Tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butan one (NNK) induces cell proliferation in normal human bronchial epithelial cells through NFkappaB activation and cyclin D1 up-regulation.

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摘要

Abstract

Cigarette smoke contains several carcinogens known to initiate and promote tumorigenesis as well as metastasis. Nicotine is one of the major components of the cigarette smoke and the 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a tobacco-specific carcinogen. Here, we demonstrated that NNK stimulated cell proliferation in normal human bronchial epithelial cells (NHBE) and small airway epithelial cells (SAEC). Cells exposed to NNK resulted in an increase in the level of cyclin D1 protein (as early as 3-6 h). Increased phosphorylation of the Rb Ser(795) was detected at 6-15 h after NNK treatment and thereby promoted cells entering into the S phase (at 15-21 h). The increased cyclin D1 protein level was induced through activation ofthe transcription factor, nuclear factor kB (NFkappaB), in the NHBE cells. Treatment of the NHBE cells with PD98059, an ERK1/2 (extracellular signal-regulated protein kinase)-specific inhibitor, specifically suppressed the NNK-induced IkappaBalpha phosphorylation at position 32 of the serine residue, suggesting that the ERK1/2 kinase was involved in the IkappaBalpha phosphorylation induced by NFkappaB activation. To determine whether the NNK-induced

NFkappaB activation and cyclin D1 induction were also observed in vivo, A/J mice were treated with NNK (9.1 mg) for 20 weeks and the results showed a significant induction of cyclin D1 and NFkappaB translocation determined by immunoblotting analyses. We further demonstrated that the nicotine acetylcholine receptor (nAchR), which contains the alpha3-subunit, was the major target mediating NNK-induced cyclin D1 expression in the NHBE cells. In summary, our findings demonstrate for the first time that NNK could stimulate normal human bronchialcell proliferation through activation of the NFkappaB, which in turn up-regulated the cyclin D1 expression.