BRIEF REPORT

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Curcumin suppresses intestinal polyps in APC Min mice fed a high fat diet

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Colorectal cancer (CRC) is a leading cause of cancer deaths in the United States. Various risk factors have been associated with CRC including increasing age and diet. Epidemiological and experimental studies have implicated a diet high in fat as an important risk factor for colon cancer. High fat diets can promote obesity resulting in insulin resistance and inflammation and the development of oxidative stress, increased cell proliferation, and suppression of apoptosis. Because of the high consumption of dietary fats, especially saturated fats, by Western countries, it is of interest to see if non-nutrient food factors might be effective in preventing or delaying CRC in the presence of high saturated fat intake. Curcumin (*Curcuma longa*), the main yellow pigment in turmeric, was selected to test because of its reported anti-tumor activity. APC Min mice, which develop intestinal polyps and have many molecular features of CRC, were fed a diet containing 35% pork fat, 33% sucrose, and a protein and vitamin mineral mixture (HFD) with or without 0.5% curcumin. These cohorts were compared to APC Min mice receiving standard rodent chow (RC) with 8% fat. APC Min mice fed the HFD for 3 months had a 23% increase in total number of polyps compared to APC Min mice on RC. Curcumin was able to significantly reverse the accelerated polyp development associated with the HFD suggesting it may be effective clinically in helping prevent colon cancer even when ingesting high amounts of fatty foods. The anti-tumor effect of curcumin was shown to be associated with enhanced apoptosis and increased efficiency of DNA repair. Since curcumin prevented the gain in body weight seen in APC Min mice ingesting the HFD, modulation of energy metabolism may also be a factor.

Keywords: *colon cancer*; *high fat diet*; *curcumin*; *DNA damage*; *apoptosis*; *oxidative stress*

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Colorectal cancer (CRC) is a leading cause of cancer deaths in the United States. Various risk factors have been associated with CRC including increasing age and diet. Diet is an important risk factor for colon cancer, which has been established in many epidemiological and experimental studies (1, 2). In particular, diets high in fat (3–5) promote obesity. Obesity is rapidly becoming a global epidemic and its relation to CRC stems from insulin resistance and inflammation, which result in oxidative stress, increased cell proliferation, and suppression of apoptosis. Dietary fat can promote secretion of the pro-carcinogen bile acids (6), enhance serum prostaglandins E2 (PGE2) concentration, and modulate the host inflammatory and immunocompetence. There is also an increase in serum insulin (7) and an increase in serum triglycerides levels resulting in activation of ligand-activated transcription factors such as peroxisome proliferator activated receptor (8).

There is now increasing evidence that dietary factors and non-nutrient chemicals in foods can reduce the risk of CRC (9–14). One such food component is curcumin. Curcumin (*Curcuma longa*) is the main yellow pigment in turmeric (15). Curcumin has been reported to prevent intestinal malignancies in chemically induced tumors in rats (16), mice (17), and reduce intestinal polyps in the APC Min mice (18, 33). Several clinical studies reported that dietary curcumin reverses, stops, or suppresses tumor progression in high-risk patients (19). The exact anti-tumor mechanism of action is yet to be fully understood. Curcumin has been shown to protect DNA from damage induced by different carcinogens in both initiation and progression (16, 20, 21). It possesses antioxidant activities (22–24) and has been shown to increase the activity of antioxidant enzymes (25, 26). It has also been reported that curcumin inhibits mutagenicity of 7,12-dimethylebenza(a)anthracene (27) and B (a) P induced strand breaks (28).

Because of the high consumption of dietary fats, especially saturated fats, by Western countries, it is of interest to see if curcumin might be effective in preventing

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or delaying CRC in the presence of high saturated fat intake. The APC Min mouse with intestinal polyps is a well known and highly used model that has many molecular features of CRC and has been shown to develop increased numbers of polyps when fed diets high in fat. We report here that when curcumin is fed to APC Min mice with high dietary fat intake, the accelerated increase in intestinal polyps is reversed due in part to increased apoptosis and DNA repair activity.

Material and methods

Animals

Eight week old male APC Min mice on the C57BL/6 background (JAX) were housed in a specific pathogen-free facility and bred to wild-type C57BL/6 females. Pups were genotyped as heterozygotes by PCR and randomly assigned to two groups according to their genotype and to three groups according to diet consisting of standard rodent chow, high fat, and high fat plus curcumin. Mice were kept on the standard chow diet until 5 weeks of age when the high fat diets were started. There were a minimum of 15 mice per gender per genotype for each cohort. All diets were given *ad libidum*. The animal housing room was maintained on a 12 hour to 12 hour light and dark cycle with the dark cycle starting at 6 PM. Animals were monitored daily for signs of illness such as lethargy, rough hair coat, or weight loss. All animal experimentation was approved by the University of Washington Institutional Animal Care and Use Committee.

Diets

The diets used in our studies were standard rodent chow (RC) (5053; Picolab, Richmond, Indiana) containing 20% (wt/wt) protein, 4.5% fat (ether extract), 55% carbohydrate (primarily starch), and a high-fat, high-sucrose diet without curcumin (HFD) or with 0.5% curcumin added (HFD+C) (S3282; Bio-Serv, Frenchtown, New Jersey) containing 20% protein, 36% fat (primarily lard), and 36% carbohydrate (primarily sucrose). Food intake was measured every 3 weeks. Two to three mice of the same genotype were housed per cage and food intake was measured as the weight of food a cage consumed over a 24-hour period and averaged between the number of mice in each cage. Food was weighed three times in a row over the course of 3 days and averaged.

Tumor counts

Following CO_2 euthanasia at 16 weeks of age, the intestinal tract was removed and flushed with ice-cold phosphate-buffered saline and immediately fixed in 10% neutral buffered formalin for 48 hours. The small intestine was measured into three equal sections for identifying polyp location. Polyps were counted blindly under a dissecting microscope and categorized as small (1–3 mm), or large (>3 mm).

Immunohistochemical staining

For apoptosis, formalin fixed sections of the small intestine were deparaffinized and re-hydrated using xylene and ethanol washes. Antigen retrieval was done by microwaving samples for 5 min then endogenous peroxidases were blocked using 3% H_2O_2 in water for 30 min. An Avidin/Biotin blocking step was performed, then slides were incubated overnight at 4°C with cleaved caspase 3 rabbit polyclonal IgG (cell signaling technology) at 1:400 dilution as described (29). Non-specific binding of secondary antibody was performed using 5% normal goat serum (Vector Rabbit Kit) at room temperature, and slides were incubated with 2% biotin-labeled secondary antibody for 30 min at room temperature followed by 30 min incubation with ABC reagent. Tissue sections were then visualized by DAB chromogene and countered stained using Hematoxylin (Fisher). The apoptotic index was generated by counting 10 high-power randomly selected fields for caspase 3-positive cells and calculated as the number of apoptotic cells/10 high-power field.

For 8-oxoG and XRCC1, staining was performed using a mouse on mouse (MOM) vector kit since both involved the use of primary mouse monoclonal antibodies (N54.1, Japan Institute for the Control of Aging, Shizuoka, Japan for the oxidative adduct 7,8-dihydro-8-oxo-2′-deoxyguanosine [8-oxoG]; and ABCAM for XRCC1). Formalin-fixed, paraffin embedded sections were prepared in the same manner as for caspase 3 staining. Sections were then incubated with 5% mouse IgG blocking reagent using the MOM peroxidase kit (Vector Laboratories, Burlingame, California) overnight at 4°C. Slides were then incubated with each primary mouse monoclonal antibody for 30 min at room temperature followed by 10 min incubation with the MOM biotinylated anti-mouse IgG secondary antibody (1:400 for 8-oxoG and 1:50 for XRCC1). Tissues sections were visualized with the mouse Vectastain Elite ABC kit and diaminobenzidine. Quantitation of 8-oxoG and XRCC1 staining was determined by densitometric analysis using the gray scale method and NIH ImageJ 5.1.1 software. The index quantitation was calculated using the formula index = Σ [(X – threshold) $\times$area (pixels)]/total cell number as described (30) with slight modifications.

Clinical chemistries

Starting at week 6, blood glucose was recorded bi-weekly. Food was removed from mice 6 hours before blood was drawn by tail pricking. Analyses were performed using a glucometer and Comfort Curve test strips (Advantage; Accu-Chek, Roche, Basel, Switzerland).

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Statistical analysis

For evaluation of tumor number between groups, size and location, the student *t*-test, ANOVA, and STATA 0.9 software for windows were used. For evaluation of immunohistological staining density, the mean index values were compared for each treatment group by using the student *t*-test. All values are presented as a mean value $\pm$SD, with a *p*-value of 0.05 or less considered statistically significant.

Results and discussion

High fat diet-induced increase in polyp number is blocked by curcumin. APC Min mice fed the high fat diet (HFD) for 3 months had a 23% increase in total number of polyps compared to APC Min mice on the standard rodent chow (RC). When calculated according to tumor size, the HFD seemed to be more associated with small-sized (up to 3 mm) polyps with a 35% increase compared to APC min mice on regular rodent chow (Fig. 1). Large-sized polyp numbers were increased by 29%. The lower increase in large polyps may reflect the tumors that were already developing in the young mice before starting the HFD. When APC Min mice were fed a HFD in combination with curcumin, the number of polyps was significantly reduced. Interestingly, curcumin reduced the number of small-sized polyps by 29% ($p \leq 0.05$), but had no effect on large-sized polyps (Fig. 1).

Curcumin enhances apoptosis independent of dietary fat intake. The HFD has been suggested to suppress apoptosis as one of the mechanisms of enhancing tumorigenesis (31). We observed a decrease in the apoptotic index in both non-polyp and polyp tissue from the distal segment of the small intestine from APC Min mice fed the HFD, but neither value reached statistical significance (data not shown). Based on our data, it appears that enhanced apoptosis was responsible, at least in part, for the anti-tumor effect of curcumin since polyp tissue showed a 39% increase in apoptosis (Fig. 2).

Our data confirm a role for increased apoptosis as a partial explanation for the anti-tumor effect of curcumin as reported by others (32, 33). It is of interest to note that this was not simply a reversal of suppression of apoptosis by the HFD. Indeed, the HFD failed to significantly decrease apoptosis in polyp tissue. Therefore, curcumin directly activates apoptosis as one of the mechanisms for preventing increased tumor numbers associated with a HFD. Molecularly, it has been shown that curcumin creates a cellular environment that influences the expression of the growth arrest and DNA damage-inducible 153 (GADD153) gene (34). The GADD153 appears to have a direct role in initiating apoptosis. Activation of apoptosis may be part of the mTOR signaling pathway as curcumin has been shown to inhibit phosphorylation of mTOR and its downstream effector target S6K1 during apoptosis (35).

Curcumin increases expression of DNA repair activity. We were interested in determining if oxidative stress and DNA damage might be playing a role in polyp development. We used the adduct 8-oxoG as a tissue marker for oxidative DNA damage and showed a decrease in both polyp and non-polyp tissue in mice on the HFD (Fig. 3) suggesting that damaged bases are not associated with the tumor enhancing effects of dietary fat. We saw a significant decrease in expression of the DNA repair gene product XRCC1 in polyp tissue (Fig. 4) suggesting that suppression of DNA repair is associated with DNA damage. When

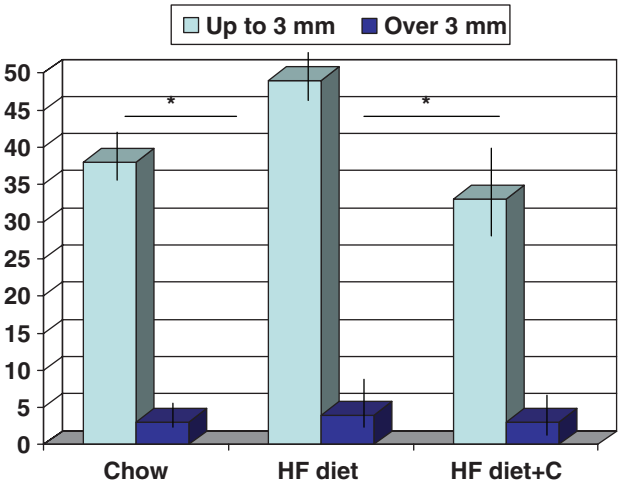

Fig. 1. The number of small-sized polyps (up to 3 mm in diameter) in the small intestine of APC Min mice fed a high fat (HF) diet is increased compared to the number of polyps in mice fed chow (*$p \leq 0.05$). When curcumin (C) is added to the HF diet, small-sized polyp numbers are attenuated compared to polyp numbers in mice ingesting HF diet without curcumin (*$p \leq 0.05$). $N = 15$–18 mice for each of the three cohorts.

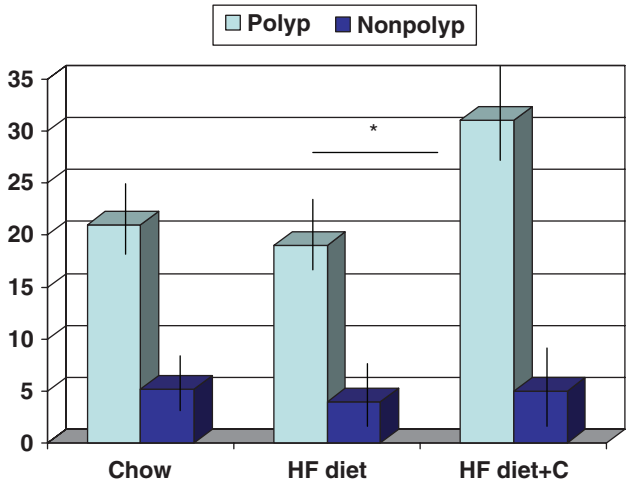

Fig. 2. Apoptosis, as assessed immunohistochemically by apoptotic index, is increased in intestinal polyps from APC Min mice ingesting high fat (HF) diet with curcumin (C), but not in polyps from APC Min mice ingesting HF diet without curcumin or regular rodent chow diet (*$p \leq 0.05$). $N = 15$–18 mice for each of the cohorts.

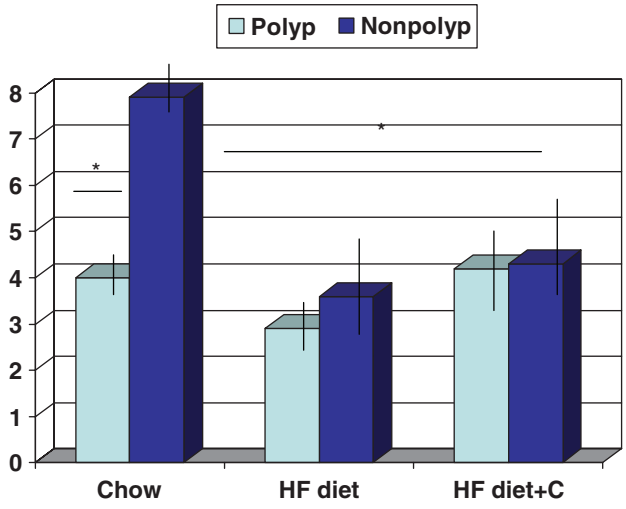

Fig. 3. Oxidation-induced DNA damage, as assessed immunohistochemically by 8-oxoG index, in intestinal polyps from APC Min mice is not affected by ingestion of a high fat (HF) diet with or without curcumin. However, ingestion of the HF diet appears to attenuate oxidation-induced DNA damage observed in non-polyp tissue from APC Min mice ingesting regular rodent chow (*$p \leq 0.05$). $N = 15$–18 mice for each of the cohorts.

curcumin was added to the diet, there was an increase in the 8-oxoG index in polyp tissue (Fig. 3) and a 64% increase in XRCC1 expression in non-polyp tissue (Fig. 4). This was opposite to that seen in APC Min mice fed regular rodent chow. The robust increase in XRCC1 expression in non-polyp tissue in the presence of curcumin suggests that curcumin can activate DNA repair and may be an additional mechanism by which this dietary chemical exerts anti-tumor activity.

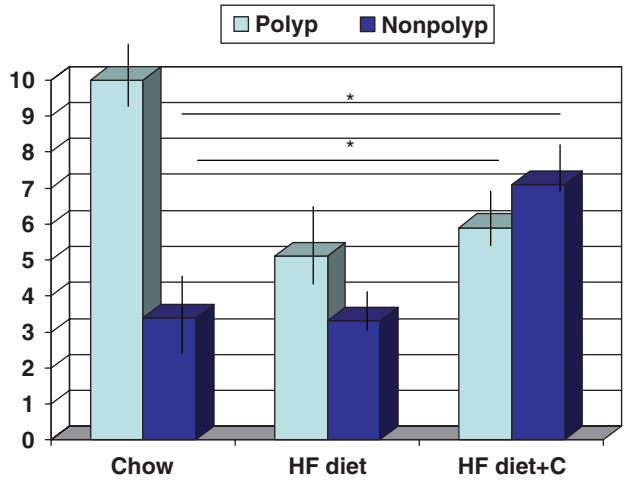

Fig. 4. DNA repair activity, as assessed immunohistochemically by XRCC1 expression index, is increased in intestinal polyps from APC Min mice fed high fat (HF) diet with curcumin (C) compared to APC Min mice ingesting HF diet without curcumin or regular rodent chow (*$p \leq 0.05$). Interestingly, the XRCC1 expression index is decreased in intestinal non-polyp tissue from APC Min mice ingesting HF diet with or without curcumin compared to APC Min mice ingesting regular rodent chow (*$p \leq 0.05$). $N = 15$–18 mice for each of the cohorts.

The base excision repair (BER) pathway is the primary mechanism for repair of oxidative base lesions such as 8-oxoG. The ROS-induced DNA damage is believed to contribute to carcinogenesis. Oxidative damage to DNA may lead to mutations that activate oncogenes or inactivate tumor suppressor genes. Our thinking was that since diet-induced obesity is associated with a state of chronic inflammation, there would be an increase in ROS-induced DNA damage. The 8-oxoG is one of the most abundant and well-characterized DNA lesions generated by ROS and high levels have been found in urine and tumor tissue from patients with a variety of malignancies (36). It is therefore of interest that our data in APC Min mice fed the HFD do not show increased 8-oxoG in tumor tissue. There was, in fact, a significant decrease in 8-oxoG in polyps from APC Min mice ingesting high dietary fat, suggesting this type of diet may actually protect against oxidative DNA damage, at least for the DNA base guanine. The 8-oxoG lesions were higher in non-polyp tissue but the same significant decrease was seen with the HFD.

We selected the BER gene XRCC1 to assess DNA damage response in APC Min mice. The XRCC1 is a scaffold protein that facilitates the BER process and has been extensively evaluated in cancer association studies based on several single nucleotide polymorphisms (37). The XRCC1 was prominently decreased in polyps from APC Min mice fed HFD compared to regular chow. This may be a reflection of decreased 8-oxoG lesions, but since XRCC1 did not decrease in non-polyp tissue in mice on HFD compared to regular chow, some other mechanism is necessary to help explain the decrease. It is of interest that when curcumin was added to the high fat diet, XRCC1 was not significantly changed in polyp tissue. However, there was a significant increase in XRCC1 in non-polyp tissue from APC Min mice fed HFD with curcumin compared to HFD without curcumin, indicating that curcumin can activate XRCC1 by increasing DNA damage. This could in part explain the decrease in tumor numbers in mice receiving curcumin by increasing the efficiency of DNA repair and suppressing the propagation of mutagenic lesions not associated with 8-oxoG.

Curcumin prevents increased body weight associated with a high fat diet. Body weight was significantly higher in APC Min mice fed the HFD compared to mice receiving the HFD plus curcumin (Fig. 5) suggesting curcumin has anti-obesity effects. There was no difference in food consumption or tibia lengths indicating curcumin had no effect on growth and development. Blood glucose levels were increased in a similar manner in APC Min mice fed the HFD either with or without curcumin (data not shown).

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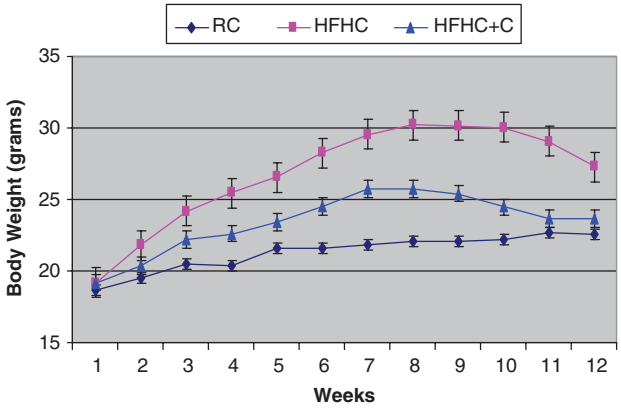

Fig. 5. Body weights of APC Min mice fed a diet high in fat and calories with curcumin added (HFHC+C) or without curcumin (HFHC) or fed regular rodent chow (RC). Starting at week 4, body weight is significantly lower in APC Min mice ingesting the high fat diet containing curcumin ($N=32$) compared to APC Min mice ingesting the high fat diet without curcumin ($N=32$; $p<0.01$) and is comparable to body weight of APC Min mice ingesting regular rodent chow.

The enhanced polyp development seen with ingesting a high fat diet in our study is in agreement with other published studies (38). Mice had significant weight gains and increased fat stores. Epidemiological studies are in general agreement, although there are some inconsistencies reported. The large Nurses Health Study found that those with the highest intake of animal fat were at almost twofold greater risk for developing colon cancer than those with the lowest intakes. However, studies looking at total fat intake are inconsistent. What may be more relevant is the association of obesity with colon cancer, with evidence that abdominal or visceral adiposity is a highly significant risk factor along with insulin resistance (39). These are conditions associated with excess energy intake and can be reversed with decreased energy intake and/or increased physical activity. An inverse relationship between physical activity and colon cancer has consistently been demonstrated (40). In this regard, increased energy intake can be balanced by dietary factors that modulate energy metabolism in adipose tissue. Interestingly, curcumin has been found to prevent obesity in C57BL/6 mice most likely by inhibiting angiogenesis in adipose tissue and activating apoptosis of adipocytes (41). Although we did not look at this in our study, it may be an additional mechanism to help explain not only the decreased body fat in APC Min mice fed HFD with curcumin, but also the anti-tumor effect. In this regard, APC Min mice fed a Western-style diet high in fat and performing regular moderate intensity exercise did not have reduced polyp number or mass, although polyp number and size were reduced in control diet-fed mice (38). This suggests that clinical trials combining physical exercise and daily consumption of curcumin may be worth considering for the prevention of CRC.

Summary

We have shown that the dietary phytochemical curcumin is able to reverse the accelerated polyp development associated with a high fat diet in APC Min mice suggesting it may be effective clinically in helping prevent colon cancer even when ingesting high amounts of fatty foods. Our data show that one of the mechanisms involved in the anti-tumor effect of curcumin is enhanced apoptosis. In addition, it appears that curcumin also activates DNA repair thereby preventing the development of tumorigenic mutations.

Conflict of interest and funding

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