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SPECIAL REPORTS AND REVIEWS

The Role of Prostaglandins and Other Eicosanoids in the Gastrointestinal Tract

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally prescribed to ameliorate symptoms associated with acute pain and chronic inflammatory diseases such as arthritis. Recent epidemiologic studies and clinical trials indicate that use of NSAIDs and cyclooxygenase (COX)-2 selective inhibitors are associated with a reduced risk of certain malignancies, especially gastrointestinal cancer. The cyclooxygenase enzymes are the best known targets of NSAIDs; this diverse class of compounds blocks conversion of arachidonic acid to prostanoids. Prostaglandins and other eicosanoids derived from COX-1 and COX-2 are involved in a variety of physiologic and pathologic processes in the gastrointestinal tract. Recent efforts to identify the molecular mechanisms by which COX-2-derived prostanoids exert their proneoplastic effects have provided a rationale for the possible use of NSAIDs alone or in a combination with conventional or experimental anticancer agents for the treatment or prevention of gastrointestinal cancers.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to exert their anti-inflammatory, analgesic, and antipyretic effects mainly by inhibiting the biosynthesis of prostaglandins.[1] Because prostaglandin H synthases (commonly referred to as cyclooxygenases) catalyze the rate-limiting step in prostaglandin synthesis from arachidonic acid, one plausible mechanism for the anti-inflammatory, analgesic, and antineoplastic effects of NSAIDs is their inhibition of eicosanoid formation. When tissues are exposed to diverse physiologic and pathologic stimuli, polyunsaturated fatty acids such as arachidonic acid are liberated from membrane phospholipids by the action of phospholipase A_2. Arachidonic acid can be metabolized through 1 of 3 major pathways: the cyclooxygenase pathway, the lipoxygenase pathway, or the cytochrome P-450 monooxygenase pathway.

In the cyclooxygenase (COX) pathway, free arachidonic acid is converted to a variety of eicosanoids, including prostaglandins (PGs) and thromboxanes (TXs), by the prostaglandin biosynthetic machinery[2–5] (Figure 1). The key regulatory step in this process is the enzymatic conversion of arachidonate to PGG_2, which is then reduced to an unstable endoperoxide intermediate, PGH_2. Specific PG synthases in turn metabolize PGH_2 to at least 5 structurally related bioactive lipid molecules, including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2 (TXA_2), in a cell type-specific manner. For example, cytosolic or microsomal PGE_2 synthases are able to convert PGH_2 to PGE_2. Two cytosolic PGE_2 synthases include cytosolic glutathione transferases (GSTM2-2 and GSTM3-3), which catalyze the conversion of PGH_2 to PGE_2 in the human brain in a thiol-dependent manner.[6] The microsomal PGE_2 synthases, characterized to date, include mPGES1 and mPGES2. mPGES1 exhibits a higher catalytic activity than the other PGES isomerases, indicating that it likely plays a key role in the synthesis of PGE_2 from PGH_2.[7,8]

Regulation of COX and COX-Derived Prostaglandins

There are 2 cyclooxygenase isoforms commonly referred to as COX-1 and COX-2 for the temporal order of their discovery. Although both COX-1 and COX-2 are up-regulated in a variety of circumstances, normally, COX-1 is constitutively expressed in a broad range of cells and tissues. COX-1 expression remains constant under most physiologic or pathologic conditions, and COX-1-derived prostaglandins are thought to play a role in many normal physiologic processes. In the gut, COX-1-derived PGs play an important role in protecting the gastroduodenal mucosa from injury. Most studies indicate that COX-1-derived PGs are produced by epithelial

Abbreviations used in this paper: APC, adenomatous polyposis coli; COX, cyclooxygenase; CRC, colorectal cancer; NSAIDs, nonsteroidal anti-inflammatory drugs; PGs, prostaglandins; PPARs, peroxisome proliferator-activated receptors; TXs, thromboxanes.

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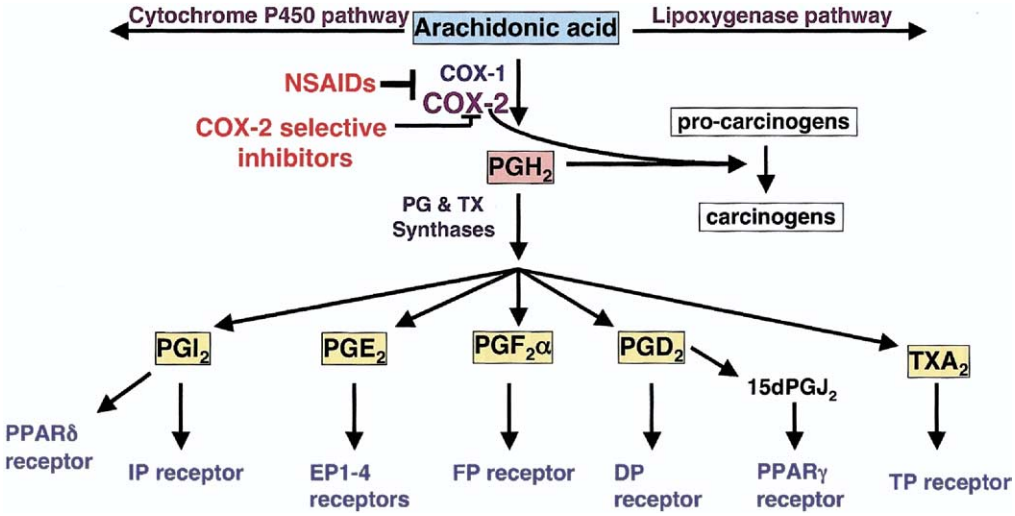

Figure 1. Overview of prostaglandin synthesis. Arachidonic acid is metabolized by at least 3 different pathways: the cyclooxygenase pathway, the lipoxygenase pathway, and the cytochrome P-450 monooxygenase pathway. COX-2 is induced under a variety of pathologic conditions, and subsequent prostaglandin production is thought to mediate downstream effects via receptor-mediated signaling pathways.

and stromal cells in subepithelial tissues of the colon.[9–11] For example, PGI_2 is a major prostaglandin product in the gastrointestinal tract[12,13] and plays a key role in the cytoprotection of gastric mucosal surfaces and the normal vasculature.[14] In addition, PGI_2 appears to be important in protecting cardiomyocytes from oxidative stress.[15] COX-2, by contrast, is an immediate-early response gene normally absent from most cells but highly inducible in response to inflammatory stimuli, including endotoxin, cytokines, hormones, and tumor promoters.[3] For example, transforming growth factor-α (TGF-α), oncogenic Ha-Ras, and the tumor promoter tetradecanoyl phorbol acetate (TPA) have been shown to induce COX-2 expression and stimulate the production of PGs in normal rat intestinal epithelial (RIE-1) cells and in some human colorectal carcinoma cells.[16–18] Bombesin, a homolog of gastrin-releasing peptide (GRP), stimulates COX-2 expression and release of PGE_2 in intestinal epithelial cells through multiple AP-1 and ERK5-dependent pathways.[19] Finally, gastrin and K-Ras also regulate COX-2 expression in certain contexts.[20–22]

A germ-line mutation of the adenomatous polyposis coli (APC) gene is found in the inherited predisposition to colon cancer known as *familial adenomatous polyposis* (FAP). Moreover, loss of APC is found in 80% of sporadic colorectal carcinomas. In normal colorectal tissue, APC binds to β-catenin, targeting it for degradation and inhibiting entry to the nucleus. APC is inactivated by truncating mutations in a majority of colorectal cancers, leading to loss of β-catenin binding. Loss of functional APC results in a failure of β-catenin degradation, thus allowing β-catenin to accumulate in the nucleus where it acts as a transcriptional cofactor through binding to the transactivation domain of Tcf-4.[23] Emerging data suggest that COX-2 is one of the targets of Tcf/Lef in mouse colonic epithelial cells.[24,25] Both increased Wnt-1 expression and loss of APC function can activate a common signaling pathway involving transcriptional activation mediated by β-catenin/Tcf complexes. Over-expression of oncogenic Wnt-1 in the mouse mammary epithelial lines RAC311 and C57MG induces COX-2 expression,[26] and transgenic mice over-expressing Wnt-1 in the breast develop mammary tumors with elevated COX-2 expression.[27,28] Others have shown that over-expression of Wnt-3 or mutant β-catenin also lead to an increase in COX-2 expression.[29,30] Finally, the PEA3 family of transcription factors may mediate Wnt-1 and APC signaling to activate COX-2 transcription through binding the NF-IL6 site in the COX-2 promoter.[27] Collectively, these data support the hypothesis that COX-2 is a downstream target of the β-catenin/Tcf signaling pathway.

Increased levels of COX-2-derived prostaglandins not only mediate acute inflammatory responses but are also involved in a variety of other pathophysiologic processes, including tumor promotion, tumor-associated angiogenesis, and thrombosis. Prostaglandins exert their cellular functions by binding cell surface receptors that belong to the family of 7 transmembrane G-protein-coupled rhodopsin-type receptors. These cell surface receptors are designated DP for the PGD_2 receptor, EP (EP1, EP2, EP3, and EP4) for the PGE_2 receptors, FP for the $PGF_{2\alpha}$ receptor, IP for the PGI_2 receptor, and TP for the TXA_2 receptor. The action of prostaglandins is associated with changes in the levels of second messengers.[31] For example, activation of DP, IP, EP2, and EP4 receptors increase intracellular levels of cyclic AMP (cAMP), whereas EP1, FP, and TP do not modulate cAMP levels. However, DP, EP1, FP, and TP increase cytosolic levels of free Ca^{2+}. The other receptor, EP3, decreases intracellular cAMP levels. In some cases, however, certain prostaglan-