

P009 Is COX-2 a 'collateral' target in cancer prevention?

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Nonsteroidal anti-inflammatory drugs (NSAIDs) prevent colon and other cancers. The fact that NSAIDs inhibit the eicosanoid pathway prompted mechanistic drug developmental work focusing on cyclooxygenase (COX) and its products. The increased prostaglandin E₂ levels and the overexpression of COX-2 in colon and many other cancers provided the rationale for clinical trials with COX-2 inhibitors for cancer prevention or treatment. However, one COX-2 inhibitor has been withdrawn from the market due to cardiovascular side effects and there are concerns about a class effect. Evidence suggests that COX-2 may not be the only or the ideal target for cancer prevention. For example, COX-2 is not expressed in human aberrant crypt foci, the earliest recognizable premalignant lesion in the colon; COX-2 is expressed in less than half of the adenomas; *in vitro* data show that NSAIDs do not require the presence of COX-2 to prevent cancer; in familial adenomatous polyposis, the COX-2 inhibitor celecoxib had a modest effect, which was weaker than that of a traditional NSAID; and COX-2 specific inhibitors have several COX-2 independent activities, which may account for part of their cancer preventive properties. The multiple COX-2-independent targets, and the limitations of COX-2 inhibitors suggest the need to explore targets other than COX-2.