

Smoking Out the Cholinergic Component in Lung Cancer

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Translational Relevance

Recent studies strongly suggest that receptors for nicotine play a significant role in lung cancer predisposition and natural history. These data give a new thrust to research efforts assessing the potential curative (antitumor) value of natural compounds that are well-known powerful antagonists to this family of molecules. Recent studies have shown that $\alpha 7$ is the main nicotine acetylcholine receptor (nAChR) subunit that mediates the proliferative effects of nicotine in cancer cells. As a result, $\alpha 7$ nAChR might be a valuable molecular target for therapy of cancers such as lung cancer and mesothelioma. Future studies involving the design of nAChR antagonists with improved selectivity might identify novel strategies for the treatment of tobacco-related cancers.

Smoking remains an important risk factor for lung cancer, and a clear association among single nucleotide polymorphisms in the chromosome 15q24/15q25.1 region and lung cancer susceptibility has been recently shown in three comprehensive wide genome association studies (1–3). In brief, although Hung et al. (1) reports that a strong susceptibility locus for lung cancer maps to nicotine acetylcholine receptor (nAChR) subunit genes, Thorgeirsson et al. (2), interestingly, identifies a common variant in the same nAChR cluster with an effect on (a) smoking quantity, (b) nicotine dependence, and (c) risk of lung cancer and peripheral arterial disease.

Simultaneously, Amos et al. (3) concludes that a variation in the region containing nAChR genes contributes to the risk of developing lung cancer. In the analysis made by Burton (4), and recently reported in *Lancet Oncology*, the central role of smoking in lung cancer risk is matched with, and again underlined in light of the three reported wide genome association studies (1–3), focusing on similar candidate polymorphisms in the same genomic region.

Although additional evidence is needed, the message that genes in this chromosomal region could interact directly with

tobacco to cause lung cancer or to determine an increase in tobacco smoking dependency is very clear.

More information on this relevant topic is available in the results reported by Lam et al. (5); in fact, they have identified differential gene expressions in non-small cell lung cancers with class-predictive significance: whereas nicotine exposure was significantly present at elevated levels of expression for the nicotinic subunit genes (*CHRNA1*, *CHRNA5*, and *CHRNA7*) shown. These data led researchers to the conclusion that nicotine receptor subunit genes could play an important role in the pathogenesis of bronchogenic carcinoma and may mediate the effects of nicotine addiction in lung cancer patients of different gender.

Furthermore, up-regulation of the $\alpha 7$ nicotinic subunit gene was found in normal human bronchial epithelial cells upon exposure to nicotine (6) and in small cell lung cancer cell lines leading to increased proliferation (7). nAChRs were first implicated in the growth regulation of lung cancer when nicotine was found to stimulate DNA synthesis in human lung cancer cell lines and this was supported by subsequent identification that the receptor involved was nAChR $\alpha 7$ (8, 9).

We have a longstanding interest in this topic, and in our previous studies, we have shown that nicotine exposure of non-small cell lung cancer cells induces an overexpression of the $\alpha 7$ nicotinic receptor subunit and that the expression of $\alpha 7$ -nAChR in human non-small cell lung cancer tissues was higher in smokers who developed squamous cell carcinoma compared to those with adenocarcinoma, as well as in smokers who were males compared with females (10).

All these findings of functional acetylcholine receptors on lung epithelial cells and lung tumors raise the extremely important question of whether chronic exposure to nicotine could also participate in lung cancer pathogenesis. The matter is particularly relevant for current smokers who might feel protected by annual CT screening and abandon any attempt of quitting tobacco.

If it is true that nicotine dependence induces nAChR's clustering into categories and influences lung cancer predisposition, nicotine very easily could act on lung tissue at a posttranscriptional and posttranslational level inducing differences in nAChR's expression and biological responses that might influence cancerogenesis downstream as well.

All these findings strongly implicate the participation of the nonneuronal cholinergic system in lung cancer biology, and suggest screening for new therapy targeted at $\alpha 7$ -nAChR.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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