Leukotriene A₄ Signaling, Inflammation, and Cancer

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Chen et al. report in this issue of the Journal that leukotriene A₄ hydrolase (LTA₄H) was overexpressed in 10 rat esophageal adenocarcinomas compared with matched normal tissue samples (1). They also report that LTA₄H was expressed in infiltrating inflammatory cells and in the columnar cells in human esophageal adenocarcinomas. Bestatin, an LTA₄H inhibitor, reduced the incidence of esophageal adenocarcinomas by approximately 30% in a rat esophageal carcinoma model. On the basis of these findings, the authors conclude that LTA₄H overexpression appears to be an early event in esophageal adenocarcinogenesis and is a potential target for the prevention of esophageal cancer. Chen et al. had previously reported that LTA₄H was overexpressed in both human and rat esophageal adenocarcinomas (2). The current results are not too surprising in light of previously published data by this group indicating that nordihydroguaiaretic acid, a lipoxygenase inhibitor, also decreased tumor incidence in this same rat model (3). Cyclooxygenase inhibitors, however, were also effective in reducing the incidence of esophageal adenocarcinomas. Thus, the current study by Chen et al. (1) is a follow-up study evaluating more samples and using an LTA₄H inhibitor in vivo. Others (4) have previously reported that LTA₄H (also known as Grp94) is overexpressed in lung cancer. About a decade ago, this gene was shown to be overexpressed in a rat kidney fibroblast cell line transformed by v-Ki-ras (5), indicating its potential link to cell transformation.

It is generally agreed that chronic tissue inflammation leads to an increase in the risk for the development of cancer (6). After tissue damage or injury, a multifactorial network of molecular signals initiates and maintains a host response. This response involves the activation and directed migration of immune cells. Diseases involving inflammation of the gastrointestinal tract, such as chronic viral hepatitis, ulcerative colitis, and Barrett’s esophagus, lead to an increased risk of cancer in the corresponding site (7,8). Many of the specific mediators associated with chronic inflammation that increase cancer risks have yet to be completely elucidated. However, eicosanoids, such as leukotrienes and prostaglandins, that are bioactive lipid products of arachidonic acid metabolism are mediators of inflammation and have been linked to carcinogenesis (9). The two main pathways for arachidonic acid metabolism involve cyclooxygenases or lipoxygenases. The role of the cyclooxygenase pathway has been reviewed elsewhere (10–12). The precise role of the lipoxygenase pathway in cancer is less clear; however, a convincing story is developing (9).

Leukotrienes, such as LTA₄ and LTB₄, are made predominantly by inflammatory cells such as polymorphonuclear leuko-
cytes, macrophages, and mast cells (13). Cellular activation by bacterial peptides or other inflammatory stimuli elicit a sequence of events that includes the translocation of cytosolic phospholipase A2 and 5-lipoxygenase to the nuclear envelope. 5-Lipoxygenase, a nonheme iron dioxygenase, is the key enzyme in this cascade and is located in the nucleus in some cell types and in the cytosol of other cell types. 5-Lipoxygenase and the 5-lipoxygenase–activating protein convert arachidonic acid to the epoxide LTA₄. LTA₄ and LTB₄ are produced on either side of the nuclear envelope by nuclear or cytosolic pools of 5-lipoxygenase and LTA₂H (a bifunctional zinc-containing enzyme with epoxide hydrolase and aminopeptidase activities). LTA₄ undergoes transformation by one or more of three possible routes: hydrolysis to yield LTB₄, conjugation with glutathione leading to inactivation, or transcellular metabolism to generate bioactive eicosanoids. Hydrolytic attack of LTA₄ by LTA₂H in the cytoplasm yields LTB₄, a potent neutrophil chemo-attractant that also stimulates leukocytes to adhere to endothelial cells. After LTB₄ is transported out of the cell, it can bind to either of two G-protein–coupled receptors: the high-affinity leukotriene B₄ receptor 1, which is present on neutrophils, or the low-affinity leukotriene B₄ receptor 2, which is present in most tissues. In fact, it would be quite interesting if specific antagonists of these receptors could be developed and tested for their effects in the rat model system to determine whether these receptor-mediated signaling pathways play a role in esophageal adenocarcinogenesis. LTB₄ has also been reported to act intracellularly on the nuclear peroxisome proliferator–activated receptor α transcription factor, which has been linked to hepatocellular carcinoma in rats (14). Hence, further dissection of this pathway downstream of LTA₂H may be warranted.

It is becoming quite clear that targeting a single pathway for the prevention of solid tumors is not the answer. Treatment of esophageal adenocarcinomas with the LTA₂H inhibitor, bestatin, resulted in only a 30% reduction of the tumor burden. LTA₂H should now be included on a list of many other candidates, such as cyclooxygenase 2 and the epidermal growth factor receptor, as potential targets for cancer prevention. The full potential of targeting the LTA₂H pathway with regard to esophageal cancer is ripe for further exploration.

REFERENCES