ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 1 & 2, 2006

Forum Review

Nrf2: A Potential Molecular Target for Cancer Chemoprevention by Natural Compounds

WOO-SIK JEONG[1], MIRA JUN,[2] and AH-NG TONY KONG[3]

ABSTRACT

One of the most prominent strategies of cancer chemoprevention might be protecting cells or tissues against various carcinogens and carcinogenic metabolites derived from exogenous or endogenous sources. This protection could be achieved through the induction of phase 2 detoxifying enzymes and antioxidant enzymes such as glutathione S-transferase, NAD(P)H quinone oxidoreductase 1, and heme oxygenase-1, a process that is mediated mainly by the antioxidant response elements (ARE) within the promoter regions of these genes. Nuclear factor-erythroid 2-related factor 2 (Nrf2), a member of the Cap 'n' collar (CNC) family of basic region-leucine zipper transcription factors, plays a key role in ARE-mediated gene expression. Under normal condition, Nrf2 is sequestered in the cytoplasm by an actin-binding protein, Kelch-like ECH associating protein 1 (Keap1), and upon exposure of cells to inducers such as oxidative stress and certain chemopreventive agents, Nrf2 dissociates from Keap1, translocates to the nucleus, binds to AREs, and transactivates phase 2 detoxifying and antioxidant genes. Several upstream signaling pathways including mitogen-activated protein kinases, protein kinase C, phosphatidylinositol 3-kinase, and transmembrane kinase are implicated in the regulation of Nrf2/ARE activity. Furthermore, many natural chemopreventive agents are known to induce Nrf2/ARE-dependent gene expression, also in part by regulating the turnover of the Nrf2 protein itself. This review discusses our current understanding of the Nrf2/ARE pathway as a potential molecular target for cancer chemoprevention, as well as the feasibility of screening natural compounds for activation of this pathway and as potential cancer preventive agents for human use. *Antioxid. Redox Signal.* 8: 99–106.

INTRODUCTION

Cancer is a major public health problem in developed countries and causes one in four deaths in the United States (21). Although significant progress has been made in understanding the molecular mechanisms of carcinogenesis in recent years, research on effective strategies to prevent or inhibit the carcinogenic process lag behind. Carcinogenesis is a multiple-step process, typically classified into three stages including initiation, promotion, and progression (41). These carcinogenic processes can be intervened by various natural and synthetic chemicals, so-called chemopreventive agents. Chemoprevention has been defined as a cancer-preventive approach that utilizes natural or synthetic pharmacological agents to impede, arrest, or reverse carcinogenesis at its early stages (50). Phytochemicals from foods and edible plants have gained much attention as potential chemopreventive agents due to their relatively low toxicity, low cost, and easy availability, as well as their general implications as health foods (23). One of the most prominent strategies of cancer chemoprevention, therefore, might be the use of dietary chemopreventive agents for protecting cells and tissues against various carcinogens and

[1]Food Science Institute, School of Food & Life Science, College of Biomedical Science & Engineering, Inje University, South Korea.
[2]Bioanalytical/Preclinical Department, Celgene Corporation, Warren, New Jersey.
[3]Department of Pharmaceutics, Ernest-Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey.

carcinogenic metabolites that could be derived from exogenous or endogenous sources. This may be achievable through the induction of phase 2 detoxifying and antioxidant enzymes such as glutathione *S*-transferase (GST), NAD(P)H quinone oxidoreductase 1 (NQO1), and heme oxygenase-1 (HO-1), a process mediated at least in part by the antioxidant response element (ARE) in the promoter region of these genes (32).

Nuclear factor-erythroid 2-related factor 2 (Nrf2), a member of the Cap 'n' collar (CNC) family of basic region-leucine zipper (bZIP) proteins, plays a key role in ARE-dependent gene expression and, therefore, has been of great interest as a potential molecular target for cancer prevention. Many natural antioxidants and potential chemopreventive agents including isothiocyanates, diallyl sulfides, indoles, terpenes, and phenolic compounds such as tea catechins and curcuminoids, increase Nrf2 protein levels by inhibiting its turnover and induce ARE-mediated gene expression (2, 4, 21, 28, 41, 56, 62, 63). This review discusses our current understanding of the Nrf2/ARE pathway as a potential molecular target for cancer chemoprevention and the feasibility of utilizing natural compounds that activate this pathway as potential cancer preventive agents for human use.

ROLE OF PHASE 2 DETOXIFYING AND ANTIOXIDANT ENZYMES AND Nrf2 IN CHEMOPREVENTION

Wattenberg originally introduced the classification of chemopreventive agents into two major categories, blocking agents and suppressing agents, based on their potential targeting of the carcinogenesis stages (59). Blocking agents inhibit early mutagenic events—those caused by endogenous or exogenous carcinogens in the initiation stage of carcinogenesis—by inducing detoxification of carcinogens or thwarting their metabolic activation. On the other hand, suppressing agents interfere with the stages of promotion and progression whereby the mutated cells transform into malignant tumor cells. In order to prevent cancer development, protecting cells from initiation of the carcinogenesis process would be a logical strategy.

Induction of phase 2 detoxifying and antioxidant enzymes has been suggested as an effective and sufficient blocking strategy to protect cells tissues from the toxic and neoplastic effects of many carcinogens (52). Besides GST, NQO1, and HO-1, this group of enzymes include aldehyde reductase (AR), glutathione reductase (GR), epoxide hydrolase (EH), UDP-glucuronosyltransferase (UGT), and γ-glutamylcysteine synthetase (γ-GCS) (4). These enzymes protect cells against toxic reactive species (and potential carcinogens) through a variety of reactions including 1) conversion to less reactive and toxic materials by conjugation with endogenous substrates such as glutathione, glucuronide, or sulfate, leading to an increase in their solubility and excretion; and 2) augmentation of cellular antioxidant capacity by generation of endogenous antioxidant molecules such as GSH and bilirubin (52).

Induction of these antioxidant enzymes is mediated primarily by the antioxidant or electrophile response elements (ARE/EpRE), which are found in the 5'-flanking region of many of the phase 2 and antioxidant genes (1, 13, 47). Nrf2 is known to play a key role in ARE-mediated gene expression. Increased levels of Nrf2 are reported to up-regulate gene expression induced by various natural antioxidants and chemopreventive agents such as isothiocyanates, diallyl sulfides, indoles, terpenes, and phenolic compounds such as tea catechins and curcuminoids (2, 4, 31, 38, 56, 62).

The critical role of Nrf2 in the expression of phase 2 and antioxidant genes has been further confirmed from studies with *nrf2*-disrupted mice. Compared to wild-type mice, *nrf2*-disrupted mice exhibit reduced levels of antioxidant enzymes and are more susceptible to carcinogens (12, 17, 46). Nrf2, therefore, has become a key molecular target in the field of chemoprevention.

REGULATION OF Nrf2/ARE SIGNALING PATHWAYS

Extensive studies in recent years have provided more insights into the regulatory mechanisms involved in Nrf2/ARE signaling pathways. These include direct regulation of Nrf2, protein abundance, as well as indirect or upstream signal transduction pathways leading to activation of the Nrf2/ARE pathway (Fig. 1). The cytoskeletal actin-binding protein Keap1 (Kelch-like ECH-associated protein 1; also referred to as INrf2, inhibitor of Nrf2) has been recently identified as a key regulator of Nrf2 activity (10, 18). Keap1 is responsible for cytoplasmic-nuclear shuttling and proteasomal degradation of Nrf2 (19, 39, 63). In the absence of Keap1, Nrf2 constitutively accumulates in the nucleus and stimulates transcription of cytoprotective genes. Furthermore, the phenotypic deficiencies observed in *keap1*$^{-/-}$ mice is reversed in Keap1/Nrf2 compound mutants, suggesting that Keap1 acts as an upstream regulator of Nrf2 in response to oxidative and xenobiotic stress (58).

Keap1 is a cysteine-rich protein and some of the 27 cysteine residues in Keap1 are postulated to play a sensory role in detecting oxidants and xenobiotics (43). In addition, certain cysteine residues (C257, C273, C288, and C297) reportedly interact with the N-terminal Neh2 domain of Nrf2 (29). Phase 2 enzyme inducers such as sulforaphane disrupt the cytoplasmic Keap1•Nrf2 complex through thiol modification of cysteine residues in Keap1, thereby releasing Nrf2 and permitting its translocation to the nucleus where it transcriptionally activates ARE-dependent genes (11). Mutations of both C273 and C288 abolish the repressive effect of Keap1 on Nrf2, suggesting a critical role of these two cysteine residues in the repression of Nrf2 (57).

Another important role of Keap1 in the Nrf2/ARE signaling pathway is its regulatory properties on the degradation of Nrf2. Under normal conditions, the half-life of Nrf2 in mammalian cells is about 15 to 45 min, depending on cell type, and this turnover is mediated primarily by the ubiquitin-26S proteasome pathway (22, 44, 51). Upon treatment with certain chemopreventive agents such as sulforaphane and electrophiles or oxidizing agents such as diethylmaleate (DEM) and cadmium, the degradation of Nrf2 appears to be delayed and thereby its stability increases(22, 39, 51). Recent studies indicate that Keap1 is a Cul3-based E3 ligase adaptor protein that target Nrf2 for ubiquitination and proteosome-dependent degra-

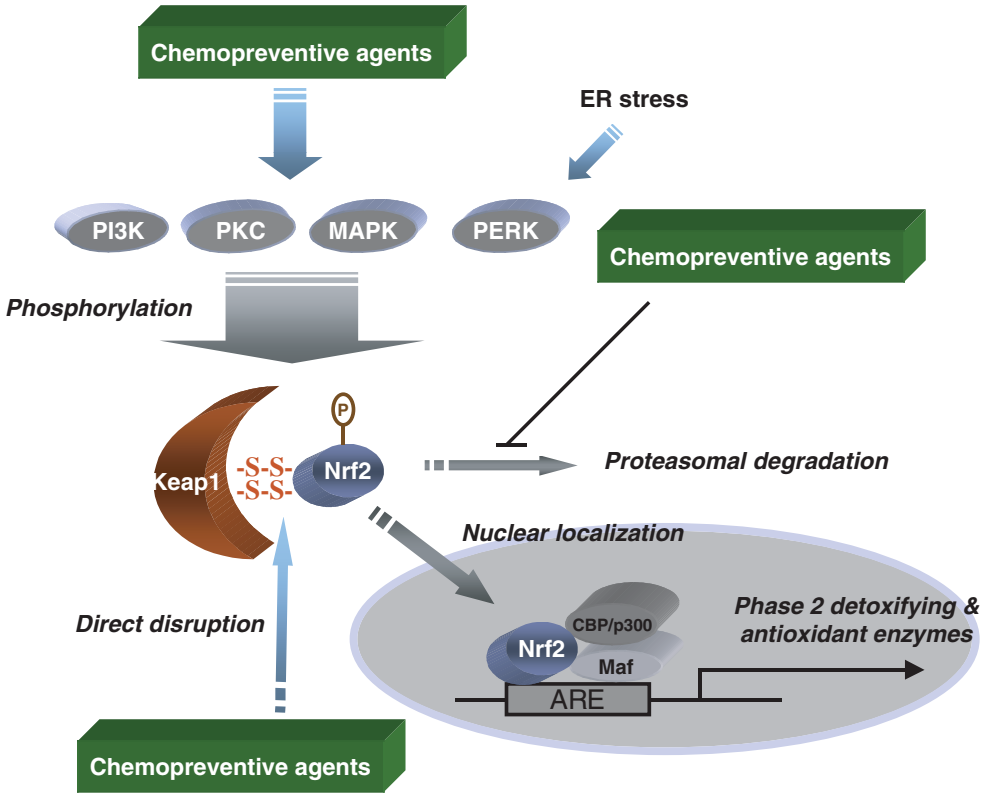

FIG. 1. Signaling pathways leading to the induction of phase 2 detoxifying and antioxidant enzymes through activation of the Nrf2/ARE.

dation (8, 63). Keap1, therefore, negatively regulates Nrf2 by both preventing its nuclear accumulation and enhancing its rate of proteasomal degradation (39). The increased stability and activation of Nrf2 by certain stimuli seem to come from their ability to repress the Keap1-dependent degradation mechanism. Interestingly, recent results from our laboratory have shown that potential chemopreventive agents such as allyl isothiocyanate, indole-3-carbinol (I3C), and parthenolide increase the Nrf2 protein level without affecting the rate of degradation, whereas sulforaphane enhances the level of Nrf2 as well as its stability, suggesting that increasing stability of Nrf2 by inhibition of Keap1 might not be the only mechanism for the activation of Nrf2 (22).

Many studies have also indicated that Nrf2 is also activated by phosphorylation. Mitogen-activated protein kinases (MAPKs), protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), and RNA-dependant protein kinase-like endoplasmic reticulum kinase (PERK) have been implicated in this process. Activation of extracellular signal-regulated protein kinase 2 (ERK2), a MAPK, by sulforaphane or *tert*-butyl-hydroquinone (tBHQ) enhances the induction of ARE-dependent phase 2 detoxifying genes in human and murine hepatoma cells, a process that may involve the direct activation of Raf-1 by these inducers (62). Treatment of HepG2 cells with pyrrolidine dithiocarbamate resulted in the transcriptional up-regulation of the γ-glutamylcysteine synthetase (γ-GCS) subunit genes through ERK- and p38-dependent phosphorylation events (64). Recently, our laboratory has demonstrated up-regulation of the Nrf2 transactivation domain by ERK and JNK pathways through the coactivator CBP (48).

PKC-directed phosphorylation of Nrf2 and ARE-mediated gene expression is also reported to be a critical event for the nuclear translocation of Nrf2 in response to oxidative stress such as tBHQ and β-naphthoflavone (15). PKC directly phosphorylates Nrf2 at Ser40 after tBHQ treatment and this modification decreases the affinity of Nrf2 for Keap1 allowing translocation of Nrf2 to the nucleus (3, 16). Of the many PKC isomers, atypical PKC has been suggested to phosphorylate Nrf2 at Ser40 (45).

PI3K is another kinase proposed to regulate the Nrf2/ARE pathway. Treatment of IMR-32 human neuroblastoma cells with tBHQ stimulated NQO1-ARE (hNQO1-ARE) activity and NQO1 protein expression in a PI3K-dependent manner as these inductions were abolished by co-treatment with LY 294002, a PI3K specific inhibitor (35). ARE-mediated rGSTA2 induction in the rat hepatoma H4IIE cells by tBHQ is also dependent on PI3K signaling (25). The exact mechanism underlying the induction of the Nrf2/ARE by PI3K, however, is not fully understood.

PERK, a transmembrane protein kinase, has been shown to phosphorylate Nrf2, resulting in its dissociation from Keap1; such phosphorylation also inhibits the reassociation of Nrf2/Keap1 complexes *in vitro* (9). Additional studies by the same investigators have demonstrated that the activation of Nrf2 through PERK contributes to the maintenance of glutathione levels, which functions as a buffer against the accumulation

of reactive oxygen species during the unfolded protein response caused by endoplasmic reticulum stress (7).

CHEMOPREVENTIVE AGENTS INVOLVED IN THE Nrf2/ARE PATHWAY

Isothiocyanates such as sulforaphane, phenethyl isothiocyanate (PEITC), and allyl isothiocyanate (AITC) are present in cruciferous vegetables including broccoli, watercress, Brussels sprouts, cabbage, and cauliflower, and have been extensively studied for their chemopreventive properties. Isothiocyanates are produced from their precursor, glucosinolates, by physical processes such as chewing or chopping as well as by the human intestinal microflora after ingestion (26). The chemopreventive properties of cruciferous vegetables have been addressed in several epidemiological studies as well as in animal models of chemically-induced carcinogenesis (53). Sulforaphane is one of the most extensively studied isothiocyanates; it is known to stimulate the induction of MAPKs, Nrf2, ARE reporter gene activity, and phase 2 detoxifying and antioxidant enzymes such as NQO1 and HO-1 (22, 28, 62, 63). An oligonucleotide microarray study has revealed that sulforaphane induces a number of Nrf2-regulated genes such as NQO1, GST, GCS, UGT, epoxide hydrolase, NADPH regenerating enzymes, various xenobiotic metabolizing enzymes, antioxidant enzymes, and biosynthetic enzymes of the glutathione and glucuronidation conjugation pathways (54). Sulforaphane has been proposed to disrupt the cytoplasmic complex between Keap1 and Nrf2 by reacting with covalent bonds between the Nrf2-Keap1 complex, thereby resulting in the release of Nrf2 to the nucleus and the activation of ARE-dependent phase 2 genes (11). Recent studies have indicated that sulforaphane stabilizes Nrf2 protein probably through its inhibition of Keap1-dependent proteasomal degradation, although other mechanisms are also possible (22, 63). A sulforaphane analog, 6-methylsulfinylhexyl isothiocyanate, also activates the Nrf2-ARE-dependent detoxification pathway *in vitro* and *in vivo* (42).

PEITC is another promising chemopreventive isothiocyanate compound. It has been shown to dose-dependently activate ARE-reporter gene activity in HepG2 hepatoma cells (27). Increased ARE-reporter gene activity was observed when the cells were transiently transfected with expression plasmids encoding wild-type Nrf2 or JNK1, while co-transfection of Nrf2 and JNK1 showed additional enhancement of reporter activity. In addition, overexpression of dominant-negative JNK1 suppressed Nrf2-induced ARE reporter gene expression in a dose-dependent manner, implying that JNK1 might be an upstream activator of Nrf2. AITC has also been found to stimulate ARE-reporter gene activity as well as protein expression of Nrf2 and HO-1 (22). However, the degradation of Nrf2 was not delayed by AITC treatment, suggestive of a Keap1-independent mechanism of Nrf2 regulation by this compound.

Diallyl sulfides such as diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) are another class of potential chemopreventive agents that are found in the Allium family including garlic, onion, and chive. DADS and DATS induce GST, glutathione reductase, NQO1, and ferritin in cultured cells and in animals (49, 55, 61). A recent study from our laboratory has also indicated the positive roles of these diallyl sulfides on the activity of ARE-mediated gene expression and expression of Nrf2, NQO1, and HO-1 proteins (4). Structure-activity relationship studies have suggested that the third sulfur in the structure of the diallyl sulfides contributed substantially to their bioactivities and that allyl-containing sulfides were more potent than propyl-containing sulfides. MAPKs such as ERK, JNK, and p38 were activated by DATS treatment although the inhibition of these MAPKs did not affect DATS-induced ARE activity. Other investigators have reported that DAS induces HO-1 through the production of ROS, and that Nrf2 and MAPK (ERK and p38) mediate the induction (14). The exact role of MAPK (ERK1/2, JNK1/2/3, ERK5, or p38s) on Nrf2/ARE-mediated gene expression probably depends on cell types, the nature of chemical inducers or inhibitors, and their respective concentrations.

Besides the sulfur-containing agents mentioned above, phenolic compounds are another major category of promising chemopreventive agents targeting the Nrf2/ARE pathway. Tea catechins such as (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epigallocatechin gallate (EGCG) are very strong antioxidant flavonoids, and their health modulating properties, including their potential beneficial roles in heart disease and cancer, are well documented (24, 34). Among tea catechins, EGCG has been shown to potently induce ARE-mediated gene expression and activate all three MAPKs (5). In addition, it stimulates caspase-3 activity and thereby induces apoptosis.

Curcumin and caffeic acid phenethyl ester (CAPE) are also potential natural chemopreventive agents found in tumeric and propolis of honeybee hives, respectively. CAPE stimulates ARE-mediated NQO1 expression (20). Curcumin and CAPE stimulate the expression of Nrf2 in a dose- and time-dependent manner in renal epithelial cells, presumably by promoting inactivation of the Nrf2-Keap1 complex; this response was associated with a significant increase in the expression and activity of HO-1 protein (2). The authors suggested an involvement of p38 MAPK in curcumin-mediated HO-1 induction.

Other natural chemopreventive agents that may induce phase 2 detoxifying enzymes through the Nrf2/ARE pathway include indoles such as indole-3-carbinol (I3C) and terpenoids. I3C has been reported to retard the progression of aflatoxin B1-induced carcinogenesis in animal at both the initiation and promotion stages. Treatment with I3C has shown significant induction of GST Yc2, aflatoxin B1 aldehyde reductase, and quinone reductase (37, 40). In HepG2 cells, I3C showed a weak induction of ARE-reporter gene activity and Nrf2 protein expression but had no effect on HO-1 protein expression (22). NQO and GST enzyme activities in the small intestine of mice were increased about two-fold after the mice were fed with a mixture of coffee diterpenes, cafestol, and kahweol palmitate (38). A sesquiterpene found in feverfew, parthenolide, stimulates ARE-reporter gene activity and potently induce expression of Nrf2 and HO-1 proteins in HepG2 cells (22).

Overall, it appears that many naturally occurring cancer chemopreventive compounds can modulate the Nrf2-Keap1 complex in the cytoplasm of cells of different organs or tissues. Their *in vivo* potency probably depends on the cellular levels of antioxidants such as reduced glutathione (GSH) (28),

and their reactivity towards sulfhydryl groups (SH) of cysteine residues or other redox-sensitive amino acids in proteins such as Keap1 or various kinases and phosphatases (6). Disruption of the Keap1/Nrf2 complex would lead to Nrf2 release, its translocation to the nucleus, and subsequent transcriptional activation of ARE-responsive genes. As a consequence, these compounds would function as cytoprotective agents against oxidative stress and carcinogenic reactive intermediates, possibly hindering the development of cancer as well as cardiovascular, inflammatory, and neurological diseases. There are, however, at least two caveats with respect to using some of these naturally occurring agents indiscriminately. The first consideration will be the absolute bioavailability, the amount of the pharmacologically active components being absorbed from the gastrointestinal tract after oral administration that will reach the target organs/sites and impart the potential beneficial effects of the compounds on that organ (30, 34). The second aspect will be the potential toxicity of these compounds (32, 33). It appears that above certain threshold concentrations of these compounds, other cellular molecules, activities or events such as AP-1, NF-κB, the cell cycle, mitochondria damage, and caspases will be modulated leading to cytotoxicity. If the cytotoxicity occurs selectively in the preneoplastic or neoplastic cells, then this would be of great benefit in cancer prevention. However, if this occurs in normal tissue, then this would certainly be detrimental. It appears that, in general, precancerous or cancerous cells harbor dysregulated survival signal transduction activities (36, 60). It is tempting to speculate that these cells may be more prone or more sensitive to perturbation of these signal transduction events by the chemopreventive compounds and therefore they are more prone/sensitive to apoptotic cell death then their normal counterpart. To test this hypothesis, more *in vivo* studies will be needed in the future. Therefore, in general, the *in vivo* therapeutic window and the risk to benefit ratio would need to be considered when we are examining the potential usage of these agents for human health including cancer prevention, cardiovascular, inflammation and neurological diseases.

CONCLUDING REMARKS

Accumulating evidence supports the premise that the Nrf2/ARE pathway plays a key role in the protective mechanism of cells, through the induction of phase 2 detoxifying and antioxidant enzymes, against exogenous and endogenous carcinogenic species. Several classes of potential natural chemopreventive agents as described in this article have been extensively studied and many other compounds are under investigation for their regulation of this protective mechanism. Given the great structural diversity amongst the chemopreventive agents targeting the Nrf2/ARE signaling pathway and the complexity of the upstream cellular signaling events, however, much more effort is needed to elucidate the complex regulation of the Nrf2/ARE signal transduction pathway by diverse classes of natural chemopreventive agents. In addition, most *in vitro* experiments using natural compounds have been carried out with much higher concentrations than could be achievable *in vivo*. Therefore, more calibrated *in vivo* approaches should be considered when these results are to be applied to human studies. Nevertheless, given their relatively low toxicity, low cost, and abundance, further analysis of the diverse natural compounds for chemopreventive activity is clearly warranted. In the final analysis, even if such studies do not lead to successful development of some of these compounds as anticancer agents, the increased understanding of their mechanism of action will certainly add value to our knowledge since these dietary compounds are consumed daily in our diets throughout the world.

ACKNOWLEDGMENT

Supported in part by grant R01-CA094828 from the National Institutes of Health (NIH).

ABBREVIATIONS

AITC, allyl isothiocyanate; ARE, antioxidant response element; bZIP, basic region-leucine zipper; CAPE, caffeic acid phenethyl ester; CNC, Cap 'n' collar; DADS, diallyl disulfide; DAS, diallyl sulfide; DATS, diallyl trisulfide; EC, (-)-epicatechin; ECG, (-)-epicatechin gallate; EGC, (-)-epigallocatechin; EGCG, (-)-epigallocatechin gallate; EpRE, electrophile responsive element; ERK, extracellular signal-regulated protein kinase; γGCS, γ-glutamylcysteine synthetase; GSH, reduced glutathione; GST, glutathione *S*-transferase; HO-1, heme oxygenase-1; I3C, indole-3-carbinol; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH associating protein 1; MAPKs, mitogen-activated protein kinases; NQO1, NAD(P)H:quinone oxidoreductase 1; Nrf2, nuclear factor-erythroid 2-related factor 2; PEITC, phenethyl isothiocyanate; PERK, RNA-dependent protein kinase-like endoplasmic reticulum kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; tBHQ, *tert*-butyl-hydroquinone; UGT, UDP-glucuronosyltransferase.

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Address reprint requests to:
Dr. Ah-Ng Tony Kong
Department of Pharmaceutics
Ernest-Mario School of Pharmacy
Rutgers, The State University of New Jersey
160 Frelinghuysen Road
Piscataway, NJ 08854

E-mail: Kong T@rci.rutgers.edu

Received for publication June 7, 2005; accepted July 8, 2005.

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