Molecular Effects of NSAIDs in Colorectal Cancer Cells

The group led by C. Rao,[9] of the Institute for Cancer Prevention, Valhalla, New York, submitted for the AACR conference the results of in vitro studies dissecting the mechanism of action of NSAIDs combined with a polyunsaturated fatty acid (PUFA), such as docosahexanoic acid (DHA), in preventing growth of colorectal cancer cells in vitro.

Many studies at the preclinical and clinical stage have suggested that NSAIDs may reduce the incidence and tumor involvement in animal models and humans,[10,11] and more clinical trials are in progress.[12] In a small, randomized, placebo-controlled trial of 32 patients with familial adenomatous polyposis, for example, **treatment with two 200-mg daily doses of the COX-2 inhibitor celecoxib induced a 14.5% reduction in involved areas vs 1.4% with placebo** (*P* = .436). **The effect was greater in patients with more extensive disease yielding a 31% reduction in duodenal polyposis after 6 months of treatment**.[13]

In the in vitro studies presented at the AACR meeting, Malisetty and colleagues[14] found that both DHA and celecoxib induced apoptosis in the colon cancer cell line HCA-7, but only at the higher doses. A combination of these agents proved more effective with induction of apoptosis, suppression of COX-2 expression, and inhibition of iNOS expression at lower concentrations of both DHA (150 mcM) and the COX-2 inhibitor (100 mcM).

Induction of apoptosis with COX-2 inhibitors was also observed in a previous study, which showed that induction of DNA fragmentation in colorectal cancer cells occurred independently of COX-2 expression and was induced by celecoxib, but not by other NSAIDs, although all suppressed production of prostaglandin E2.[15] The authors speculated that celecoxib might induce apoptosis through inhibition of the kinase Akt. Independent results presented by Malisetty and colleagues[14] at the 2003 AACR meeting showed that NSAIDs, such as celecoxib, might act by releasing the COX-2- and prostaglandin A-mediated segregation of p53 in the cytoplasm. Treatment with celecoxib (100 mcM) induced release of p53 from the cytoplasm and increased its nuclear localization in colon cancer cells in vitro. Thus, the authors concluded, NSAIDs might interfere with the oncogenic process by modulating the activity of the tumor suppressor gene p53.

The notion that n-3 PUFAs may have a synergistic effect with COX-2 inhibitors in blocking growth of cancer cells opens new avenues of investigation. Further in vitro studies with a larger collection of colon cancer cell lines and preclinical studies in suitable animal models (human tumor grafts) will help to verify these results and allow assessment of feasibility of further studies in humans.

In the meantime, other factors that are known to affect the risk of colorectal cancer should be actively brought to the attention of individuals at risk. Among them are physical inactivity, excess body weight, excess of red and processed meats in the diet, high alcohol consumption, and smoking. It is estimated that at least 70% of colon cancers may be preventable by moderate changes in diet and lifestyle.[16] So, why not give it a try?