Curcumin Activates the Aryl Hydrocarbon Receptor yet Significantly Inhibits (-)-Benzo(a)pyrene-7R-trans-7,8-dihydrodiol Bioactivation in Oral Squamous Cell Carcinoma Cells and Oral Mucosa

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ABSTRACT

The development of oral squamous cell carcinoma (SCC) shows a positive correlation with the carcinogen exposure that occurs during tobacco and alcohol use. The purpose of this study was to investigate whether the naturally occurring chemopreventive agent, curcumin, modulates expression and function of carcinogen-metabolizing enzymes in human keratinocytes isolated from oral SCC tumors. Dose-response studies demonstrated that curcumin concentrations of ≥25 μM were cytotoxic for oral SCC cells. Curcumin increased both expression (reverse transcription-PCR analyses) and function (high-performance liquid chromatography determination of ethoxyresorufin metabolism) of cytochrome P-450 (CYP) 1A1 and/or CYP1B1. The aryl hydrocarbon receptor (AhR), which up-regulates a battery of genes associated with carcinogen metabolism, is activated by polycyclic aromatic hydrocarbons such as the tobacco-associated carcinogen benzo(a)pyrene. Electromobility shift assays demonstrated that similar to the established AhR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin, curcumin inclusion resulted in AhR nuclear translocation and formation of the transcriptionally active AhR-aryl hydrocarbon receptor nuclear translocator complex. Cellular capacity to bioactivate the tobacco-associated carcinogen (-)-benzo(a)pyrene-7R-trans-7,8-dihydrodiol was determined by evaluating conversion of the carcinogenic metabolite diol epoxide to stable tetrols via high-performance liquid chromatography. Results of our metabolism studies showed that curcumin significantly inhibited CYP1A1-mediated benzo(a)pyrene diol bioactivation in both oral SCC cells and intact oral mucosa. Because CYP1A1 is one of the primary carcinogen-activating enzymes in oral mucosa, the use of curcumin as an oral cavity chemopreventive agent could have significant clinical impact via its ability to inhibit carcinogen bioactivation.

INTRODUCTION

Oral SCC, which comprises 90% of all intraoral cancers, is the seventh leading cancer in men in the United States. Oral SCC development correlates positively with the carcinogen exposure that occurs during tobacco and alcohol use. Exposure to xenobiotics such as tobacco-associated carcinogens can induce both phase I and phase II enzymes. Whereas phase I enzymes can function to either bioactivate or detoxify chemicals, phase II enzymes generally detoxify agents by increasing their water solubility and dissipating electrophilicity. The ultimate fate of these potential carcinogens is therefore dependent on whether carcinogen bioactivation or detoxification pathways prevail. Consequently, identification of methods to enhance oral mucosal carcinogen detoxification while concurrently suppressing bioactivation is a research focus.

Cancer chemoprevention is recognized as the prevention, inhibition, or reversal of carcinogenesis by intervention with chemical substances, which can be administered either as individual drugs or as naturally occurring dietary constituents. Chemopreventive agents frequently intervene at numerous biochemical pathways including induction of the phase II carcinogen detoxification enzymes and suppression of cellular proliferation. The naturally occurring chemopreventive curcumin is the major phenolic antioxidant and anti-inflammatory agent in the spice tumeric. Curcumin has demonstrated anticarcinogenic effects in numerous animal models including skin and gastrointestinal carcinomas. Curcumin also inhibited BP-induced forestomach cancer in a murine carcinogenesis model, suggesting that curcumin enhances carcinogen detoxification and/or suppresses carcinogen activation. Curcumin has demonstrated a variety of in vitro cancer-inhibitory effects including inhibition of mitogenic signaling, suppression of cell growth, and induction of apoptosis. In human leukemia cells, curcumin augmented activity of the phase II enzyme GST and increased levels of the GST cofactor, GSH. Other studies in which curcumin competitively inhibited human breast carcinoma cell bioactivation of dimethylbenzanthracene suggest that curcumin functions as a CYP1A1 substrate. Collectively, these data imply that the chemopreventive efficacy of curcumin reflects in part its modulation of cellular carcinogen metabolism.

Many toxic compounds, including the tobacco-associated carcinogen BP, share the PAH configuration. Upon cellular entry, PAHs readily interact with a cytosolic protein, the AhR. The AhR-ligand complex then translocates to the nucleus and binds to the transcription-activating factor, ARNT (10). AhR activation, nuclear translocation, and formation of the AhR-ARNT complex result in up-regulation of a battery of AhR-regulated genes (10). At least six of the AhR-responsive genes are associated with carcinogen metabolism, including the potential carcinogen bioactivator CYP1A1. Whereas the best characterized AhR ligands are PAHs such as BP and toxic halogenated compounds such as TCDD, some naturally occurring compounds with chemopreventive properties have recently been shown to act as selective AhR agonists or antagonists. Due to the vigorous xenobiotic metabolism that occurs within the oral cavity, use of chemopreventive compounds as selective AhR-modulating agents to suppress intraoral carcinogen bioactivation represents a valid strategy to reduce initiation and promotion of oral SCC.

The purpose of this investigation was to determine whether curcumin modulates expression and function of carcinogen-metabolizing enzymes in oral human keratinocytes and to assess the effects of
curcumin on oral mucosal carcinoma bioactivation. We report, for the first time, that curcumin initiates AhR nuclear translocation and formation of the active AhR-ARNT complex in human oral keratinocytes and that curcumin significantly inhibits CYP1A1-mediated bioactivation of the tobacco-associated carcinogen BP in both human oral SCC keratinocytes and human oral mucosal tissues.

MATERIALS AND METHODS

Cell Culture. Five cell lines derived from oral SCCs of the tongue that developed in men between the ages of 25 and 70 years were obtained from American Type Culture Collection. All of the SCC cell lines are aneuploid, immortalized, have an epithelial morphology, and show growth rates ranging between 0.8 and 1.0 population doubling level/day. Our laboratory has confirmed that these SCC cell lines retain many characteristics of oral mucosa, including the capacity for carcinogenic metabolism and preservation of AhR-responsive phase I and II enzymes. The cell lines were cultured in their optimal medium (DMEM/Ham’s F-12, 90%; heat-inactivated fetal bovine serum 10%) at 37°C, 5% CO₂.

Curcumin Dose-response Studies. On the day of assay, curcumin working concentrations (1, 5, 10, 25, and 50 μM) were prepared in cell culture medium. Control cultures received medium containing a comparable DMSO concentration (0.05%) contained in the highest curcumin dose. Fresh medium containing either the appropriate curcumin dose or DMSO was added every 24 h. Cell harvests were conducted at 24, 48, and 72 h after curcumin challenge. Cell counts were conducted using a hemocytometer, and viabilities were determined using trypan blue dye exclusion. Previous studies conducted by our laboratory have shown an excellent agreement (viabilities comparable within 1%) between trypan blue exclusion and lactate dehydrogenase release assays (12).

Determination of CYP1A1 and/or CYP1B1 Monooxygenase Activity by ER-O-deethylation Assay. The monooxygenase activities of CYP1A1 and CYP1B1 were determined by evaluating cellular O-deethylation of ER to the fluorescent compound resorufin. ER studies used a 24-h incubation and used the following experimental groups: (a) 10 μM ER + growth medium; (b) cells + 0.05% DMSO; (c) cells + 10 μM ER; (d) cells + 5 μM curcumin + 10 μM ER added concurrently; and (e) 10-hr cellular pretreatment with 5 μM curcumin then, 5 μM curcumin and 10 μM ER added concurrently. The fluorescence of resorufin present in the eluate was monitored at an excitation wavelength of 585 nm and an emission wavelength of 585 nm by a method developed by our laboratory (13). Enzyme activity was reported as nmol resorufin/10⁶ cells.

Determination of Cellular GST Activity. The method of Habig and Jakoby (14) was used to determine total cellular GST activities. A concurrent 5-point GST standard curve was conducted with every assay. GST activity was expressed as units/mg protein, with 1 unit of GST activity being equivalent to the conversion of 1 μmol of GSH/mg protein.

RESULTS

Curcumin Doses ≥ 25 μM Decrease Cell Viability, and Doses > 10 μM Decrease Proliferation. Viabilities of the 0, 1, and 5 μM curcumin groups remained constant over the assay course. At every time point, the viabilities of the 0, 1, and 5 μM curcumin groups were greater than that of the 50 μM curcumin group. At the 48

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72 h time points, the viabilities of the 0, 1, and 5 μM curcumin groups were higher than those of the 25 μM curcumin cultures. (Fig. 1A; P < 0.001).

Cell numbers in the 0, 1, and 5 μM curcumin groups increased approximately 4-fold over the course of the 72-h treatment (Fig. 1B). At the 72 h harvest, cell numbers in the 0, 1, and 5 μM curcumin groups were greater than those in the 10, 25, or 50 μM curcumin groups (Fig. 1B; P < 0.001). Subsequent studies used the 5 μM curcumin dose.

**Inclusion of 5 μM Curcumin Increases GSH Levels Relative to Log Growth Controls.** We hypothesized that the antioxidant properties of curcumin may conserve the primary intracellular antioxidant, GSH. Time course studies (harvests at 24, 48, and 72 h) were conducted to determine the effect of curcumin on cellular GSH levels using the following experimental groups: (a) vehicle control (cells + medium containing 0.05% DMSO); and (b) 5 μM curcumin treatment. Both groups showed a decrease in GSH levels over the experimental time course, a finding that likely reflects cultures reaching confluence. The culture GSH levels (nmol GSH/mg protein, reported as mean ± s.e.m.; n = 4 for every group; mean = 72 h harvests) were: 43.2 ± 5.1, 26.2 ± 4.3, and 18.3 ± 4.7 (control) versus 52.0 ± 4.7, 45.5 ± 7.6, and 44.6 ± 1.4 (curcumin inclusion).

Curcumin inclusion increased GSH levels (P < 0.010) at every timed harvest point (24, 48, and 72 h; comparison of same cell line control versus curcumin inclusion). Notably, cell numbers between the two groups were comparable at all harvest points (mean ± s.e.m.; n = 4 for every group; mean = 72 h harvests): 3.07 ± 0.39, 4.41 ± 0.59, and 4.71 ± 0.42 (control) versus 3.01 ± 0.30, 4.46 ± 0.72, and 5.12 ± 0.33 (curcumin inclusion).

**Curcumin Pretreatment Increases CYP1A1/CYP1B1 Metabolism as Assessed by Resorufin Formation.** Whereas concurrent addition of 5 μM curcumin resulted in a slight, insignificant decrease in resorufin formation (2.0% decrease relative to cell-ER controls), a 72-h pretreatment with 5 μM curcumin significantly increased cellular ER metabolism by 28.7% relative to cell-ER controls (P < 0.05; Fig. 2A). No ER metabolism/resorufin formation was detected in either the cell-free medium ER controls (group 1) or the cell-medium only (group 2) controls.
Incubation with ER Increases GSH Levels, Regardless of Inclusion or Exclusion of Curcumin. ER incubation increased cellular GSH levels relative to control cultures, regardless of the presence or absence of curcumin \((P < 0.001;\) Fig. 2B).

SCC Cells Possess High Levels of GST That Are Independent of Curcumin or ER Inclusion. GST functional assays showed that SCC cells possess high GST functional activity, regardless of inclusion of either curcumin or ER. The GST assay results \((n = 6\) for every group; mean units/mg protein ± s.e.m.) were 74.8 ± 14.8 (log growth + 10 \(\mu\)M ER, 24-h incubation), 80.0 ± 18.3 (24-h pretreatment with 5 \(\mu\)M curcumin), 89.8 ± 20.9 (5 \(\mu\)M curcumin concurrently delivered with 10 \(\mu\)M ER, 24-h incubation), and 79.7 ± 12.5 (log growth control).

Curcumin Inclusion Results in Nuclear Translocation of the AhR and Formation of the Transcription-activating Complex AhR-ARNT. All of the human SCC cell lines retained expression of the AhR during proliferative growth (Fig. 3A). Inclusion of 5 \(\mu\)M curcumin in sera-deprived cultures resulted in nuclear translocation and formation of the biologically active AhR-ARNT complex in every cell line evaluated (Fig. 3B). Whereas AhR nuclear translocation was apparent after a 3-h curcumin incubation, all cell lines showed comparable or greater AhR activation after a 24-h curcumin exposure (Fig. 3B). Relative to 5 \(\mu\)M BP, curcumin resulted in comparable or greater AhR activation in every cell line. Curcumin exposure resulted in comparable levels of AhR nuclear translocation as 5 \(n\)TCD, the potent, high-affinity, nonmetabolized AhR ligand. Whereas proliferative growth cultures showed nuclear translocation of the AhR, the AhR activation status was reduced by sera deprivation (Fig. 3B).

Curcumin Up-Regulates Expression of CYP1A1 and CYP1B1 in Oral Keratinocytes. RT-PCR analyses showed that expression of a battery of carcinogen-metabolizing genes was cell line dependent. Furthermore, gene expression was generally constant regardless of the inclusion or exclusion of serum or curcumin. Notable exceptions were the effects of curcumin on expression of the CYP1A1 and CYP1B1 carcinogen-metabolizing enzymes. Whereas serum deprivation reduced expression in two of four cell lines (CYP1A1) and three of four cell lines (CYP1B1), curcumin inclusion induced expression of CYP1A1 in all four cell lines and induced expression of CYP1B1 in three of four cell lines. CYP1B1 expression was constantly high in the metastatic SCC 2095 cell line. Constant low levels of the AhR-modulated GST gene \((GSTA1)\) were only detectable in two cell lines \((SCC 4\) and SCC 2095). Expression of the other non-AhR-responsive GST isoforms \((GSTM1, GSTP1,\) and \(GSTT1)\) was high regardless of culture conditions. NADPH quinone reductase was expressed at high, constant levels in all cell lines. In contrast, GSH peroxidase and UDP-glucuronosyltransferase expression was cell line dependent and was not modulated by experimental conditions. Expression levels of the housekeeping gene, GAPDH, remained constant (data not shown).

Curcumin Significantly Inhibits Oral Keratinocyte Bioactivation of the Tobacco-associated Carcinogen BP-7,8-diol. Tetrads were detected at the 24-h time point in the cell-free base medium \((DMEM/Ham’s F-12) + BP-7,8-diol samples. Additional experiments, which showed that tetrat formation occurred in base medium in a time-dependent fashion, confirmed that the presence of tetrat was due to a pro-oxidant medium. Our results also showed that curcumin inclusion inhibited tetrat formation in base medium.

No tetrat formation was detected in samples that contained cells + base medium + curcumin. In every cell line, tetrat I-1 was the major BP-7,8-diol-derived tetrat formed, followed by tetrats II-1, II-2, and II-2. Cellular metabolism of BP-7,8-diol was determined to be cell line dependent. Curcumin inhibited cellular BP-7,8-diol bioactivation in every cell line evaluated \((P ≲ 0.028;\) Table 1).

Curcumin Also Inhibits BP-7,8-diol Formation in Clinically and Histologically Normal Oral Mucosa. Our results (Table 1) showed that a 10-fold molar excess of curcumin significantly inhibited oral mucosal bioactivation of BP-7,8-diol \((P < 0.016)\). Curcumin
incubation with 25°CYP1B1. Data from our curcumin dose-response studies showed that after a 24-h incubation with 25 μM curcumin, cellular viabilities remained comparable to those of the control cultures (Fig. 1A). For the competitive metabolism studies, curcumin was included at a 5-fold molar excess for the cell studies and at a 10-fold molar excess for the oral mucosa experiments. Curcumin inhibits cellular bioactivation of BP-7,8-diol as measured by HPLC determination of total tetrol formation, expressed as nmol/mg protein (P ≤ 0.028, oral keratinocytes) and fmol/mg protein (P < 0.016, oral mucosa).

A. Cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Cells + 5 μM BP-7,8-diol</th>
<th>Cells + 5 μM BP-7,8-diol + 25 μM curcumin</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC 2095</td>
<td>1.67</td>
<td>0.06</td>
<td>96.1</td>
</tr>
<tr>
<td>SCC 9</td>
<td>3.42</td>
<td>0.55</td>
<td>84.0</td>
</tr>
<tr>
<td>SCC 4</td>
<td>1.10</td>
<td>0.06</td>
<td>94.4</td>
</tr>
<tr>
<td>SCC 25</td>
<td>1.01</td>
<td>0.05</td>
<td>95.0</td>
</tr>
</tbody>
</table>

B. Tissue samples

<table>
<thead>
<tr>
<th>Tissue sample</th>
<th>Tissue + 10 μM BP-7,8-diol</th>
<th>Tissue + 10 μM BP-7,8-diol + 100 μM curcumin</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM 300</td>
<td>643.1</td>
<td>18.7</td>
<td>97.1</td>
</tr>
<tr>
<td>MM 400</td>
<td>534.0</td>
<td>137.7</td>
<td>74.2</td>
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<tr>
<td>MM 700</td>
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<td>75.5</td>
</tr>
</tbody>
</table>

inclusion inhibited bioactivation of BP-7,8-diol in every tissue evaluated. Relative to the SCC cell cultures, oral mucosa showed appreciably lower total tetrol formation (nmol versus fmol).

DISCUSSION

This study evaluated the effects of curcumin on carcinogen-relevant metabolic pathways including expression of phase I and II enzymes and activation of the primary xenobiotic and carcinogen-responsive transcription activating factor, i.e., the AhR-ARNT complex. Our results show that curcumin inclusion initiates AhR nuclear translocation in human oral SCC cells and that curcumin increased expression and function of CYP1A1. Curcumin also inhibited bioactivation of BP-7,8-diol in both oral SCC cells and oral mucosal tissues. Collectively, our data suggest that the chemopreventive effects of curcumin reflect its multiple mechanisms of action that include scavenging of reactive species, nuclear translocation of the AhR, and inhibition of CYP-mediated carcinogen bioactivation.

Our curcumin dose-response studies showed that sustained administration of curcumin concentrations of ≥25 μM resulted in cytotoxicity. These data agree favorably with the curcumin dose-response data of several other investigators who used similar cellular models, including Khamis et al. (6) and Eltair and Virgi (7). Dietary substances are generally regarded as nontoxic. However, during the incubation of DMSO, cellular curcumin uptake was greatly facilitated relative to normal gastrointestinal absorption. Our toxicity data likely reflect a curcumin-mediated increase in CYP1A1 activity that is accompanied by increased mesosomal generation of potentially cytotoxic ROS. Another consideration is the location of CYP1A1, i.e., between the inner and outer mitochondrial membranes (10). A marked increase in ROS generation directly within the mitochondrion could precipitate mitochondrial release of cytochrome c and induction of apoptosis. This latter explanation is consistent with our data showing that curcumin doses of ≥10 μM reduce cell growth.

GSH, the primary intracellular free thiol, fulfills many critical roles including quenching reactive species, maintaining protein-bound thiols in their reduced, active forms, and serving as a cofactor for the phase II enzymes GSTs and GSH peroxidase (17). Our findings, which show that curcumin inclusion increased cellular GSH levels, likely reflect the antioxidant and therefore GSH-sparing properties of curcumin. We also determined that the CYP1A1 and CYP1B1 substrates, ER, also caused a GSH increase. Our data suggest that SCC cells compensate for the CYP-associated increase in ROS via GSH augmentation. These findings are consistent with previous studies conducted by our laboratory that showed similar cellular adaptive increases in GSH synthesis after oxidative stress (18).

In contrast to the findings of Singh et al. (8), our results did not show an increase in GST activity after curcumin inclusion. This discrepancy may reflect the site of cellular origin and the high rate of carcinogen metabolism that occurs within the oral mucosa. Human oral SCC cells possess markedly higher levels of GST activities relative to the human leukemia cell line used by Singh et al. (8) or human cervical keratinocytes (Ref. 19; ~180-fold higher than leukemia cells and ~1.5 × 10^6 greater than cervical keratinocytes, CDNB-based GST assay). Due to high endogenous GSH levels in oral SCC cells, their CDNB-metabolizing GSTs, which include the GSTA1, GSTM1, and GSTP1 isoforms, may already be functioning near maximal capacity and therefore may not be capable of further induction. Also, one would not anticipate that GSTM1 and GSTP1 expression would be up-regulated by an AhR-mediated mechanism.

Consistent with the findings of Ciocino et al. (9), our EMSAs showed that curcumin induced nuclear translocation of the AhR in human SCC cells. These data may reflect the ability of curcumin to directly act as an AhR ligand. Alternatively, curcumin may be metabolized to an AhR ligand or may cause release of endogenous intracellular ligands. We also demonstrated the formation of the transcriptionally active AhR-ARNT complex within curcumin-treated nuclear extracts. Through activation of the xenobiotic response element, curcumin functions as a bifunctional inducer of both phase I and II AhR-responsive carcinogen-metabolizing enzymes (2). Consistent with our findings that curcumin increased ER metabolism, RNA analyses showed that curcumin increased SCC cell expression of CYP1A1 and CYP1B1. Our results also showed that SCC phase II enzyme expression was cell line dependent, which is consistent with the accepted variation in human carcinogen-metabolizing enzymes (1, 13). The highest overall expression levels of phase I and II enzymes were detected in the most aggressive cell line used, SCC 2095. Progressed tumors frequently overexpress cytoprotective enzymes such as GSTs, which partially accounts for their resistance to chemotherapeutics (20).

BP metabolism studies showed approximately 3- and 6-fold differences in tetrol formation among the SCC cell lines and oral mucosal tissues, respectively, which likely reflects the established heterogeneity in human xenobiotic metabolism (1, 13). Our tobacco-associated carcinogen metabolic studies revealed that curcumin significantly inhibited CYP1A1- and/or CYP1B1-mediated BP-7,8-diol bioactivation in both human oral SCC cells and intact oral mucosa. This finding was not donor dependent because bioactivation was suppressed in all cell lines and tissues.

Our data, which show that curcumin increases CYP1A1 activity while concurrently decreasing CYP1A1-mediated BP-7,8-diol bioactivation, may initially appear counterintuitive. Although we did not conduct labeled substrate assays, there are several lines of evidence that suggest curcumin serves as a competitive substrate during CYP1A1 metabolism. First, curcumin is structurally similar to established CYP1A1 substrates such as the PAHs. Secondly, curcumin was present in a 5-fold (cell) and 10-fold (tissue) molar excess during the BP bioactivation studies. We also determined that curcumin pretreatment increased cellular GSH levels. Whereas this finding could reflect GSH sparing, we speculate that it represents a compensatory GSH
increase in response to higher CYP-associated metabolism. This conclusion is supported by our results showing that the established CYP1A1 substrate, ER, also caused GSH increases.

Because CYP1A1 is one of the primary carcinogen-activating enzymes in human oral mucosa (1), the use of curcumin as an oral cavity chemopreventive agent could be clinically significant. Notably, curcumin also suppressed tetrol formation that resulted from Fenton chemistry-generated oxidants in the cell-free, Cu-containing, and Fe-containing base medium. The antioxidant properties of curcumin could therefore provide additional cytoprotection by scavenging reactive species capable of diol activation generated by either transition metal chemistry or related oxidative enzymes such as prostaglandin synthase.

Smoking cessation remains the best route to inhibit tobacco-associated malignancies, which include oral, lung, and renal cancers. Realistically, however, many current smokers are recalcitrant to smoking cessation programs. Our data introduce the possibility of incorporation of naturally occurring agents such as curcumin in cigarette and smokeless tobacco formulations. A complementary application would entail use of curcumin-releasing troches to distribute curcumin throughout the oral cavity. In these functions, the multimodal mechanisms of action of curcumin, including its antioxidant properties and modulation of AhR-responsive enzymes, could significantly reduce intraoral tobacco-associated carcinogen bioactivation and toxicity.

REFERENCES

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