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Title: Cyclooxygenase-2 in neoplasias of the lung and the stomach

ABSTRACT

Since the discovery of acetylsalicylic acid (ASA) over a century ago this compound and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been used successfully for the treatment of pain and inflammation. The principal mechanism of action of these drugs was discovered in 1971 when Sir John Vane demonstrated that the anti-inflammatory effect of ASA-like NSAIDs was via inhibition of prostaglandin synthesis. Cyclooxygenase (COX) enzyme is an important enzyme in the conversion of arachidonic acid to prostanoids. COX enzymes are coded by two distinct genes and they result in production of enzymatically quite similar isoenzymes, COX-1 and COX-2. All classical NSAIDs inhibit both COX-1 and COX-2. However, regulation of gene expression of these enzymes differs drastically. While COX-1 is constitutively expressed and the expression is not usually regulated, expression of COX-2 is low or not detectable in most tissues, but can be highly induced in response to cell activation by hormones, proinflammatory cytokines, growth factors and tumor promoters. A new class of drugs has been introduced that selectively inhibits COX-2. These drugs have been shown to be effective anti-inflammatory agents, and they cause less frequently severe gastrointestinal adverse-effects than conventional NSAIDs.

Epidemiological studies suggest that prolonged use of ASA and other NSAIDs associates with reduced risk of gastrointestinal, and possibly lung and breast, cancers. Expression of COX-2 is elevated in several human malignancies and in animal models of

carcinogenesis. The aim of the present study was to investigate expression of COX-2 in malignant tumors and in their precursor lesions in the lung and the stomach. Our data indicate that COX-2 mRNA and protein are expressed in lung adenocarcinomas, and expression was lower in poorly differentiated adenocarcinomas and in squamous cell carcinomas. COX-2 was also expressed in atypical alveolar epithelium of the lung, which is a precursor for lung adenocarcinoma. COX-2 was localized to cancer cells. In the stomach COX-2 is expressed predominantly by the intestinal type adenocarcinoma, but not by the diffuse type as detected by immunohistochemistry. The frequency of COX-2 positive intestinal type gastric adenocarcinomas was 58 %, and the COX-2 immunoreactivity localized to the cancer cells. In addition COX-2 is expressed in dysplasias of the stomach, which is considered to be a precursor lesion for the intestinal type gastric cancer.

We also investigated COX-2 expression and the effect of COX-2 selective inhibitor celecoxib in a mouse model for gastric neoplasia. Mice deficient for trefoil factor 1 (TFF1) develop gastric adenomas with full penetrance. COX-2 mRNA and protein were strongly expressed in the pyloric adenomas of the TFF1 deficient mice, and it was localized to the stroma. After treatment with celecoxib all adenomas in the celecoxib treatment group were ulcerated and contained a heavy infiltration of inflammatory cells. This combination of ulceration and inflammation was exclusively observed in the drug treated TFF1 knockout mice group. Since celecoxib caused no injuries in nonneoplastic gastric mucosa or small intestinal mucosa in either wild type or TFF1 knockout mice, our data suggest that the effect of the drug was adenoma specific.

Our data show that COX-2 is highly expressed in certain histological types of lung and stomach carcinomas. COX-2 localized primarily to the neoplastic cells. Since COX-2 is already expressed in preinvasive neoplasms, our data suggest that COX-2 expression is a relatively early event in tumorigenesis. The COX-2 selective drug celecoxib caused an adenoma specific injury in TFF1 knockout mice without any apparent adverse-effects. Thus it is possible that inhibition of COX-2 can be used as a chemopreventive target.