Cyclooxygenase-2 as a Target for Cancer Prevention and Treatment

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Summary

This chapter reviews our current understanding of the relationship between Cox-2 expression and activity and tumor promotion. In addition, this chapter reviews the status of clinical trials of Cox-2 inhibition in both pre-malignant and cancer treatment settings.

Key Words: Cyclooxygenase-2; inflammation; prostaglandins; tumorigenesis.

1. INTRODUCTION: CANCER AND INFLAMMATION

The disease states of cancer and inflammation have been linked in medical knowledge from the earliest recorded times. The term “tumor” comes from Latin, tumere, meaning “to swell.” In his 1837 text, Surgical Observations on Tumours (1) the Boston surgeon John C. Warren noted, “A third supposable mode of the production of tumours is chronic inflammation of a natural texture, …most frequently in parts disposed to inflame.” A crucial mechanistic link between inflammation and cancer was discovered in the early 1990s with the identification of cyclooxygenase-2 (Cox-2). Researchers studying the acute inflammatory response identified a Cox-related gene product that was induced in response to serum and was inhibited by glucocorticoids (2). Structural studies confirmed the presence of a second form of cyclooxygenase, termed Cox-2, produced in response to inflammatory mediators and mitogens (reviewed in ref. 3). The mechanisms of Cox-2 activity and their relationship to cancer have been the subject of intense investigation in recent years. This work has been facilitated by the development of selective Cox-2 inhibitors, which have now been tested in human cancer clinical trials.

This chapter will review the mechanisms by which Cox-2 and related substances promote and maintain tumors. It will also describe evidence for the anti-cancer effects
of Cox inhibitors, including the selective Cox-2 inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs).

2. THE BIOLOGY OF COX-2

2.1. Arachidonic Acid Metabolism

The inflammatory response is mediated by a cascade of bioactive substances that are produced in response to trauma or other stimuli. This response begins with the release of arachidonic acid from the cell membrane, followed by its metabolism through a series of tissue-specific reactions. The products of arachidonic acid metabolism exert a vast range of downstream effects on cell-signaling pathways. In a highly complex network of cell signaling, these mediators influence many different systems, including those governing cell proliferation and differentiation [e.g., mitogen-activated protein kinase (MAPK) and peroxisome proliferator-activated receptors (PPARs)], cytoskeletal dynamics (e.g., Rho GTPases), apoptosis (e.g., Akt and PI\(_3\)K), and ion transport (e.g., Ca\(^{2+}\) channels).

In a resting cell, arachidonic acid is stored by esterification to glycerol in membrane phospholipids, especially phosphatidylethanolamine, phosphatidylcholine, and the phosphatidylinositides. Arachidonic acid is released from the cell membrane by phospholipase A2 (PLA2), in response to local trauma or activation of a G-protein-coupled receptor by a growth factor or cytokine. Free arachidonate is metabolized to bioactive substances known as eicosanoids by three distinct enzyme pathways, defined by the activities of Coxs, lipoxygenases, and cytochrome P450. The prefix eicosa- (from the Greek for twenty) denotes the number of carbon atoms in arachidonic acid. The term “eicosanoids” is used as a collective name for molecules derived from 20-carbon fatty acids, including the prostanoids and leukotrienes, as well as several other classes such as the isoprostanes, lipoxins, and epoxyeicosatrienoic acids (EETs). Prostanoids are the subset of eicosanoids that are produced by Cox activity and include prostaglandins (PGs), prostacyclin, and thromboxanes (Txs). Leukotrienes are a family of active hydroperoxy derivatives resulting from metabolism of arachidonic acid by lipoxygenases. The numbering of eicosanoids is used to denote the number of double bonds in each molecule. The arachidonic acid-derived prostanoids [e.g., prostaglandin E\(_2\) (PGE\(_2\))] contain two double bonds, whereas the leukotrienes (e.g., LTB\(_4\)) have four (reviewed in ref. 4).

Prostanoids are produced from arachidonic acid through sequential metabolism by Cox to the intermediate, short-lived prostaglandins PGG\(_2\) and PGH\(_2\), respectively (5). PGH\(_2\) is then converted by tissue-specific isomerases to other PGs [PGD\(_2\), PGE\(_2\), PGE\(_{2\alpha}\), and prostaglandin I\(_2\) (PGI\(_2\))] as well as Tx and prostacyclins (Fig. 1). Cell-specific profiles of arachidonic metabolites exist because of differential expression of both downstream metabolizing enzymes and receptor isoforms. For example, epithelial cells contain PG synthetase, leading to the production of PGE\(_2\), platelets contain Tx synthetase and therefore produce thromboxane A\(_2\) (TxA\(_2\)), and endothelial cells produce PGI\(_2\), also known as prostacyclin, through the activity of prostacyclin synthase. Prostanoids mediate their local effects on cells by binding to G-protein-linked receptors, which are also present in a tissue-specific distribution. There are at least nine known PG receptor forms, conveying an additional level of tissue specificity to PG-mediated activities. Four of the receptor subtypes bind PGE\(_2\) (EP\(_1\)–EP\(_4\)), two bind PDG\(_2\) (DP\(_1\) and