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Green Tea Polyphenol (−)-Epigallocatechin-3-gallate Inhibits Cyclooxygenase-2 Expression in Colon Carcinogenesis

Guang Peng,[1] Dan A. Dixon,[2] Stephanie J. Muga,[1] Theresa J. Smith,[3] and Michael J. Wargovich[1]*

[1]*Department of Pathology and Microbiology, School of Medicine, The University of South Carolina, and South Carolina Cancer Center, Columbia, South Carolina*
[2]*Department of Biological Sciences, The University of South Carolina, and South Carolina Cancer Center, Columbia, South Carolina*
[3]*College of Pharmacy, The University of South Carolina, and South Carolina Cancer Center, Columbia, South Carolina*

Tea, one of the most widely consumed beverages worldwide, has been shown to have anti-cancer activity in various cancers including colon cancer. It has been demonstrated that overexpression of the inducible isoform of cyclooxygenase (COX-2) occurs during colon tumorigenesis and inhibition of COX-2 by non-steroidal anti-inflammatory drugs (NSAIDs) is chemopreventive. To determine whether the anti-cancer effect associated with green tea impacted COX-2 expression levels, human colorectal cancer cell lines HT-29 and HCA-7, were treated with (−)-epigallocatechin-3-gallate (EGCG), the most abundant and effective polyphenol of green tea. EGCG significantly inhibited constitutive COX-2 mRNA and protein overexpression. The inhibitory effects of EGCG on signaling pathways controlling COX-2 expression were examined. We observed that EGCG downregulated the ERK1/2 and Akt pathways in colon cancer cells. The effect of EGCG on COX-2 expression resulted in decreased COX-2 promoter activity via inhibition of nuclear factor κB (NF-κB) activation. EGCG also promoted rapid mRNA decay mediated through the COX-2 3′untranslated region (3′UTR). In conclusion, these data suggest that inhibition of COX-2 is a mechanism for the anti-proliferative effect of green tea and emphasizes the role that dietary factors have as anti-cancer agents.

Key words: EGCG; COX-2; gene expression; NF-κB; MAPKs; colon cancer cells

INTRODUCTION

Colorectal cancer is a leading cause of cancer and cancer-related deaths among both men and women in the United States [1]. Colon carcinogenesis is a multistep process described as a series of tumor suppressor gene inactivation paired with oncogene activation [2]. Considerable experimental evidence demonstrates that dysregulation of cyclooxygenase 2 (*COX-2*) gene expression occurs in the early stage of colon carcinogenesis, resulting in overexpression of COX-2 in approximately 40% of adenomas and 80% of adenocarcinomas [3]. Data from epidemiological and animal models indicate that non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit COX activity, reduce the relative risk of colon cancer and promote tumor regression [4]. Additionally, genetic evidence establishes an association between COX-2 expression and colon cancer. Adenomatous polyposis coli (APC) mutant mice ($Apc^{\Delta 716}$) develop hundreds of intestinal polyps, whereas $Apc^{\Delta 716}$/COX-2 double knockout mice have approximately 90% reduction in tumor burden [5]. While demonstrating that inhibition of COX-2 and associated prostaglandin synthesis can limit the development and progression of colon cancer, these findings indicate the efficacy of COX-2 as a viable target for natural product chemoprevention.

COX-2 is an inducible isoform of COX, which is a key enzyme in the biosynthesis of prostaglandins from arachidonic acid (AA). In normal cells, COX-2 expression is low or not observed, but it can rapidly increase in response to various stimuli (growth factors, cytokines, and tumor promoters). It has been well established that COX-2 expression is regulated at both transcriptional level and posttranscriptional level in colon cancer [6–8]. Examination of the *COX-2* gene has identified a number of transcription factor

Abbreviations: EGCG, (−)-epigallocatechin-3-gallate; COX-2, cyclooxygenase-2; NF-κB, nuclear factor κB; NSAIDs, non-steroidal anti-inflammatory drugs; 3′UTR, 3′ untranslated region; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3 kinase; ERK, extracellular signal regulated kinase; RT, room temperature; CMV-β-Gal, β-Galactosidase plasmid; CMV, cytomegalovirus; GAPDH, glyceraldehyde 3 phosphate dehydrogenase.

*Correspondence to: Wargovich, South Carolina Cancer Center, 14 Richland Medical Park Drive, Suite 500, Columbia, SC 29203.

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