Imagine preventing cancer before it even starts. Of course, cancer prevention starts at home. We can stay away from smoke, solvents, and sunlight, avoiding unnecessary risks to our cells. We can also eat healthy foods like fruits and vegetables that are filled with protective antioxidants and cleansing fiber. But researchers are now looking to chemistry to provide new compounds to reduce the risk of cancer. The goal is to create a long-term preventive therapy that blocks the early steps of cancer formation and progression, providing extra protection for susceptible individuals.

Surprisingly, a drug that is probably already in your medicine cabinet may be a candidate. Evidence is mounting that regular doses of aspirin, or other nonsteroidal anti-inflammatory drugs, can decrease the risk of cancer, in particular, of colon cancer. Aspirin is a true wonder drug: an effective painkiller, a tool in the fight against heart disease and stroke, and now, a potential new weapon in the arsenal against cancer.

As one might expect from a drug with such profound and manifold effects, aspirin acts at a central point of communication in the body, attacking the messages that are delivered by prostaglandins. Smooth muscle contraction, pain signaling, and inflammation are all modulated by prostaglandin molecules. Aspirin attacks the first step in the synthesis of these important messengers. Arachidonic acid

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**The Molecular Perspective: Cyclooxygenase-2**

*D AVID S. GOODSELL*

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**Figure 1. Cyclooxygenase-2.** The enzyme is a dimer of two identical subunits, and each subunit contains two separate active sites. Two small arms attach the enzyme strongly to the inner surface of smooth endoplasmic reticulum. In the illustration, the membrane is shown with blue shading. The cyclooxygenase active site, which performs the first reaction in prostaglandin synthesis, is found deep within a pocket that opens into the membrane, allowing easy access to insoluble arachidonic acid. In the illustration at right, the nonsteroidal anti-inflammatory drug molecule indomethacin is shown in green bound inside the pocket. The peroxidase active site is on the upper surface of the enzyme. It converts a peroxide on the prostaglandin molecule into a less dangerous hydroxyl group, using a heme group (shown in light green in the right image) for chemical leverage. Atomic coordinates were taken from the file 4COX in the Protein Data Bank (http://www.rcsb.org/pdb).

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(a fatty acid, more snakelike than spidery, which is clipped from membrane lipids) is converted into prostaglandins by the enzyme cyclooxygenase (COX), also known as prostaglandin H2 synthase. This enzyme actually contains two active sites, a cyclooxygenase and a peroxidase, performing the first two chemical reactions of prostaglandin synthesis (Fig. 1). Aspirin arrests the first reaction, insinuating itself into the deep cyclooxygenase active site and bonding directly to a serine amino acid. This glues the drug in place, effectively blocking the entry of arachidonic acid.

The connection between overactive cyclooxygenases and cancer is an area of active study. Two similar forms of cyclooxygenase are constructed by our cells: COX-1 is found in nearly every cell and is used for basic housekeeping functions, and COX-2 is found in specialized cells, where it is synthesized on demand to assist with the process of inflammation. This inducible form of the enzyme, COX-2, has been implicated in cancer progression. Several mechanisms have been proposed. Side effects of the cyclooxygenase reaction may be the problem. Many xenobiotic (“strange biological”) compounds, such as aflatoxin, are oxidized by the enzyme, forming potent mutagens. This may be particularly important in the colon, where cells are exposed to many strange molecules in the diet. Or, the prostaglandins themselves may be the problem. They degrade into mutagenic compounds such as malondialdehyde, which can form harmful adducts with DNA. An overabundance of prostaglandins may also send an improper cellular signal, stimulating cell growth inappropriately or reducing the cleansing effect of apoptosis (programmed cell death).

The search is on for effective drugs to block COX-2, while leaving the essential COX-1 enzymes untouched. Aspirin is too harsh for long-term use in chemoprevention. It blocks COX-1 as well as COX-2, disrupting stomach and kidney function as the normal levels of prostaglandins are disturbed. Subtle differences between the two enzymes are currently being explored, and oddly-shaped molecules created to favor the contours of the proper target.
ADDITIONAL READING


