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Lung alert

Tobacco-specific carcinogen NNK has an important role in lung cancer

Lung cancer is the leading cause of mortality in industrialised countries and 85–90% of lung cancers are caused by cigarette smoking. DNA methyltransferase 1 (DNMT1), an enzyme that catalyses DNA methylation, is reported to be overexpressed in patients with lung and liver cancer who are smokers. The tobacco-specific carcinogen NNK also induces DNA methylation. Unravelling how NNK induces DNMT1-mediated promoter hypermethylation will improve the understanding of tobacco carcinogenesis and may provide an important link between tobacco smoking and lung cancer.

In this study, using lung cancer as a model, animal and clinical studies were undertaken to analyse the molecular mechanisms of DNMT1 overexpression in relation to NNK. DNMT1 overexpression strongly correlated with smoking status and poorer prognosis in patients with lung cancer. NNK was found to increase DNMT1 protein expression and activity by prolonging DNMT1 protein stability through AKT signalling. NNK treatment induced DNMT1 accumulation in the nucleus and in mouse lung adenoma tissues.

These findings provide evidence for the relevance of DNMT1 overexpression in tobacco carcinogenesis and help explain how DNMT1 overexpression may serve as a prognostic factor in smoking-related cancer. Drugs aimed at DNMT1 depletion may prove to be a good therapeutic strategy in the future.

► **Lin RK**, Hsieh YS, Lin P, *et al*. The tobacco-specific carcinogen NNK induces DNA methyltransferase 1 accumulation and tumor suppressor gene hypermethylation in mice and lung cancer patients. *J Clin Invest* 2010;**120**:521–32.

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