Resveratrol Inhibits Cyclooxygenase-2 Transcription in Human Mammary Epithelial Cells

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ABSTRACT: A large body of evidence suggests that inhibiting cyclooxygenase-2 (COX-2), the inducible form of COX, will be an important strategy for preventing cancer. In this study, we investigated whether resveratrol, a chemopreventive agent found in grapes, could suppress phorbol ester (PMA)-mediated induction of COX-2 in human mammary and oral epithelial cells. Treatment of cells with PMA induced COX-2 mRNA, COX-2 protein, and prostaglandin synthesis. These effects were inhibited by resveratrol. Nuclear runoffs revealed increased rates of COX-2 transcription after treatment with PMA, an effect that was inhibited by resveratrol. Resveratrol inhibited PMA-mediated activation of protein kinase C and the induction of COX-2 promoter activity by c-Jun. Phorbol ester-mediated induction of AP-1 activity was blocked by resveratrol. These data are likely to be important for understanding the anticancer and anti-inflammatory properties of resveratrol.

INTRODUCTION

Cyclooxygenases (COX) catalyze the synthesis of prostaglandins (PGs) from arachidonic acid. There are two isoforms of COX, designated COX-1 and COX-2. COX-1 is expressed constitutively in most tissues and appears to be responsible for housekeeping functions.1 By contrast, COX-2 is not detectable in most normal tissues but is induced by oncogenes, growth factors, carcinogens, and tumor promoters.2-4

Multiple lines of evidence support the idea that COX-2 is important in carcinogenesis. Thus, COX-2 is upregulated in transformed cells2,5,6 and in malignant tis-