung cancer to invade and metastasize. Data demonstrate that nicotine and activation of nAChRs can promote migration, invasion, and epithelial to mesenchymal transition (EMT). Repeated exposure of SCLC to nicotine increases collagen breakdown and transmigration in conjunction with increased tumor growth, vascularity, and resistance to chemotherapy.[69] Nicotine increases migration and invasion of lung cancer cells through activation of the α7nAChR, c-Src, and PKCiota.[97] The critical role of the α7nAChR on nicotine-induced migration or invasion is also observed in other cancer cells.[98-101] Recent data suggest that MUC4 and ID1 (inhibitor of differentiation-1) are important to the angiogenic effects of nicotine and/or cigarette smoke[98,102] NNK can also increase migration and invasion of lung cancer cells through activation of MEK and downstream activation of calpains.[103] The effects of NNK also appear to be dependent upon the α7nAChR.[104] Although nicotine increases the migration and invasion of cancer cells, the opposite appears to occur with immune cells. *In vivo*, nicotine administration appears to decrease migration of leukocytes and decreases chemotaxis of peripheral blood mononuclear cells.[105]

Nicotine can also increase malignancy through EMT. In A549 lung cancer cells, nicotine increases proliferation, migration, invasion, and EMT.[106] Many of the effects of nicotine are prevented through inhibition of the α7nAChR or Src and similar results are observed in breast cancer cells. In a separate study, nicotine increases aldehyde dehydrogenase expressing cells (a marker for EMT) in breast cancer through activation of the α7nAChR.[107]

Cell death and apoptosis

Beyond simply promoting tumor growth, nicotine also decreases the effectiveness of cancer treatment. Numerous studies demonstrate that nicotine decreases the effectiveness of chemotherapy through decreased apoptosis. The anti-apoptotic effects of nicotine are observed in multiple cell lines treated with multiple chemotherapeutic agents.[108] Activation of PI3K leading to increased XIAP, survivin, and recruitment of E2F1 to the genome appears to be important for the pro-survival effects of nicotine.[108] Nicotine decreases apoptosis in lung cancer cells through inactivation of PP2A, Bax phosphorylation, and decreased cytochrome c release.[109] Similar observations are noted with NNK through phosphorylation of Bcl-2 at Ser70.[90] Several studies suggest that activation of PI3K, Akt, and NFκB are critical to the pro-survival effects of nicotine on chemotherapy.[88,110-112] Nicotine also decreases the cytotoxicity of several treatments (cisplatin, UV irradiation, and gamma irradiation) through decreased apoptosis, but not through changes in DNA repair or adduct formation.[113] Interestingly, acute nicotine or NNK decreases apoptosis

from cisplatin, but the effects of NNK are much more potent than nicotine. However, although long-term nicotine or nicotine combined with NNK continued to confer resistance to cisplatin, long-term NNK had no significant effect on apoptosis.[114]

Activation of β-AdrRs is also implicated in the pro-survival effects of nicotine and its metabolites. In A549 lung cancer cells, NNK increases survival following chemotherapy through activation of β-AdrRs, Src, PKCiota, and phosphorylation of Bad.[115] However, in SCLC, NNK activates Bcl-2 leading to decreased apoptosis through activation of the α7nAChR.[90] Nicotine-induced phosphorylation of Bax and associated decrease in cisplatin-induced apoptosis are prevented with inhibition of the β-AdrR, but not with inhibition of the α7nAChR.[111] These apparent conflicting results between cell lines may potentially be explained by differences in receptor expression between cell lines coupled by similar parallel downstream pathways after activation of β-AdrRs or nAChRs.

Recent data demonstrate that nicotine decreases the effectiveness of radiotherapy (RT) and/or chemoradiotherapy (CRT) *in vivo*.[116] *In vitro*, nicotine increased survival in H460 and A549 lung cancer cells treated with RT through activation of PI3K. *In vivo*, nicotine decreases the effectiveness of RT and CRT on lung cancer xenografts. Importantly, the effects of nicotine only during RT/CRT appear to be identical to the effects of nicotine during and following RT/CRT suggesting that nicotine exposure specifically during the time of RT/CRT is the critical determinant of therapeutic response. Additional examination demonstrates that nicotine increases hypoxia inducible factor 1-alpha (HIF-1α) in a PI3K-dependent manner *in vitro* and nicotine specifically increases HIF-1α expression in a specific morphological pattern without altering pathological markers of hypoxia *in vivo*.[116] Collectively, this study suggests that nicotine decreases therapeutic response during treatment through alterations in protein expression in specific subpopulations of tumor cells.

CONCLUSIONS

Data suggest that nicotine may have a broad spectrum of tumor-promoting activities in lung cancer. Nicotine and its metabolites increase proliferation, migration, invasion, EMT, and angiogenesis with a concomitant decrease in sensitivity to chemotherapy and/or radiotherapy [Figure 2]. The effects of nicotine occur through activation of nAChRs and β-AdrRs leading to common downstream activation of Src, Ras-Raf-MAPK-MEK-ERK pathways, and PI3K-Akt pathways that further drive several parallel oncogenic pathways. Nicotine and its metabolites can promote tumor progression through modulation of oncogenic signals in both cancerous and non-cancerous tissues. Substantial work is required to definitively test the effects of nicotine on clinical outcomes in cancer patients, but current data suggest that nicotine is not a benign substance in cancer progression and therapy.

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