

# Cyclooxygenase-2: From Arthritis Treatment to New Indications for the Prevention and Treatment of Cancer

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Arthritic conditions most likely have existed as long as human beings have walked the earth, but the first recorded history of treating inflammatory rheumatic diseases was discovered on ancient stone tablets from the Sumerian period. The tablets describe the use of willow leaves to treat these painful conditions. The Egyptians also understood the analgesic properties of the willow leaves and the decoction of myrtle for the relief of joint and uterine pains (Jack, 1997; Pepper, 2000). The history of humankind's endeavors to treat painful joint and musculoskeletal conditions has progressed from the 18th through the 21st centuries with the development of acetylsalicylic acid (i.e., aspirin), corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs), ultimately leading to the discovery of a new class of agents known as the cyclooxygenase-(COX-) 2 inhibitors.

## The Inflammatory Process

Understanding the mechanism of action of NSAIDs and COX-2 inhibitors begins with knowledge of the inflammatory process. Inflammation is the body's response to tissue injury and is a complex process initiated by a variety of foreign insults. This process causes vasodilation and increased vascular perme-

The discovery of the isoenzymes cyclooxygenase-(COX-) 1 and COX-2 led to the development of newer nonsteroidal anti-inflammatory drugs (NSAIDs) designed to block COX-2, such as rofecoxib, celecoxib, and valdecoxib. Because of the specificity of COX-2 expression, COX-2 inhibitors have the potential to reduce the risk of gastrointestinal bleeding experienced with the use of classic NSAIDs. With their crucial role in the control of inflammation, the COX-2 agents originally were marketed for the treatment of rheumatoid and osteoarthritis. However, promising new indications for COX-2 agents in the prevention and treatment of cancer are under investigation. The role of aberrant COX-2 expression in the development of cancer has been studied most widely in patients with colon cancer and adenomas. Recent studies suggest that COX-2-derived prostaglandins may play an important role in tumor viability, growth, and control of metastasis. Possible new indications for the use of COX-2 inhibitors to prevent and treat cancers may be monumental. However, therapy with these agents is not without risk. Oncology nurses must be aware of the potential problems inherent in the use of COX-2 as well as COX-2 agents for chemoprevention in certain cancers.

**Key Words:** chemoprevention; cyclooxygenase inhibitors; anti-inflammatory agents, non-steroidal

ability, permitting fluid, protein, and cells to migrate to the affected site to facilitate tissue repair and healing (Carpenter, 2001; Fung & Kirschenbaum, 1999).

Inflammatory mediators are released from infiltrating cells during an inflammatory response. These mediators, the prostanoids, are

performed and exist in cytoplasmic granules; some are formed from the metabolism of membrane phospholipids, such as prostaglandins (PGs) and leukotrienes (Carpenter, 2001). PGs are short-lived local hormones that mediate inflammation and have a key role in tissue homeostasis and function. PGE<sub>2</sub>, a potent vasodilator, is primarily responsible for erythema, edema, and pain caused by inflammation (Carpenter). Leukotrienes also are powerful mediators and cause bronchoconstriction, leukocyte adhesion to vessel walls, vasodilation, and edema (Simon, 1999).

Arachidonic acid (AA) is stored in the cellular membrane of all cells and is central to the generation of PGs and leukotrienes. AA is released from cellular membranes by phospholipase enzymes and, once released, is oxidized directly or converted by two distinct pathways—the COX pathway and the lipoxygenase pathway—to form PGs or leukotrienes (Halverson, 1999;

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