Combination Chemoprevention for Colon Cancer Targeting Polyamine Synthesis and Inflammation
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with DFMO (20), can suppress arginine-induced intestinal carcinogenesis. Together with the studies of Bernstein et al. (17, 18), these latter studies suggest a linkage between polyamines and inflammation, and polyamines, inflammation, and colon cancer.

This linkage may be more than simply an association. Microarray analysis of human colon cancer–derived cells identified the spermidine/spermine acetyltransferase (SAT1) as a target of the nonsteroidal anti-inflammatory drug sulindac (21). Sulindac and other nonsteroidal anti-inflammatory drug act by distinct transcriptional mechanisms to induce SAT1 and promote the export of diamines and acetylpolyamines (the products of SAT1) in both human cell and mouse models (14, 22). Acetylation and export work in concert with inhibition of polyamine synthesis to lower cell and tissue polyamine contents. A diamine and acetylpolyamine exporter has recently been identified as a component of the solute carrier protein SLC3A2 (23).

Polyamines contribute to inflammatory responses by mechanisms in addition to those affecting tissue arginine levels. Polyamines are oxidized by several amine oxidases to produce reactive oxygen species and aldehydes (Fig. 1B; ref. 25). Polyamines can also influence the expression of the proinflammatory gene cyclooxygenase 2 by a posttranscriptional mechanism (26).

Fig. 1. A, ODC expression is regulated by a number of signaling pathways. The APC tumor suppressor gene influences the expression of the MYC oncogene and the MYC antagonist MAD1 (34). These E-box transcription factors, in turn, bind to consensus elements, including two E-boxes flanking a SNP which has functional consequences for transcription factor binding, to regulate ODC transcription (27). ODC expression is also regulated by the K-RAS oncogene (35). ODC converts ornithine to the diamine putrescine. This diamine is the precursor for the longer chain amines spermidine and spermine. Genetic and pharmacologic evidence shows that this pathway is essential for normal growth, development, tissue repair, and neoplasia (3). B, the relationship between polyamine metabolism and inflammatory pathways in the colonic mucosa are depicted in this panel. Abbreviations include the following: reactive oxygen species (ROS), nitric oxide (NO), arginine (Arg), ornithine (Orn), putrescine (Put), cyclooxygenase (COX), nitric oxide synthase (NOS), ODC, and SAT1. Diamines, including putrescine, monoacetylspermidine, and diacetylspermidine, are exported by a common transporter (36), which was recently identified by us to including the solute carrier protein SLC3A2 (23). SLC3A2 partners with members of the Y+LAT family to form an arginine transporter. The roles of luminal factors, including polyamines and secondary bile acids, and stromal factors, such as prostaglandins, are shown. DFMO and sulindac lower polyamine contents in colonic epithelial cells by suppressing polyamine synthesis and activating polyamine catabolism and export. Sulindac also inhibits mucosal cyclooxygenases, which are predominately expressed in the colonic stroma before the formation of epithelial neoplasia.

Clinical-Translational Advances

The hypothesis that increased arginine might be associated with colon carcinogenesis in humans was evaluated in a genetic and dietary epidemiology study of patients in a cancer registry (9). Increased survival in colon cancer patients with a family history of this disease was associated with low consumption of red meat, which was used as a surrogate for arginine consumption.
The hypothesis that polyamines, inflammation, and carcinogenesis are linked is strengthened by several genetic epidemiology studies. Our group first reported that a single nucleotide polymorphism (SNP) in the ODC promoter, which displayed functional consequences for E-Box activator (e.g., MYC) and repressor (e.g., MAD1) binding (see Fig. 1A), was associated with risk of recurrence of colon polyps in a clinical cancer prevention trial (27). Six hundred eighty-eight individuals in the Wheat Bran Fiber prevention trial were genotyped for the ODC G316A SNP. The ODC 316AA genotype was associated with approximately a 50% reduction in risk of polyp recurrence, compared with those individuals with the ODC 316GG genotype (odds ratio, 0.48). In reported aspirin users, the ODC 316AA genotype was associated with a 90% reduction in risk of polypl recurrence, compared with nonaspirin use reporters with the ODC 316GG genotype. Hubner and coworkers (28) genotyped 546 participants for the ODC G316A SNP in the United Kingdom Colorectal Adenoma (CRA) Prevention trial of aspirin for CRA recurrence prevention. They found a similar reduction in risk of adenoma recurrence in people with the ODC 316AA genotype, compared with those with the ODC 316GG genotype (relative risk of 0.43). The risk of polyp recurrence in this trial was further decreased in the ODC 316AA group, compared with the ODC 316GG group, by aspirin use. A third group provided independent corroboration of an association between the ODC G316A SNP and aspirin use. Barry and coworkers (29) genotyped participants in a prospective, randomized study of aspirin for prevention of CRA conducted by the Polyp Prevention Study Group. The ODC G316A SNP was not an independent prognostic factor for adenoma recurrence but was a statistically significant predictor of response to aspirin for prevention of CRA recurrence in this study.

A model for the interaction between the ODC SNP and nonsteroidal anti-inflammatory drug action in colon carcinogenesis (3), which includes both cyclooxygenase-dependent and cyclooxygenase-independent actions of nonsteroidal anti-inflammatory drug, is depicted in Fig. 1B. This model has been tested over the past decade in a prospective, randomized placebo-controlled trial of combination DFMO and sulindac for prevention of recurrence in patients with prior CRA (30). Entry criteria for this trial included removal of a CRA within 1 year of study entry. Patients with genetic risk of colon cancer, such as individuals with familial adenomatous polyposis and other polyposis syndromes, were excluded. Participants with current or prior colon or other cancers were also excluded. Participants received the combination of DFMO (two 250-mg pills daily) and sulindac (one 150 mg pill daily), or placebo pills, for 3 years. Primary end points included adenoma recurrence and toxicity assessment. Treatment with DFMO and sulindac was associated with a 70% reduction in total polyps, and over a 90% reduction in both advanced adenomas and in patients with multiple recurrent adenomas, at the end of 3 years. The only statistically significant toxicity noted in this trial was a hearing loss of uncertain clinical significance, which seems to be limited to a small subset of participants (31).

The clinical trial of combination DFMO and sulindac serves as an important proof of the principle that targeting polyamine synthesis and inflammation is an effective method for prevention of recurrent colon polyps. The challenge facing us and other workers in this field is to bring this advance into clinical practice for the management of patients with high risk for colon and, potentially, other cancers. It is clear that this drug combination has some toxicities, and initial applications should be limited to those individuals where a clear positive benefit to risk ratio can be established, such as people with high risk of developing colon cancer. High-risk groups would include those with genetic risk factors, prior advanced and/or multiple colon adenomas, and prior colon cancer. Future clinical trials in all three of these risk groups are in the planning stages.

Drug availability is another serious challenge. Both DFMO and sulindac are old drugs, and DFMO has not been commercially available for some time. We have recently established a company to produce DFMO for future clinical cancer prevention and treatment trials in humans.

The time to completion of clinical trials that might support an approval by the Food and Drug Administration for a cancer prevention indication is a very serious problem that must be solved. Most epithelial cancers have long natural histories, with years often separating the development of invasive cancers after appearance of precancerous intraepithelial neoplasia (32). As evidenced by the approval of celecoxib for treatment of patients with the genetic syndrome familial adenomatous polyposis, which confers risk of colon cancer, the Food and Drug Administration has not accepted reduction in number of colon polyps as an indication of clinical benefit in this patient population. In the approval of celecoxib for familial adenomatous polyposis, the Food and Drug Administration expressed concerns regarding both clinical benefit and long term safety of the drug.

Cancer researchers should consider the example followed by investigators working to prevent deaths due to cardiovascular disease. It has been estimated that the dramatic decrease in deaths due to heart disease over the past 30 years are roughly equally divided between efforts to reduce risk factors, including use of chemoprevention methods, and mechanism-based therapies (33). Public and private sector interests involving academic research, professional medical and commercial pharmaceutical groups, aided by patient advocacy groups, need to work with the Food and Drug Administration to identify paths to implement cancer chemoprevention strategies into the standard practice of managing patients with high risk of colon and other cancers.

Disclosure of Potential Conflicts of Interest

The authors have an ownership interest in Cancer Prevention Pharmaceuticals, LLC.

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