Redox-Sensitive Transcription Factors as Prime Targets for Chemoprevention with Anti-Inflammatory and Antioxidative Phytochemicals1-3

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ABSTRACT Oxidative stress has been implicated in various pathological conditions including cancer. However, the human body has an intrinsic ability to fight against oxidative stress. A wide array of phase 2 detoxifying or antioxidant enzymes constitutes a fundamental cellular defense system against oxidative and electrophilic insults. Transcriptional activation of genes encoding detoxifying and antioxidant enzymes by NF-E2 related factor 2 (Nrf2), a member of the cap’n’collar family of basic leucine zipper transcription factors, may protect cells and tissues from oxidative damage. Many chemopreventive and chemoprotective phytochemicals have been found to enhance cellular antioxidant capacity through activation of this particular transcription factor, thereby blocking initiation of carcinogenesis. A new horizon in chemoprevention research is the recent discovery of molecular links between inflammation and cancer. Components of the cell signaling pathways, especially those that converge on redox-sensitive transcription factors, including nuclear factor-kappaB (NF-κB) and activator protein 1 (AP-1) involved in mediating inflammatory response, have been implicated in carcinogenesis. A wide variety of chemopreventive and chemoprotective agents can alter or correct undesired cellular functions caused by abnormal proinflammatory signal transmission mediated by inappropriately activated NF-κB and AP-1. The modulation of cellular signaling by anti-inflammatory phytochemicals hence provides a rational and pragmatic strategy for molecular target–based chemoprevention. J. Nutr. 135: 2993S–3001S, 2005.

KEY WORDS: ● chemoprevention ● oxidative stress ● inflammation ● Nrf2 ● NF-κB ● AP-1 ● phytochemicals

Oxidative stress and inflammation contribute to multistage carcinogenesis by several distinct mechanisms, including direct damage to genomic DNA, alteration of intracellular signal transduction leading to abnormal cellular growth, and forcing damaged or initiated cells to undergo promotion and progression. Cells are endowed with an antioxidative defense system consisting of a variety of enzymatic and nonenzymatic antioxidants to combat oxidative insults, thereby protecting cellular macromolecules from detrimental effects of exogenous or endogenous reactive oxygen species (ROS).5 Cells and tissues are also equipped with a panel of detoxifying enzymes responsible for metabolic inactivation and subsequent elimination of carcinogens (1,2). Exposure of cells and tissues to oxidative stimuli or electrophilic carcinogens, therefore, forces the cell to turn on its antioxidant-detoxification arsenal as the first line of defense. Transcriptional regulation of antioxidant or detoxifying genes is predominantly mediated by a redox-sensitive transcription factor NF-E2 related factor-2 (Nrf2). A variety of edible phytochemicals are able to activate Nrf2 signaling thereby upregulating a set of enzymes including NADP(H):quinone oxidoreductase-1 (NQO1), superoxide dismutase (SOD), glutathione S-transferase (GST), hemeoxygenase-1 (HO-1), and γ-glutamyl cysteine ligase (GCL) (1,3). On the other hand, persistently elevated ROS activate other redox-sensitive transcription factors, such as nuclear factor-kappaB (NF-κB) and activator protein 1 (AP-1).

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5 Abbreviations used: ARE, antioxidant response element; CAPE, caffeic acid phenethyl ester; COX-2, cyclooxygenase-2; DMBa, dimethylbenzo[a]anthracene; EGCG, epigallocatechin gallate; EpRE, electrophile response element; GCL, γ-glutamyl cysteine ligase; GST, glutathione S-transferase; HO-1, hemeoxygenase-1; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; Keap1, Kelch-like ECH associated protein 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappaB; NO, nitric oxide; NQO1, NADPH:quinone oxidoreductase-1; Nrf-2, NF-E2 related factor-2; PG, prostaglandin; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha; TPA, 12-O-tetradecanoyl-phorbol-13 acetate; UGT, UDP-glucuronosyltransferase.

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Oxidative stress and inflammation: a deadly duo in carcinogenesis

ROS, such as superoxide radical anion, hydroperoxyl radical, hydrogen peroxide, and hydroxyl radical, are constantly generated in cells as unwanted by-products of aerobic metabolism. Under physiological conditions, a low level of ROS is scavenged effectively by the cellular antioxidant defense system. However, an imbalance between the generation of ROS and cellular antioxidant capacity leads to a state of oxidative stress that contributes to various pathological conditions including cancer (7–9). Although certain stimuli such as growth factors, hormones, and neurotransmitters use ROS as a second messenger to execute normal physiological response (10,11), an excessive generation of ROS by external stimuli including redox chemicals, ultraviolet and ionizing radiation, bacterial or viral infection, has a deleterious effect on human health. Oxidative stress contributes to tumorigenesis either by a direct mechanism involving damage to DNA or indirectly by modulating cellular signal transduction pathways (7,12,13).

Substantial evidence supports the protective role of antioxidant and detoxification enzymes in chemically induced carcinogenesis (14–16). A higher degree of oxidative DNA damage and a dramatic increase in the tumor incidence were noted in mice lacking MnSOD (17). In addition, mouse epidermal JB6 cells transfected with MnSOD exhibited a slower growth rate and a reduced rate of colony formation in soft agar (18). The overexpression of MnSOD, a representative antioxidant enzyme, suppressed papilloma formation in a 2-stage mouse skin carcinogenesis model (16). Mice lacking CuZnSOD developed more hepatic nodules, either as hyperplasia or hepatocellular carcinoma, than the wild type counterpart (15). Similarly, the deletion of murine GST-P gene cluster led to increased papillomagenesis in GST-P1/P2−/− mice in a chemically induced multistage skin carcinogenesis model (14).

The inhibition of ROS generation has been paralleled by a decrease in rat foot pad inflammation induced by Freund's complete adjuvant (19), suggesting that accumulation of ROS in vivo leads to inflammation. It has long been suspected that inflammation is causally linked to carcinogenesis. According to an estimate, ~15% of all cancers are somehow linked to inflammation and about 5% of all human colorectal cancer is associated with ulcerative colitis (20). Growing evidence indicates that chronic inflammation may cause cancers of different organs including stomach, colon, breast, skin, prostate, and pancreas (21–24). A distinct set of proinflammatory mediators, such as cytokines, chemokines, prostaglandins (PGs), nitric oxide (NO), and leukotrienes, promote neoplastic trans-

Roles of redox-regulated transcription factors in the causation and prevention of oxidative stress- and inflammation-associated cancer

Recently, attention has been focused on intracellular signal transduction pathways regulating cell proliferation and differentiation as the molecular basis of carcinogenesis. Complo-

FIGURE 1 Role of oxidative stress and inflammation in carcinogenesis.
nants of intracellular signaling networks include the family of proline-directed serine and threonine kinases named mitogen-activated protein kinases (MAPKs); protein kinase C (PKC); phosphoinositide 3-kinase (PI3K); glycogen synthase kinase, protein kinase B; and tyrosine kinases (e.g., growth factor receptor and soluble Src kinase). Most of these upstream kinases are aberrantly turned on by diverse stimuli provoking oxidative and proinflammatory stress and often amplified via activation of a battery of redox-sensitive transcription factors including Nrf2 and NF-κB/AP-1.

Nrf2. A large variety of xenobiotic metabolizing enzymes, which catalyze phase I and phase II metabolic reactions, are involved in carcinogen activation and deactivation. The balance between carcinogen activating enzymes and detoxifying enzymes determines the ultimate risk of chemically induced carcinogenesis (35). An overall shift toward carcinogen inactivation or elimination by a panel of detoxifying and antioxidant enzymes, such as GST, NQO1, UDP-glucuronosyltransferase (UGT), microsomal epoxide hydrolase, GCL, glutathione synthetase, γ-glutamyl transpeptidase, and HO-1, protects cellular components from oncogenic insults. The induction of these enzymes facilitates inactivation and subsequent elimination of electrophilic and oxidative carcinogens (1,3).

Genomic analysis has revealed the presence of a cis-acting element known as antioxidant response element (ARE) or electrophile response element (EpRE) [5'-((G/A)TGA(G/C)n-GC(G/A)-3')] located in the promoter region of many of the genes encoding antioxidant and detoxifying enzymes. Nrf2, a member of the cap’n’collar family of bZIP transcription factors, can act as a master regulator of ARE-driven transactivation of antioxidant genes (36). A distinct set of Nrf2-regulated proteins detoxify xenobiotics, reduce oxidized proteins, maintain cellular reducing equivalents, disrupt redox cycling reactions, and counteract the noxious effects of ROS (13,37).

Nrf2 is sequestered in the cytoplasm as an inactive complex with its cytosolic repressor Kelch-like ECH associated protein 1 (Keap1). Dissociation of Nrf2 from the inhibitory protein Keap1 is a prerequisite for nuclear translocation and subsequent DNA binding of Nrf2. After forming a heterodimer with small Maf protein inside the nucleus, the active Nrf2 binds to cis-acting ARE or EpRE, also alternatively known as Maf recognition element (38) (Fig. 2). Besides the dissociation of the Nrf2-Keap1 complex that is facilitated by upstream kinase-mediated signals, covalent modification of multiple cysteine residues on Keap1 by electrophiles or inducers of detoxifying enzymes is also considered to release Nrf2 from the Keap1 repression (39). Multiple mechanisms of Nrf2 activation by signals mediated via one or more of the upstream kinases, including MAPKs, PI3K, PKC, and Akt, were recently reviewed (1,30).

The genetic ablation of the Nrf2 results in severe airway inflammation (41) and development of emphysema in mice (41). The Nrf2-null mice failed to induce many of the genes responsible for carcinogen detoxification and protection against oxidative stress (3). Moreover, the deletion of the Nrf2 gene in mice resulted in a decrease in the basal expression level of genes, including those for epoxide hydrolase, GCL, GST, HO-1, NQO1, and UGT (42–44). The Nrf2-null mice also have defects in detoxifying carcinogens such as aflatoxin B1 (40). Fibroblasts from Nrf2-null mice express only about 15% as much GCL mRNA as wild type cells (45). The significance of Nrf2 activation as a measure of chemoprevention was evident from a remarkably higher incidence of benzo[a]pyrene-induced gastric neoplasia in Nrf2-deficient mice, which were less responsive to the phase II enzyme inducer oltipraz (46). Therefore, targeted activation of Nrf2 is considered to be a rational approach for chemoprevention, especially at the initiation stage of carcinogenesis.

NF-κB. Since the discovery of leukocytes in neoplastic tissues by Rudlof Virchow in 1863, inflammation and cancer are thought to be closely associated. Virchow’s early observation is now more evident from multiple lines of studies suggesting an inflammatory microenvironment of malignant tissues. Several recent studies have identified NF-κB as a critical component to bridge inflammation and cancer (47–49). The heterodimeric protein NF-κB is a ubiquitous redox-regulated transcription factor that remains sequestered in the cytoplasm as an inactive complex with its inhibitory counterpart IκB. Exposure to oxidative or inflammatory stimuli, such as TNF-α, IL-1, phorbol ester, ultraviolet radiation or microbial infection, leads to phosphorylation and subsequent proteasomal degradation of IκBα, thereby releasing free NF-κB dimers for translocation to the nucleus (50,51), as illustrated in Figure 3.

Excessive oxidative or inflammatory stress may activate NF-κB by distinct mechanisms in a cell type- or stimuli-specific manner (4,50,52). Although it is generally accepted that degradation of IκBα is a pivotal step in NF-κB activation,
Oxidative and Inflammatory Stimuli (TNF-α, IL-1, phorbol ester, LPS, UV, etc.)

FIGURE 3

NF-κB- and AP-1-mediated signaling pathway. Exposure of cells to oxidative and proinflammatory stimuli causes activation of a series of upstream kinases such as MAPKs, IKK, PKC, and PI3K, which then activate NF-κB by phosphorylation-mediated degradation of IκBα. Activated upstream kinases may also phosphorylate p65, the active subunit of NF-κB. Free activated NF-κB, in the form of p65-p50 heterodimer, translocates to the nucleus, where it binds to κB sequences located in the promoter of a target gene. Alternatively, MAPKs can activate AP-1 components, c-Jun and c-Fos, leading to the binding of AP-1 (c-Jun-c-Fos heterodimer) to the cyclic AMP response element (CRE) sequences of the target gene promoter.

NF-κB and AP-1 are critical transcription factors in inflammation and cancer. NF-κB activation is mediated by the binding of upstream kinases to NF-κB and subsequent degradation of IκBα. AP-1 is activated by oxidative and proinflammatory stimuli such as TNF-α, IL-1, and phorbol ester. The activation of NF-κB and AP-1 leads to the expression of proinflammatory and proapoptotic genes, respectively. The diagram illustrates the regulatory interactions between NF-κB and AP-1 and their roles in inflammation and cancer.

A wide variety of chemopreventive phytochemicals prevent carcinogenesis by enhancing cellular antioxidant and detoxification enzymes via activation of Nrf2 or by suppressing induction or overexpression of proinflammatory and growth promoting gene expression driven by NF-κB or AP-1. Phytochemicals capable of activating Nrf2 are often found in fruits and vegetables, and they play a crucial role in chemoprevention.
inhibit the tumor initiation process by ameliorating oxidative DNA damage, promoting carcinogen detoxification, or both, thereby protecting important cellular macromolecules from damage, are known as blocking agents. Phytochemicals that can alter abnormal cellular signaling mediated via NF-κB and or AP-1 prevent tumor promotion or progression and are known as suppressing agents. The mechanistic basis of chemoprevention by representative antioxidative and anti-inflammatory phytochemicals that target aforementioned transcription factors is presented in subsequent sections.

**Curcumin.** Curcumin, the yellow pigment isolated from the rhizomes of *Curcuma longa* Linn (Zingiberaceae), inhibits chemically induced carcinogenesis in multiple organ sites, including forestomach, duodenum, colon, and skin, in various experimental animal models (81–86). The compound strongly inhibited TPA-induced inflammation, hyperplasia, proliferation, activation and expression of ornithine decarboxylase, generation of ROS, and oxidative DNA damage in mouse skin (83,87) and reduced anchorage-independent colony formation in mouse epidermal JB6 cells (88).

As a mechanism of anti-initiation, curcumin disrupted the Nrf2–Keap1 complex, leading to increased Nrf2 binding to ARE and subsequent increase in the expression and activity of HO-1 in cultured porcine renal epithelial proximal tubule (LLC-PK1) and rat kidney epithelial (NRK-52E) cells (89). Curcumin also increased the nuclear translocation of Nrf2; its ARE-DNA binding activity; and expression of both protein and the mRNA transcript of another phase II enzyme, GCL, in immortalized human bronchial epithelial (HBE1) cells (90). Curcumin contains 2 α,β unsaturated carbonyl moieties, each of which by acting as a Michael reaction acceptor may covalently modify cysteine thiols of Keap1, thereby releasing Nrf2 for nuclear translocation.

Molecular mechanisms underlying the anti-tumor promoting effect of curcumin have largely been attributed to its inhibitory effect on tumor promoter-induced activation of NF-κB and AP-1. Curcumin suppressed the expression of c-Jun and c-Fos in CD-1 mouse skin after treatment with TPA (88). Previous studies from this laboratory demonstrated that curcumin inhibited activation of AP-1 and NF-κB in TPA-stimulated mouse skin in vivo as well as in cultured HL-60 cells (68,91). Curcumin inhibited the expression of COX-2, which is predominantly regulated by NF-κB and AP-1, and the generation of PGE2 in TPA-stimulated mouse skin (68) and human pancreatic cancer cells (92). The nuclear translocation of p65 was suppressed by curcumin via blockade of phosphorylation-dependent degradation of IκBα (68,93). Similarly, inhibition of IκBα degradation via downregulation of NF-κB–inducing kinase and IKK by curcumin contributes to its blockade of TNF-α–induced COX-2 gene transcription and NF-κB activation in human colonic epithelial cells (94). Moreover, curcumin targeted IKK in *Helicobacter pylori*-treated gastric epithelial (95), multiple myeloma (96), and pancreatic cancer cells (92) to exert chemopreventive activities.

**Resveratrol.** Resveratrol, a phytoalexin present in grapes and other plant species, exerts antioxidative, anti-inflammatory, and chemopreventive activities by modulating diverse events in cellular signaling. The compound was reported to interfere with the initiation, promotion, and progression stages of carcinogenesis (97). Subsequent studies demonstrated that resveratrol prevented chemically induced tumorigenesis in various experimental models (98–100).

The inhibition of tumor initiation by resveratrol has been largely attributed to its suppressive effect on cytochrome p450 1A1/1A2 in murine hepatoma (Hepa1c1c7) cells (101), mammary epithelial (MCF-10A) cells treated with 2,3,7,8, tetrachlorodibenzo-p-dioxin (102), human breast cancer MCF-7 cells treated with dimethylbenz[a]anthracene (DMBA) (103), and human hepatoma (HepG2) cells stimulated with benz[a]pyrene (103). Resveratrol induced NQO, an Nrf2-regulated detoxifying enzyme, in Hepa1c1c7 cells (101). In addition, several recent studies demonstrated that the compound can induce HO-1 expression and activity in human aortic smooth muscle (38) and rat pheochromocytoma (PC12) cells (104) via activation of NF-κB and Nrf2, respectively.

The inhibition of cytokine release and proinflammatory gene expression and the downregulation of intracellular signal transducing enzymes and transcription factors that regulate expression of proinflammatory genes are key molecular mechanisms underlying anti-inflammatory and anti-tumor promoting activities of resveratrol (105). The induction of proinflammatory gene products such as COX-2 and iNOS, which have been implicated in tumor promotion (9,34), by diverse stimuli including bacterial lipopolysacharide, TPA, and interferon-γ was attenuated by resveratrol (105,106). Resveratrol suppressed activation of NF-κB and AP-1 in cell-, tissue-, and stimuli-specific fashions (105). The compound inhibited TPA-stimulated activation of AP-1 in mouse skin in vivo (105) and U937 cells (107) in culture. Moreover, resveratrol ablated TPA-induced transcriptional activity of AP-1 in human mammary epithelial cells (108,109). Resveratrol also suppressed activation of NF-κB in acute myeloid leukemia (OCI-M2) cells (110) and mouse epidermal JB6 cells stimulated with IL-1β and Cr (VI) (111), respectively. Our recent study also revealed that topical application of resveratrol attenuated NF-κB activation by blocking both IKKβ activity in TPA-treated mouse skin (J. K. Kundu and Y.-J. Surh, unpublished observation, 2005). Resveratrol attenuated TNF-α–induced activation of NF-κB in U937 cells by suppressing phosphorylation and nuclear translocation of p65 without affecting IκBα degradation (112). In normal human epidermal keratinocytes, resveratrol-inhibited UVB-induced activation of NF-κB by blocking the activation of IKKα and the phosphorylation and degradation of IκBα (113).

**Epigallocatechin gallate.** Green tea is one of the extensively investigated dietary sources of chemopreventive agents. The antioxidant phenolic compound epigallocatechin gallate (EGCC) is the major chemopreventive agent present in green tea (114). EGCC protected against UV-induced depletion of glutathione and glutathione peroxidase activity in human skin (115). The compound also restored detoxification enzymes GST, glutathione peroxidase, SOD, and catalase that were depleted as a result of DMBA treatment in mouse skin in vivo (116) and induced the ARE luciferase activity in human hepatoma HepG2 cells (117).

As an antimutagen promoting agent, EGCC suppressed malignant transformation in TPA-stimulated mouse epidermal JB6 cells through inactivation of AP-1 (118,119) or NF-κB (120). EGCC also inhibited AP-1 activity in the H-ras-transformed epidermal JB6 cells (121) and in the epidermis of transgenic mice bearing an AP-1–driven luciferase reporter gene (122). In contrast, oral administration of EGCC failed to affect TPA-induced AP-1 DNA binding (123) but inhibited activation of NF-κB by blocking degradation of IκBα in mouse skin (J. K. Kundu and Y.-J. Surh, unpublished observation, 2005).

The inactivation of NF-κB by EGCC was reported to be mediated via inhibition of IKK activity, leading to blockade of phosphorylation-dependent degradation of IκBα and subsequent decrease in nuclear localization of p65 protein (124,125). However, the modulation of NF-κB transcriptional activity by EGCC does not solely depend on IκBα degradation and subsequent release of NF-κB subunits because EGCC...
inhibited lipopolysaccharide-induced phosphorylation of IkBα without affecting NF-κB luciferase activity in human colon cancer (HT-29) cells (126). Besides interference with the IKK-IκB signaling, suppression of signal transduction mediated by MAPKs (127–129) and PI3K-Akt (130) by EGCG has been implicated in the inactivation of NF-κB and suppression of COX-2 induction.

**Caffeic acid phenethyl ester.** Caffeic acid phenethyl ester (CAPE) is the major chemopreventive principle of honey bee propolis. Treatment of rat renal epithelial cells with CAPE resulted in the increase in nuclear translocation and ARE binding of Nrf2 as well as induction of HO-1 activity (89). CAPE given during promotion of experimentally induced rat hepatocarcinogenesis suppressed the nuclear localization of p65 independently of IkBα degradation (131). Similarly, Marquez et al. (132) demonstrated that CAPE specifically inhibited both gene transcription and synthesis of IL-1β in stimulated T cells by suppressing the NF-κB-dependent transcriptional activity without affecting IkBα degradation. The compound significantly decreased the lipopolysaccharide-induced NF-κB transcriptional activity in RAW 264.7 cells (133) and attenuated NO production and iNOS expression (134,135). CAPE suppressed TPA-induced MMP-9 expression by inhibiting NF-κB but not AP-1 in HepG2 cells (136).

**Isothiocyanates.** Isothiocyanates are major chemopreventive components present in broccoli sprouts and mature broccoli. Sulforaphane [1-isothiocyanato-(4R,S)-(methylsulfinyl)butane] and its analogues inhibited chemically induced carcinogenesis in mouse skin (137) and lung (138,139). Isothiocyanates are potent inducers of ARE-regulated detoxifying enzymes (140–142). It has been reported that sulforaphane as well as phenethyl isothiocyanate regulate the activation of MAPKs and Nrf2 and the induction of phase II enzymes (143,144). Sulforaphane induced Nrf2 nuclear translocation, thereby enhancing the expression and activity of UGT in human colon cancer (Caco-2) cells (145). Moreover, sulforaphane induced Nrf2 protein expression and ARE-mediated transcriptional activation of Nrf2 resulting in HO-1 expression, partly by blocking Keap1-mediated degradation of Nrf2 (146). An Nrf2-dependent induction of GSTA1/2, GSTA3, NQO-1, and catalytic subunit of GCL by sulforaphane was recently reported (147). Sulforaphane also elevated the levels of glutathione and NQO in retinal pigment cells following an Nrf2-dependent mechanism (148). A direct covalent binding of sulforaphane with cysteine residues on Keap1 leads to thiol modification, thereby activating Nrf2 (39). Gene microarray analysis revealed that sulforaphane upregulated the expression of detoxifying enzymes including NQO1, GST, and GCL in human colon cancer (Caco-2) cells (145). Moreover, sulforaphane induced Nrf2 nuclear translocation, thereby enhancing the expression of glutathione-S-transferase and the antioxidant capacity of human colon cancer (Caco-2) cells (145). Additionally, sulforaphane has been shown to inhibit DNA binding of NF-κB and activation of its target genes in human prostate cancer (PC3) cells (151).

**Conclusion**

Although there is no magic bullet to completely cure cancer at this moment, we are now aware that many forms of cancers are at least avoidable or preventable. Remarkable progress in unfolding cancer biology in recent years led us to find several ways to intervene in carcinogenic process. Because oxidative and inflammatory stress contributes to malignant transformation, substances with antioxidative and anti-inflammatory properties would be good candidates for preventing most human malignancies. Some chemopreventive phytochemicals have been shown to modulate such redox-sensitive transcription factors as Nrf2, NF-κB, and AP-1, thereby fortifying cellular antioxidant capacity or suppressing inflammatory response. The activation of Nrf2 leading to the upregulation of cellular detoxifying and antioxidant enzymes is an effective way to block oxidative DNA damage and related events. On the other hand, targeted suppression of inappropriately activated NF-κB or AP-1 can ameliorate proinflammatory stress, thereby interfering with the tumor promotion or progression. Although a wide variety of phytochemicals has been identified as chemopreventive agents, studies directed to identify precise molecular targets are still limited. The modulation of aforementioned transcription factors by antioxidative and anti-inflammatory phytochemicals would provide ample opportunities for chemoprevention based on molecular targeting.

**LITERATURE CITED**

58. Whittman AJ, Davis RJ. Transcription factor AP-1 regulation by mito-


