Nicotinic acetylcholine receptor subunit alpha 7 mediates cigarette smoke-induced PD-L1 expression in human bronchial epithelial cells

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Abstract

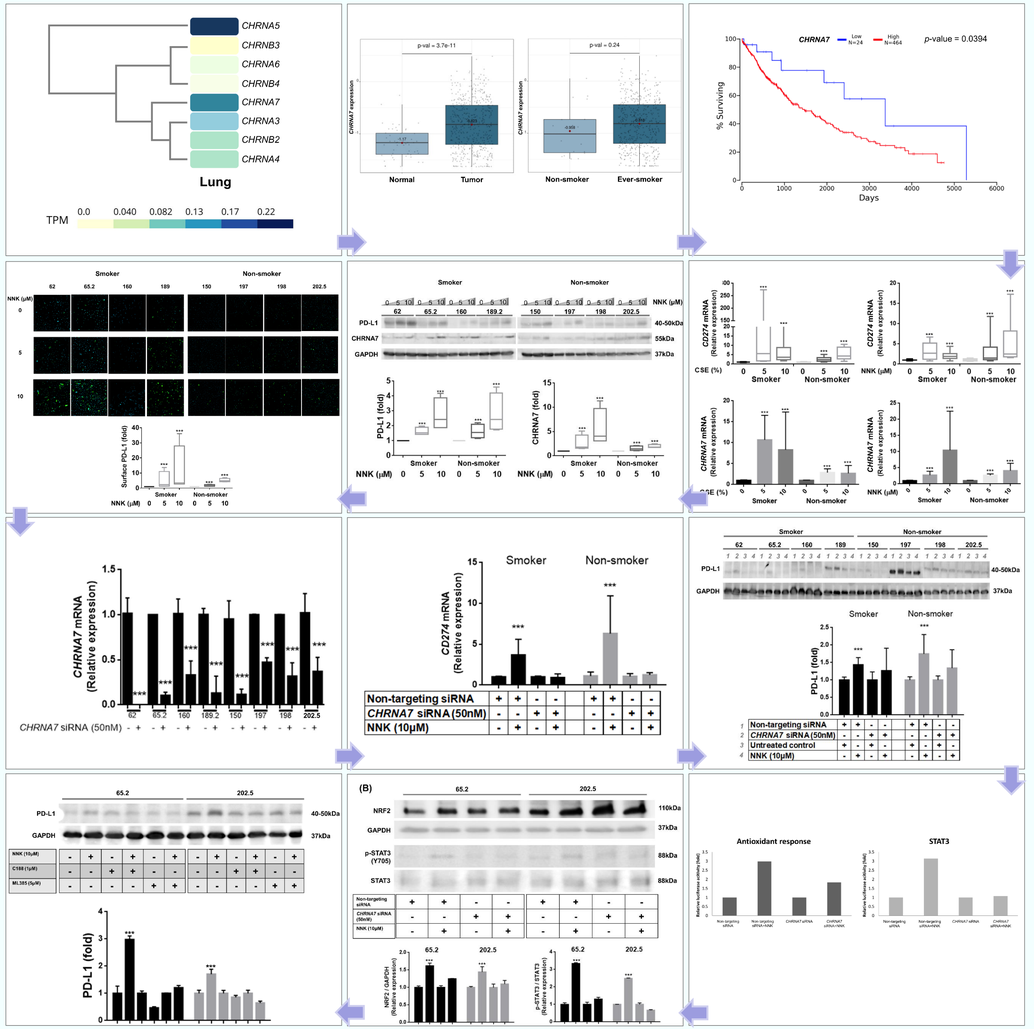
Tobacco smoking is the top risk factors for lung cancer. Nicotine in cigarette can induce addiction, and its derivatives could be potent carcinogens after metabolic activation. Lung cancer from smokers usually showed higher PD-L1 expression levels and appeared to be more responsive than non-smokers to immune-checkpoint inhibitors. This study aimed to investigate whether activation of nicotinic acetylcholine receptor subunit α7 (nAChRα7) expression would induce PD-L1 expression. Expression levels of nAChRα7 and PD-L1 in eight human bronchial epithelial cell lines (HBECs) were measured after treatment with cigarette smoke extract (CSE) or nicotine derivative. nAChRα7 was highly expressed in lung squamous cell carcinoma tissue as well as in normal lung tissue from smokers. PD-L1 expression levels increased in HBECs after exposure to CSE and nicotine derivative. This induction of PD-L1 expression by CSE could be diminished by nAChRα7 small-interfering RNA, with relevant signaling mediated via STAT3 phosphorylation or NRF2 expression. This study demonstrated the linkage on the well-known nicotine derivative-activated nAChRα7-induced STAT3/NRF2 pathways and revealed PD-L1 as the downstream signaling target in normal lung epithelial cells. This may provide insight into the possible mechanism of cigarette smoke-induced pre-cancerous immune invasion mediated through nicotine and its derivative, with activation of nAChRα7-induced STAT3/NRF2 pathways leading to cellular growth and proliferation.

Introduction

- Tobacco smoking is the top risk factor for lung cancer.
- Nicotine itself is not directly carcinogenic, but its metabolite 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) is a potent carcinogen.
- Previous genome-wide association studies (GWAS) showed that genetic variations on chromosome 15q25 were found to be associated with increased risks of developing lung cancer in smokers.
- The 15q25 region harbors three nicotinic acetylcholine receptor (nAChR) subunit genes, which suggested that ligand activated nicotinic acetylcholine receptor may contribute to lung cancer development.
- The use of immune checkpoint inhibitor has emerged as an important treatment strategy for advanced stage NSCLC in recent years.
- Good treatment response was shown only in patients with high tumor expression levels of programmed death receptor ligand-1 (PD-L1), but the molecular mechanisms of PD-L1 expression in lung cancer are not fully understood.
- It is important to explore novel combination regimens to extend the efficacy of immune checkpoint therapy in lung cancer patients.
- The aim of this study was to delineate how the expression levels of CHRNA7 mediate the effects of smoking on PD-L1 expression in HBECs.

Methodology

Eight immortalized human bronchial epithelial cell lines (HBECs) were exposed to cigarette smoke extract. Expression levels of nAChRs and associated proteins were determined by real-time PCR, Western blot analysis and immunofluorescence staining.

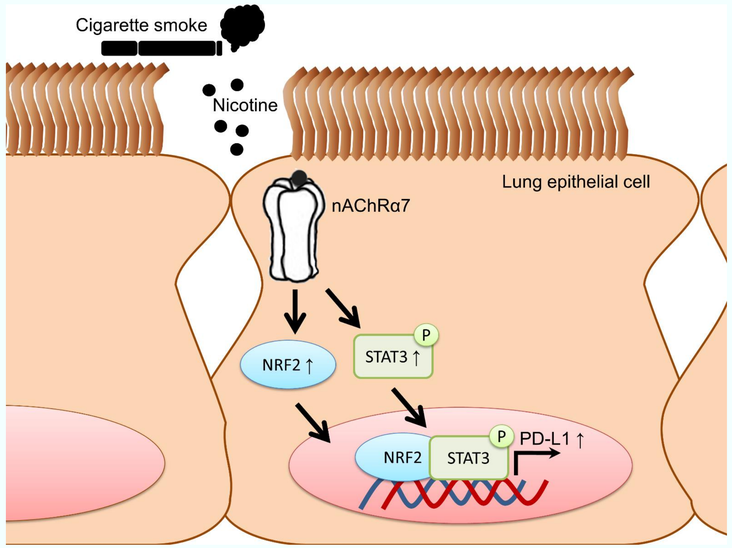


Discussion

- In this study, we confirmed the involvement of nAChRα7 mediation in nicotine derivative-induced PD-L1 expression in HBECs.
- Whether nicotine and its derivatives could contribute to pre-malignant immune invasion through PD-L1 expression is unknown before.
- This study demonstrated the linkage of nicotinic acetylcholine receptor activated STAT3/NRF2 pathways with downstream PD-L1 expression.
- Nicotine and its derivatives can also bind with nAChRs and induce various aberrant cellular signaling processes involved in tumorigenesis.
- Studies in different cancers suggested that PD-L1 expressions are upregulated in pre-malignant lesions, and early PD-1 blockade may prevent cancer development.
- This may further promote pre-cancerous immune evasion which may ultimately lead to cancer formation.
- Indeed, there are a number of on-going clinical trials to investigate the possibility of prevention of malignant transformation by treating high risk smokers with PD-1 inhibitor.
- Further study is warranted to examine the upstream inhibition of PD-L1-related pathways, which could be mediated through nicotinic acetylcholine receptors in smokers.
- However, direct systemic administration of most nicotinic acetylcholine receptors antagonists can cause a variety of side effects due to the lack of nAChR subtype specificity.
- Site-specific and subtype specific inhibition of nAChRα7 may be able to address the controversial effects of nAChRα7 on tumor progression in different tissues.

Conclusion

In summary, the results indicate that cigarette smoke could induce PD-L1 expression on HBECs through the activation of CHRNA7 and subsequently the STAT3 and NRF2 pathways.



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