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Chemoprevention of Colon Cancer

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Colon cancer is one of the most common malignancies in humans, and the search for effective chemopreventive agents is an important and urgent task. Expression levels of inflammation-related enzymes, cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS) are elevated in colon cancers, and their products, prostaglandins and nitric oxide, are suggested to be involved in colon carcinogenesis. Thus, inhibition of COX and NOS activity is thought to be an appropriate approach for chemoprevention.

Clear suppressive effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on colon cancer development have been reported and considered attributable to inhibition of COX, both constitutive COX-1 and inducible COX-2 forms, being involved in a resultant decrease in PGE_2 production. Genetic and pharmacological approaches have revealed that PGE_2 is responsible for colon carcinogenesis through its binding to PGE_2 receptor subtypes EP_1, EP_2 and EP_4. Based on these observations, we have demonstrated that COX-1 or COX-2 selective inhibitors, and EP_1- or EP_4- selective antagonists are good candidate chemopreventive agents against colon cancer in animal experiments. In addition to COX inhibitors and PGE_2 receptor antagonists, the NOS inhibitors, L-NAME and ONO-1714 could be shown to also reduce azoxymethane-induced colonic aberrant crypt foci formation in rats. The way forward in the identification of new and safer chemopreventive agents for colon cancer will be discussed.