ANNALS of THE NEW YORK ACADEMY OF SCIENCES

Resveratrol Inhibits Cyclooxygenase-2 Transcription in Human Mammary Epithelial Cells

KOTHA SUBBARAMAIAH,[a,b,c,f] PEDRO MICHALUART,[d] WEN JING CHUNG,[a] TADASHI TANABE,[e] NITIN TELANG,[c] AND ANDREW J. DANNENBERG[a,b,c]

Departments of [a]Medicine and [b]Surgery, the New York Presbyterian Hospital-Cornell, New York, New York 10021, USA

[c]Anne Fisher Nutrition Center at Strang Cancer Prevention Center, New York, New York 10021, USA

[d]Head and Neck Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA

[e]Department of Pharmacology, National Cardiovascular Center Research Institute, Osaka, Japan

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 cells[2,5,6] and in malignant tis-

[f]Address for communication: New York Presbyterian Hospital-Cornell, Division of Gastroenterology, Room F-201, 1300 York Avenue, New York, NY 10021. Voice: 212-746-4402; fax: 212-746-4885.

e-mail: ksubba@mail.med.cornell.edu