

## Perspective

Perspective on Carroll et al., p. 354

## Curcumin Chemoprevention: The Long Road to Clinical Translation

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### Abstract

Curcumin exhibits significant antitumorigenic activity in various preclinical models; data supporting its chemopreventive activity in humans, however, are lacking. To our knowledge, the first published results of a phase II chemoprevention study of curcumin are reported in this issue of the journal by Carroll and colleagues (beginning on page 354), who examined the effects of oral curcumin on various putative biomarkers of colonic tumorigenesis in smokers. This perspective discusses the potential significance and limitations of the current study findings in addressing the question of whether curcumin is clinically active as a chemopreventive agent. *Cancer Prev Res*; 4(3); 296–8. ©2011 AACR.

The common food spice tumeric has been used as a medicine for millennia in India (1). Curcumin (diferuloylmethane), a polyphenolic natural extract of tumeric, modulates many putative molecular cancer targets, including cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF- $\kappa$ B), tumor necrosis factor alpha (TNF- $\alpha$ ), and cyclin D1, and exhibits significant anti-inflammatory and anti-tumorigenic activity in various preclinical models (2–6). Based on this promising preclinical activity, clinical studies have finally begun to test curcumin's chemopreventive effects in humans (7).

The safety and tolerability of oral curcumin quickly became evident in phase I studies, even when escalated to doses as high as 8 g per day (1, 7–9). However, the agent's low systemic bioavailability also became apparent in phase-I pharmacokinetic studies (8–10). Healthy volunteers who received a single curcumin dose of less than 10 g had undetectable levels of curcumin in the serum in one phase I study (8). Nonetheless, longer oral intake of curcumin (3 months) achieved average serum levels of 0.51  $\mu$ mol/L at a dose of 4,000 mg/day in a phase-I study of 25 subjects with various premalignant lesions. The dose was escalated to 8,000 mg/day with little toxicity (9). A daily dose of 3.6 g of curcumin for 4 months also produced detectable serum and urine levels in another phase I study of colorectal cancer patients (11). This low bioavailability of curcumin has spurred research interest in developing a

better formulation and chemical structure modification of curcumin to enhance its bioavailability (12, 13).

The low oral bioavailability of curcumin is due to its rapid metabolism, largely through conjugation to sulfates and glucuronides (14, 15). This metabolism may differ in some regards between humans and rodents (16), occurring in humans probably mostly in the gastrointestinal (GI) tract rather than in the liver (16). Whatever its underlying cause, the very low bioavailability of curcumin is puzzling in view of reports of possible systemic curcumin effects such as in treating inflammatory eye disorders (14). If these effects are real, it is not clear if they occur because of the potency of the amounts that reach the general circulation with high doses, because of the effects of unmeasured curcumin metabolites, or for other reasons.

Several clinical studies have been initiated to test the activity of curcumin against a range of cancers and other disorders (<http://clinicaltrials.gov> and ref. 14). Because oral curcumin seems preferentially distributed into colorectal mucosa (normal and malignant) compared with its distribution in other organs such as the liver (17), much clinical testing of curcumin has naturally focused on colorectal diseases, most notably colorectal cancer. Until now, the only clinical results available regarding the effects of curcumin in the colorectum come from a single report of 5 patients with familial adenomatous polyposis (FAP) treated with a combination of curcumin and quercetin (18). The numbers and sizes of polyps were reduced in all 5 patients after 6 months of treatment (18). Interpretation of this study, however, was limited by its small size, lack of control group, and the combination treatment arm.

The study reported by Carroll and colleagues in this issue of the journal (19) is thus a welcome addition to the curcumin literature. A small phase II study, it has the advantage of 2 treatment arms (but unfortunately no placebo). This open-label study enrolled smokers who had aberrant crypt foci (ACF) on screening colonoscopies.

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doi: 10.1158/1940-6207.CAPR-11-0060

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Forty-one of the 44 patients completed the protocol prespecified 30-day treatment of daily curcumin at either 2 g (22 patients) or 4 g (19 patients). The primary study endpoint was the change in the levels of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and 5-eicosatetraenoic acid (5-HETE) levels in ACF and normal colonic mucosa samples obtained via endoscopy before and after curcumin treatment.

PGE<sub>2</sub> and 5-HETE are oxidative metabolites of arachidonic acid that have been linked to tumorigenesis (20–22). The selection of PGE<sub>2</sub> as a molecular biomarker has a particularly strong rationale: knockout of the PGE<sub>2</sub> receptor suppressed experimental carcinogenesis in the large bowel, and PGE<sub>2</sub> is clearly carcinogenic in colon models (23, 24). Cigarette smoke extract has been shown in preclinical models to promote colorectal tumorigenesis via increased production of PGE<sub>2</sub> and leukotriene B<sub>4</sub> (the terminal metabolite of 5-HETE; refs. 25, 26). Tobacco smoking has also been associated with an increase in the number of ACF (27) and with the production of PGE<sub>2</sub> and leukotriene B<sub>4</sub> in humans (28). Change in the number of rectal ACF and in the cell-proliferation marker Ki-67 expression was measured as secondary endpoints.

The choice of ACF as a biomarker of carcinogenesis has limitations. The majority of ACF detected endoscopically in humans are hyperplastic, not dysplastic (29, 30), and the authors could not assess the histology of the lesions they studied. Although various animal studies of colonic tumorigenesis have supported the concept that ACF are early precursors of colorectal adenomas and cancer, the putative role of ACF as an intermediate biomarker of human colonic tumorigenesis has recently been challenged by findings of large clinical studies (29–31).

Carroll and colleagues' measurements of tissue and plasma levels of both natural curcumin and its conjugates with a highly sensitive mass spectrophotometry method provide some interesting (and unexpected) findings. In addition to documenting both the low bioavailability of curcumin and the predominance of the conjugated forms in the general circulation, the study reported a high prevalence of detectable curcumin conjugates in plasma at baseline. This last finding is surprising, as the low bioavailability of curcumin implies that detectable levels should only be seen in individuals using curcumin supplements. Perhaps low intake, if long-term, can suffice. If confirmed, the finding that individuals in the general population have detectable conjugate levels raises the possibility that serum measurements can be used in epidemiological studies of the curcumin association with disease occurrence.

Results involving the examined chemoprevention biomarkers were negative in most regards, showing no significant effects for curcumin on the primary endpoint PGE<sub>2</sub> or 5-HETE in either normal or ACF rectal mucosa. The authors interpreted these findings as providing evidence for a lack of effects of these eicosanoids on early stages of colonic tumorigenesis. In support of this conclusion, PGE<sub>2</sub> and 5-HETE levels were in fact similar between the normal and ACF mucosa, with a trend even toward higher levels in normal mucosa than in ACF. To further question the utility

of these eicosanoids as carcinogenesis biomarkers, they also cited findings from a prior study showing that celecoxib, a selective COX-2 inhibitor, failed to reduce mucosa PGE<sub>2</sub> levels while inhibiting polyp formation in FAP patients (32). Findings from this and the current study could be interpreted as suggesting that PGE<sub>2</sub> promotes colonic tumorigenesis at stages later than ACF and adenomas. Of note, a recently published study has showed no significant change in leukotriene B<sub>4</sub> levels during colonic tumorigenesis (33), calling into question whether 5-HETE really is a biomarker for colorectal tumorigenesis. The current study is limited in assessing the role of these pathways in colonic tumorigenesis by its relatively small sample size and single pathological endpoint. Therefore these interesting results need to be interpreted with caution; future studies are needed to further examine the role of these and other eicosanoids as biomarkers for early colorectal carcinogenesis.

Curcumin treatment also showed no effects on Ki-67 expression. Unfortunately, apoptosis markers were not included, although prior studies have demonstrated that apoptotic measurements predict curcumin chemopreventive activity in preclinical models (34). Evaluation of apoptotic markers in future translational studies in this setting would be welcome.

An interesting finding of the study is that curcumin significantly reduced ACF numbers at the 4-g but not the 2-g daily dose level. Although tantalizing, the significance of this finding is uncertain. The uncertainty regarding the role of ACF as an intermediate biomarker of colorectal cancer makes interpretation of the result difficult, and the possibility of an unintentional bias in the ACF assessment cannot be totally excluded because the study endoscopists were unblinded to treatment status.

Whether curcumin might have effects in the colorectum through systemic or topical exposure is an unanswered question in the current study. The investigators utilized a highly sensitive mass spectrophotometry method for measuring curcumin and its metabolites in both serum and rectal tissue samples. Following curcumin treatment, some, but not all, subjects had detectable levels of either curcumin or its metabolites in rectal tissues. More important, the detection of curcumin and its metabolites in rectal tissues did not correlate with the reduction in ACF formation. These findings lend no support to the concept that curcumin suppression of ACF formation depended on its topical effects through rectal tissue bioavailability. Curcumin metabolites, however, were detected in the serum of all of the examined subjects in the 4-g dose group, a finding that might argue for systemic effects. Examination of whether curcumin serum metabolite levels were different between the 2 dose levels and between the responders and nonresponders could help address this question. The small number of subjects in the subgroups, however, will limit the statistical power of these analyses.

What is the significance of the current findings of Carroll and colleagues? The ACF results provide hints of efficacy

and could be one of the first signs of the long-anticipated clinical activity of curcumin for chemoprevention. Unfortunately, this study provides only hints, and confirmation of curcumin's activity continues to be elusive. The intriguing finding that curcumin metabolites may be a suitable avenue for observational studies could help to lay the groundwork for a full (expensive and time-consuming) randomized controlled clinical trial. We therefore need to stay tuned for more data from the completed and ongoing clinical studies of curcumin, which it is hoped

will be reported soon to further address the question of whether curcumin is an effective chemopreventive agent in humans.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Received December 23, 2010; revised January 26, 2011; accepted January 26, 2011; published online March 3, 2011.

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*Cancer Prev Res* 2011;4:296-298.

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