Editorial

Role of curcumin in preventing familial adenomatous polyposis

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Colorectal cancer (CRC), an age-related disease, which equally affects both males and females, is the third leading malignancy world-wide (1). In the United States and most of the western countries, CRC is estimated to be the second and third leading cause of cancer-related deaths in men and women respectively (2).

CRC is a multi-step process. Two models of CRC have been proposed to explain the occurrence of this malignancy. In the first model of CRC, the malignancy begins with somatic mutations in adenomatous polyposis coli (APC) gene, initiating transformation of the normal mucosa to adenoma (class I), which is shown to be associated with hyper-proliferation (3-5). The hyper-proliferation is brought about by the activation of Wnt/β-catenin signal transduction pathways (4-6), followed by the activation of the proto-oncogene K-ras, a process that typically induces the transformation of an early adenoma to a class II type intermediate adenoma (5-7). These processes are then followed by the loss of function of the gene DCC (deleted in colorectal cancer DCC) resulting in the formation of class III adenoma (4). The last step involves *p53* gene mutation, which is thought to transform an adenoma into an invasive or early cancer (5-7). The whole process is found to take about 10 years and hence a 10-year interval is often recommended as the screening interval for colonoscopy in people exhibiting normal colonic mucosa at initial colonoscopy (4). The second model of CRC is based on "Microsatellite Instability". This event is associated with mutations in DNA mismatch repair genes, which leads to accumulation of uncorrected replication errors resulting in hyper-proliferation and eventually carcinoma (5,6).

In the CRC model of Vogelstein, which has recently been modified by Fearon *et al.*, the commonly affected gatekeeper genes are *Ras*, *EGFR*, *PIK3CA*, *BRAF*, *cMYCp53*, *APC*, *PTEN*, *SMADS* (2-4) and *TGFβ-2* (5,6). Since gastrointestinal (GI) cancers, specifically CRC is an age-related disease; we have examined age-associated changes in some of these critical genes in the gastric mucosa of healthy human subjects and found *APC*, *p53*, and *DCC* genes to be inactivated in the GI mucosa in older subjects, indicating a greater risk in developing GI cancer with advancing age (8).

Familial adenomatous polyposis (FAP), an inherited disorder which leads to malignancy is caused by a germline mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q21 (9). FAP is characterized by cancer of the colon and rectum and is associated with the development of thousands of adenomas during the second decade of life. People with the classic FAP are likely to exhibit multiple noncancerous (benign) polyps in the colon in their teenage years. However, most patients do not show symptoms for many years until the adenomas are large and numerous. These changes may lead to rectal bleeding, anemia and ultimately cancer. Incidence of FAP at birth is about 1/8,300 (10) and manifests equally in both sexes. It accounts for less than 1% of CRC cases. Life expectancy is greatly reduced in patients with FAP (10).

While colectomy remains the optimal prophylactic treatment for FAP, efforts have been and continue to be made to identify effective chemopreventive agent(s) to inhibit and/or arrest the growth of polyps in the intestine. Chemoprevention is defined as a way to prevent, slow-down, or reverse cancer through administration of one

or more naturally occurring and/or synthetic agents. The concept of chemoprevention was initially introduced in the mid-1970s by Sporn and colleagues (11). It was referred to the use of pharmacologic or natural agents to inhibit, delay, or reverse carcinogenesis before invasion either by blocking damage to the DNA or by arresting or reversing the progression of premalignant cells, where the damage has already occurred.

All cancers are thought to be preventable and lifestyle plays a significant role in prevention of cancer. It has been estimated that 30% to 40% of all cancers could be preventable by consuming a healthy diet and life-style that among others include regular physical activity, maintenance of body weight and consumption of fruits and vegetables (12). Since fruits, vegetables and various dietary elements (phytochemicals and minerals) are considered to be safe with low toxicity and possessing antioxidant properties they are being investigated for prevention of cancer. Numerous recently published reports have indicated the usefulness of natural agents in reversing the recurrence of various malignancies including colorectal cancer.

Many clinical trials have been and are being conducted with most promising natural agents to examine their effectiveness in combating different cancers (13). They include, but are not limited to EGCG (green tea), curcumin, resveratrol, genistein, pomegranate, lycopene, omega-3 poly unsaturated fatty acids, folic acid, ellagic acid, lupeol and betulinic acid for targeting many malignancies including those of the GI tract (13). Almost all of these natural agents have also been found to act synergistically to increase the efficacy of other drugs *in vitro* in a cell culture system and in animal models of carcinogenesis (13-15). Interestingly, these agents are thought to prevent or delay the progression of cancer by inhibiting proliferation of pluripotent, chemotherapy-resistant cancer stem cells (CSC) and by attenuating Wnt/β-catenin and Hedgehog signaling pathways. The evidence is also strong that demonstrates that natural compounds such as EGCG, curcumin, resveratrol and omega-3 poly unsaturated fatty acids can be used to re-sensitize chemotherapy-resistant CSCs, which are greatly increased during recurrence of cancer.

In the current issue of this journal, Cruz-Correa and her associates have described a double-blind placebo-controlled trial where FAP patients (18–85 years old), who were not subjected to colectomy or had colectomy with ileorectal anastomosis or ileal anal pouches, were given curcumin (3 g/d) for 12 months. The primary objective of this clinical trial was to determine whether curcumin (diferuloylmethane), the major active ingredient of turmeric (*Curcuma longa*) with no discernible toxicity and possessing the ability to inhibit the growth of transformed cells and colon carcinogenesis (16) would be safe and effective in suppressing the growth and/or formation of new polyps in patients with FAP. Cruz-Correa and her associates have found the treatment with curcumin for 12 months to be well tolerated by the patients. However, they observed no significant change either in the number or size of polyps following curcumin treatment. This observation is in contrast with what was observed by the same investigators in their previous pilot study where they found colonic polyps to regress in patients when they were treated with curcumin that contained piperine, a compound that enhances the absorption of curcumin (17). Likewise, regression of intestinal adenomas in five FAP patients was observed following treatment with curcumin and quercetin (18). However, whether the curcumin mediated regression of polyps could be attributed to increased absorption of the compound was not investigated. Majority of preclinical and clinical studies thus far have found a poor oral bioavailability of curcumin (19). Earlier studies have also demonstrated that most of the ingested curcumin is present in the feces as authentic curcumin sulfate (19). While 20–25% is found in the colonic mucosa, only 5–10% is present in the small intestine (19). It has been demonstrated that in mice, when fed 0.2% curcumin, only 100 pm/g of curcumin was found in the liver and approximately 0.001% of that is present in the intestinal mucosa. After consumption of curcumin is finished, its levels in the tissue decline rapidly to unquantifiable amounts within the next 3–6 h, whereas fecal levels decline more slowly, revealing a half-life of about 23-h. Despite poor bioavailability of curcumin, Carroll *et al.* (20) have reported that 4 g curcumin when given orally for a month causes a small but significant 40% reduction in the number aberrant crypt foci (ACF), a lesion considered to be the precursor of adenoma and colon cancer.

To overcome the drawbacks of limited bioavailability and rapid metabolism and to gain efficacy with reduced toxicity, several new analogues of curcumin have been developed and their properties described in details in a review article by Vyas et al (21). Unfortunately, none of the newer curcumin analogues has been evaluated for their preventive or therapeutic efficacy for colon cancer, particularly in patients with FAP.

Recent studies have demonstrated that bioavailability of curcumin is increased by 7–10-fold when it is complexed with essential turmeric oils (referred to as ETO-curcumin; a product of Dolcas Biotech; Chester, NJ, USA) (22). This

particular formulation of curcumin (ETO-Curcumin) has been shown to exert anti-tumorigenic effects by inducing differentiation of cancer stem cells, reversing epithelial-to-mesenchymal transition and by enhancing the efficacy of 5-FU in cancer cells *in vitro* and *in vivo*. (23). In our preliminary investigation, we found ETO-curcumin to synergize with tocotrienol-rich fraction (TRF) of palm oil and together they inhibited the growth of xenograft of FOLFOX-resistant colon cancer cells in SCID mice (24). This was accompanied by a marked reduction in inflammatory cytokine TNF-α in the tumor and dysbiosis of gut microbiome (24). Further studies are undoubtedly needed to examine the efficacy of ETO-curcumin and TRF each alone and in combination in inhibiting/preventing colorectal cancer.

Although curcumin alone is found to be ineffective in inhibiting polyps in FAP patients, as reported in the current issue by Cruz-Correa and her associates, curcumin together with other natural or pharmacological agents has been shown to be highly effective in preventing pre-neoplastic and neoplastic lesions (16). We found curcumin to synergize with the natural agent resveratrol and together they were highly effective in inhibiting the growth of colon cancer cells *in vitro* and *in vivo* in SCID mice xenograft of colon cancer cells (15). In addition to resveratrol, curcumin has been found to synergize with the chemotherapeutic agent dasatinib, a highly specific inhibitor of Src family kinases, to inhibit proliferation of colon cancer cells *in vitro* and to cause regression of intestinal adenomas in $Apc^{min-/+}$ mice (25). This inhibition was associated with marked suppression of several growth factor receptors, specifically EGFR and IGFR signaling pathways leading to inhibition of NF-kβ activity (25). Many independent studies have demonstrated that the combinatorial treatment of curcumin and a chemotherapy drugs such as cisplatin, daunorubicin, doxorubicin, and vincristine enhances the cellular accumulation of these drugs leading to increased cells' sensitivity to the chemotherapeutics (19). These observations strongly suggest that curcumin in combination with chemotherapeutic agents holds a great promise as an anti-cancer therapy. Whether such therapeutic strategy would be effective in preventing the growth and number of polyps in FAP remains to be evaluated.

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