



Title	Mechanism of inflammation-associated colonic tumorigenesis promoted by cigarette smoke
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GIH-23 Cigarette smoke promoted human xenograft tumors through the upregulation of cyclin D₁ and cyclin-dependent kinases

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Introduction: Previous studies reported that cigarette smoke could delay gastric ulcer healing, however, its effect on gastric tumor growth is not well established. Cell cycle control is important in carcinogenesis and cancer growth. Cyclin D₁ and cyclin-dependent kinase (Cdk) are necessary for the transition from early to mid G₁ phase. These cell regulators are actively involved in human gastric cancer. This study aims to delineate the biological pathways of how cigarette smoke promotes gastric cancer in humans.

Method: Male athymic BALB/c nude mice were used as a human gastric cancer model to study the biological actions of cigarette smoke. Human gastric carcinoma cells (AGS) were implanted into the gastric walls of the mice. Cells were pretreated in the presence or absence of cigarette smoke extract (CSE, 100 µg/ml) prior to the injection of cells into the stomach.

Results: Cigarette smoke promoted the growth of xenograft tumors, which was accompanied with the upregulation of cyclin D₁. Overexpression of cyclin D₁ were found in all tumor tissues, and cigarette smoke further upregulated this protein by 30%. Tumor tissues had a 5-fold increase in the expression of Cdk6, and cigarette smoke promoted this protein upregulation. Cdk4, another important binding partner of cyclin D₁, was also induced by cigarette smoke when compared with the normal tissues. In CSE-treated group, the expressions of tumor suppressor proteins (p21^{WAF1/Cip1} and p27^{Kip1}) were decreased by 20% and 30% respectively in tumor tissues.

Conclusion: These results suggested that cigarette smoke promoted the growth of gastric tumor through the modulation of cell cycle regulatory proteins. High expression of cyclin D₁ and Cdks are important parameters for the progression of gastric tumor growth induced by cigarette smoke. This study provides an insight to develop a new strategy for the treatment of gastric cancer in humans.

GIH-24 Mechanism of inflammation-associated colonic tumorigenesis promoted by cigarette smoke

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Introduction: Our previous study showed that passive cigarette smoking promoted inflammation-associated adenoma formation in colon, but the underlied mechanism remains unknown. 5-lipoxygenase (5-LOX) is an enzyme that converts arachidonic acid to 5-s-HETE, which in turn is converted to LTA₄ and then to LTB₄, LTC₄ and LTD₄. Several studies have suggested that 5-LOX and its products can enhance tumorigenesis. The purpose of the present study was to investigate the possible involvement of 5-LOX in the tumorigenesis enhanced by cigarette smoke in the colon.

Method: Male balb/c mice were allocated into 4 groups: control, cigarette smoke (CS), dextran sulfate sodium (DSS) and DSS+CS. They were given water or 3% DSS in drinking water for 7 days to induce colitis, with or without 1-hour daily exposure to 2% CS. They were then allowed to drink water for 14 days. The cycle of 7-day DSS ± CS/14-day H₂O treatment was repeated twice. Mice were sacrificed either immediately (when no adenoma was found) or 1 month after the three cycles of treatments (when cigarette smoke promoted inflammation associated adenoma formation). Colon tissues were collected for assessment.

Results showed that: (1) After 3 DSS cycles, 5-LOX protein expression was significantly increased in the DSS+CS group compared with the control and the DSS groups. Similar results were found with vascular endothelial growth factor (VEGF) and matrix metalloproteinase-2 (MMP-2) which are important mediators for tumor progression and angiogenesis; (2) One month after the cycles, 5-LOX was enhanced only in adenomas induced in the DSS+CS group but not in the DSS group, while VEGF and MMP-2 were both increased in the tumors induced in either DSS or DSS+CS group. In addition, we also found that mice treated with MK886 (a specific 5-LOX inhibitor, 20mg/kg P.O. once daily) throughout the whole 3 DSS cycles significantly reduced tumor formation promoted by cigarette smoke. This was associated with the down-regulation of VEGF and MMP-2 expression. Moreover, we found that cigarette smoke extract had a direct effect on colon cancer cells to release these angiogenic mediators.

Conclusion: Taken together, these results strongly suggest that 5-LOX is involved in the formation of colonic adenoma which is promoted by cigarette smoke. This action is probably via the VEGF and MMP-2 activation on the angiogenic pathway.