

Redox regulation in cancer

A double-edged sword with therapeutic potential

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Abbreviations: DMBA, 7-12 dimethylbenz [a] anthracene; GPx, glutathione peroxidase; GST, glutathione-S-transferase; SOD, superoxide dismutase; HO-1, heme oxygenase 1; ER, estrogen receptor; PR, progesterone receptor; LPS, lipopolysaccharide; TNF, tumor necrosis factor; GCL, glutamate cysteine ligase; SAPK, stress-activated protein kinase; JNK, Jun-amino-terminal kinase; PMA, phorbol 12-myristate 13-acetate; NQO1, NAD(P)H quinone oxidoreductase 1; ARE, antioxidant response element; TRX, thioredoxins; GRX, glutaredoxins

Oxidative stress, implicated in the etiology of cancer, results from an imbalance in the production of reactive oxygen species (ROS) and cell's own antioxidant defenses. ROS deregulate the redox homeostasis and promote tumor formation by initiating an aberrant induction of signaling networks that cause tumorigenesis. Ultraviolet (UV) exposures, γ -radiation and other environmental carcinogens generate ROS in the cells, which can exert apoptosis in the tumors, thereby killing the malignant cells or induce the progression of the cancer growth by blocking cellular defense system. Cancer stem cells take the advantage of the aberrant redox system and spontaneously proliferate. Oxidative stress and gene-environment interactions play a significant role in the development of breast, prostate, pancreatic and colon cancer. Prolonged lifetime exposure to estrogen is associated with several kinds of DNA damage. Oxidative stress and estrogen receptor-associated proliferative changes are suggested to play important roles in estrogen-induced breast carcinogenesis. BRCA1, a tumor suppressor against hormone responsive cancers such as breast and prostate cancer, plays a significant role in inhibiting ROS and estrogen mediated DNA damage; thereby regulate the redox homeostasis of the cells. Several transcription factors and tumor suppressors are involved during stress response such as Nrf2, NFκB and BRCA1. A promising strategy for targeting redox status of the cells is to use readily available natural substances from vegetables, fruits, herbs and spices. Many of the phytochemicals have already been identified to have chemopreventive potential, capable of intervening in carcinogenesis.

Introduction

Death resulting from cancer has not changed significantly for last three decades although US government has given a lot of

stress in search for the cure of cancer. In the beginning, cancer cells are more vulnerable to chemotherapy and radiotherapy than normal cells, but, as the disease progresses, they lose their preferential sensitivity to the same treatments. All these therapeutic approaches as well as exposure to environmental carcinogens like ionizing radiations (IR), ultraviolet (UV) exposures and other environmental carcinogens generate reactive oxygen species (ROS) in the cells, which can act in both beneficial and detrimental ways. ROS exerts oxidative stress in the cells which deregulate the body's cellular defense system leading to genomic instability and cancer.¹⁻³ Moreover, oxidative stress can result from a number of endogenous sources, including the production of oxygen-free radicals by mitochondrial oxidative phosphorylation. Mitochondria are the significant source of ROS as they are the major consumers of molecular oxygen in cells.^{4,5} Cellular defense system is comprised of several Phase II detoxification enzymes such as glutathione-S-transferases (GSTs), NAD(P)H quinone oxidoreductase (NQO1), Glutathione peroxidases (GPx), Catalase, superoxide dismutases (SODs), epoxide hydrolase, heme oxygenase (HO-1), UDP-glucuronosyl transferases (UGTs), gamma-glutamylcysteine synthetase and many others. Expression of these proteins protects cells from oxidative damage and can prevent mutagenesis and cancer.⁶⁻¹¹ Apart from cancer, oxidative stress has been implicated in several chronic diseases and natural process such as aging, atherosclerosis, diabetes mellitus, arthritis and neurodegenerative disease including Alzheimer's and Parkinson's disease.¹²⁻¹⁷ Due to scope and limitation, this review will focus on the (1) Role of ROS in pathophysiological implications of altered redox regulation in breast, prostate, colon and pancreatic cancer; (2) Involvement of BRCA1, as a protectant against oxidative stress; (3) Modulation of redox environment in cancer stem cells; (4) Targeting redox system by phytochemicals for therapeutic interventions; (5) Function of antioxidants, antioxidation enzymes and transcription factors in the maintenance of cellular defense system; (6) Finally we will discuss the future perspectives on addressing the question; 'Where are we leading to with these innovations and what

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should be done so that everybody can lead a better and relaxed life in this hazardous environment?

Reactive Oxygen Species (ROS) Mediated Carcinogenesis

Oxidative stress promotes damage to the cell structure including proteins, lipids, membranes and DNA, that plays a key role in the development of cancer.^{2,12-15,18} Mitochondrial electron-transport chain and other oxidizing agents are the prime pathways that generate excess ROS in vivo, leading to several types of DNA damage, including depurination and depyrimidination, single- and double-stranded DNA breaks, base and sugar modifications and DNA-protein crosslinks.¹⁹⁻²¹ Permanent modification of genetic material resulting from the oxidative damage is one of the vital steps involved in mutagenesis that leads to carcinogenesis. Stimulation of DNA damage can either arrest or induce transcription, signal transduction pathways, replication errors and genomic instability, all of which are associated with carcinogenesis.^{18,22,23} The most frequent DNA mutations caused during oxidative stress, initiated by ionizing radiation and other environmental carcinogens are 7,8-dihydro-8-oxoguanine (8-Oxo-G) and Thymine Glycol (TG). Thymine glycol blocks transcription and causes cell death both in cancer and non-cancer cells. These oxidized DNA products are relatively easy to generate during oxidative stress and are both mutagenic and carcinogenic. Thus they are considered as useful markers of oxidative stress and potential biomarkers of carcinogenesis.²⁴⁻²⁶ To counterbalance the oxidative damage from ROS, aerobic organisms have created a variety of antioxidant mechanisms to maintain their genomic stability. These mechanisms include phase II detoxification and other antioxidant enzymes that act in cellular defense such as catalase and SOD, GPx, GST, other constitutive and inducible antioxidants, DNA repair enzymes, and other cellular mechanisms of genomic surveillance, such as cell cycle checkpoint control systems.²⁷ Moreover, several growth factors such as serum, insulin like growth factor I, or fibroblast growth factor 2 generates ROS in MIA PaCa-2 and PANC-1 cells, which are human pancreatic adenocarcinoma cells that promotes cell survival. Inhibiting ROS generation with the antioxidants or NADPH oxidase (Nox4) antisense, or MnSOD overexpression would stimulate apoptosis in PaCa-2 and PANC-1 cells. This mechanism might play an important role in pancreatic cancer resistance for treatment and thus represent a novel therapeutic target.²⁸ In gastrointestinal and colon cancer, oxidative pentose pathway (OPP) and the glutathione (GSH) antioxidant defense system play an important role in the regulation of cell growth and apoptosis. The OPP modulate intracellular redox status and provides NADPH for the synthesis of GSH, which is responsible for the inactivation of intracellular ROS that induce apoptosis and cell injury. Depletion of GSH increases the sensitivity of cells to ROS. Therapeutic inhibition of the OPP and/or the GSH defense system might increase the sensitivity of gastric and colon cancer cells to anti-cancer therapy.²⁹ Recent studies have shown that the enzymatic product of thymidine phosphorylase (TP) generated ROS within cancer cells that help in maintaining the growth of colon cancer cells thus

may provide improved therapeutic results as well as a preventative effect on carcinogenesis of the colorectum.³⁰ Emerging evidence also suggests that supranutritional doses of selenite could induce typical apoptosis in colorectal cancer cells in vitro and in xenograft tumors by inducing ROS. It indicates that selenite can activate the apoptotic machinery through redox-dependent activation and could be useful in cancer therapy.³¹

BRCA1 Functions in Oxidative Stress Responses

The breast cancer susceptibility gene, BRCA1, encodes a tumor suppressor protein, mutations of which account for about 40–50% of hereditary breast cancers.^{32,33} In sporadic (non-hereditary) breast cancers, BRCA1 expression is absent or decreased in about 30–40% of cases. Environmental and genetic factors are the important contributors of the neoplastic transformation leading to breast cancer. BRCA1 has several important functions and one of them is to render protection to the cells during oxidative stress. BRCA1 upregulates the expression of multiple genes involved in the cytoprotective antioxidant response, including GST, GPx, Oxidoreductases, and other antioxidant genes. Consistent with these findings, ectopic expression of BRCA1 conferred resistance while BRCA1 deficiency conferred sensitivity to several different oxidizing agents (hydrogen peroxide and paraquat).^{34,35} Evidences collected from the BRCA1 mouse model where mice are homozygous for full-length breast cancer-associated gene-1 (*Brcal*) deletion and heterozygous for a p53-null mutation (*Brcal^{Δ11/Δ11}p53^{+/-}*), display high frequency of spontaneous lymphoma and mammary tumor formation.³⁶ *Brcal* mutant mice also exhibit increased expression of *Redd1*, which is a developmentally regulated transcriptional target of p63 and p53, during regulation of ROS. Additionally, the same mice demonstrate elevated levels of ROS and subsequently they are more sensitive to oxidative stress induced lethality.³⁵ In addition, in the setting of oxidative stress (due to hydrogen peroxide), BRCA1 shifts the cellular redox balance to a higher ratio of reduced to oxidized glutathione (GSH).^{34,37} Higher content of reduced glutathione functions in favor of redox maintenance. The identification of transcriptional target of several antioxidant genes that are elevated during BRCA1 overexpression led to the findings that BRCA1 regulates the activity of the antioxidant response transcription factor Nrf2 and NFκB and protects cells against oxidative stress.^{34,38} This function would be consistent with the postulated role of BRCA1 as a caretaker gene in preserving genetic integrity via regulating the redox maintenance of the cells.

We have studied the antioxidant property of BRCA1 by either over- and or under-expression of BRCA1 in breast cancer cells. We have demonstrated that wild-type BRCA1 (but not a cancer-associated mutant) significantly reduced ROS levels, determined by DCF fluorescence assays using flow cytometry and confocal microscopy.³⁷ **Figure 1** demonstrates the cellular protection function of BRCA1 during oxidative stress. MCF-7 breast cancer cells were transfected with either wt BRCA1 or the background vector (pcDNA3) and simultaneously all the experimental cells were treated with tert-butyl hydroperoxide (TBHP) (Molecular Probes; Carlsbad, CA) to artificially generate cellular ROS, which is

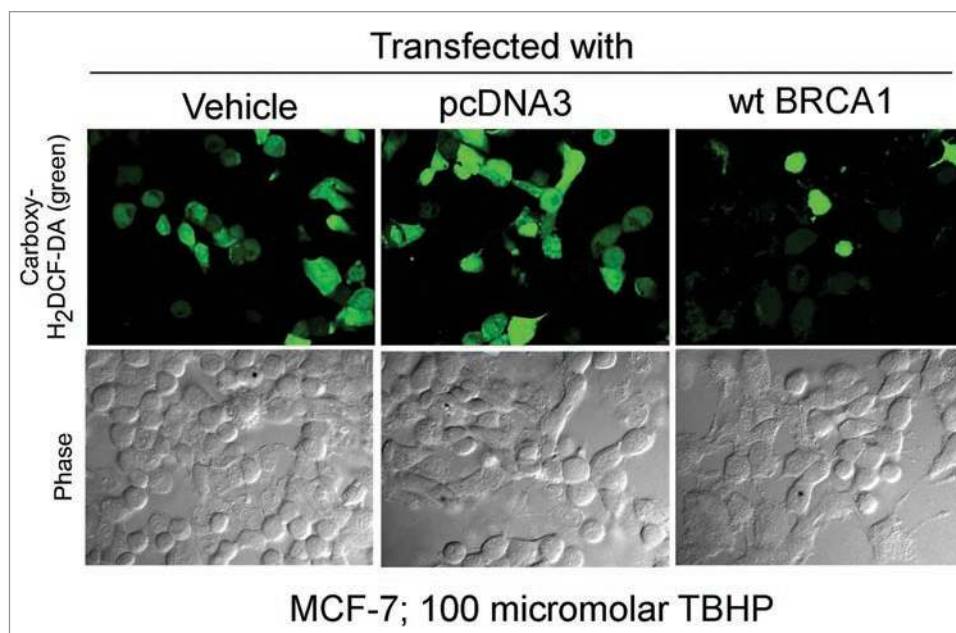


Figure 1. Wt BRCA1 downregulates the production of ROS in MCF-7 breast cancer cells. Cells were transfected either with background vector (pcDNA3) or with wt BRCA1 plasmid. Forty-eight hours post transfection all the cells were treated with 100 μ M of ROS producing agent TBHP (tert-butyl hydroperoxide) in a serum free medium. Levels of ROS were detected through confocal microscopy using carboxy-H₂DCF-DA fluorescence (first row). Second row is the phase picture of all the cells that are used for confocal staining. Decrease in the stain intensity in BRCA1 transfected cells compared to vehicle and background vector transfected cells depicts an important function of BRCA1 in protecting cells from oxidative damages.

detected by using Carboxy-H₂DCFDA (Green) (Molecular probes (I36007), Carlsbad, CA). This figure demonstrates that ectopic expression of BRCA1 significantly reduces the formation of ROS triggered by TBHP (third column) when compared to vehicle and pcDNA3 plasmid transfection (first and second column). Furthermore, expression of redox factor 1/AP endonucleases 1 (Ref1/APE1) in breast cancer cells, which has a dual role of redox regulation in cells and lyase activity in stimulating base excision repair (BER) pathway, inhibits the generation of ROS and promotes cell survival against oxidative stress, rendered by either stress producing agents.^{39,40} The BRCA1 and Ref1/APE1 pathways for reduction of ROS levels appear to exhibit cross-talk in protecting the cells from stress. BRCA1 also reduced the levels of protein nitration that exerts nitrate stress in the cells by forming harmful 3-Nitrotyrosine during H₂O₂-induced oxidative damage to proteins.³⁷ H₂O₂ caused modest but detectable increases in the levels of 8-oxo-G and thymine glycol (TG) modification in DNA. Wt BRCA1 reduced, while BRCA1-siRNA further increased the 8-oxo-G and TG levels in H₂O₂-treated cells indicating BRCA1 involves in stimulating DNA repair process to repair the oxidative lesions.³⁷

Oxidative Stress Mediated Estrogen Receptor Activity in Breast Cancer

Estrogens play a crucial role in the development and evolution of human breast cancer. Epidemiological evidence indicates that prolonged lifetime exposure to estrogen is associated with elevated breast cancer risk in women. Estrogen is converted by cytochrome P450 1B1 to 4-hydroxyestradiol (4-OHE₂),

a putative carcinogenic metabolite of estrogen.⁴¹ This catechol estrogen metabolite is oxidized further to produce a reactive quinone via semiquinone. Oxidative stress and estrogen receptor-associated proliferative changes are suggested to play important roles in estrogen-induced breast carcinogenesis.⁴²⁻⁴⁴ Treatment of the immortalized human breast epithelial cells (MCF-10F) with 17 β -estradiol (E₂), 4-hydroxyestradiol (4-OHE₂) or 2-hydroxyestradiol (2-OHE₂) induces phenotypical changes indicative of neoplastic transformation.⁴⁵ Although the precise molecular mechanisms by which E₂ induces breast cancer have not been completely understood, the estrogen implication in breast cancer has been associated mostly with the estrogen receptor^{46,47} that mediates cell proliferation. The direct role of estrogens as tumor initiators has been supported by the evidence that E₂, catechol estrogens (CEs) and their quinone derivatives exerts oxidative stress that lead to various types of DNA damage, including single strand breaks as well as stable and depurinating DNA adducts.^{48,49} 2-OHE₂ and 4-OHE₂ are the two catechol metabolites of estrogens that could be oxidized to CE quinones (CE-Q) that may react with DNA. Physiologic concentrations of estradiol (E₂) have also been reported to cause a decrease in catalase activity followed by an increase in glutathione peroxidase (GPx) activity, in MCF-10A breast epithelial cells.^{50,51} Moreover, thioredoxin (Trx) and thioredoxin reductase (TrxR) are shown to modulate H₂O₂ levels and the activity of estrogen in estrogen responsive breast cancer cells.⁵² Oxidative stress can change the structure and function of estrogen receptor and progesterone receptor (PR), altering the biology and clinical outcome of endocrine responsive (ER-positive) breast cancer.^{53,54} A subset of estrogen/ER-responsive breast cancer genes that are linked to

cell growth and invasion pathways were identified and associated with loss of PR.^{55,56} Intracellular proteins that are most susceptible to oxidant-induced structural and functional damage are redox-sensitive zinc finger transcription factors such as Sp1 and ER. Zinc finger cysteine residues of ER are readily oxidized during stress, eliminating their DNA-binding activity. Failure of DNA-binding activity of ER has been found in up to 30–35% of all ER-positive breast cancers and that correlated with loss of PR expression. Both, Sp1 and ER- α DNA-binding and transactivating functions are needed for optimal estrogenic stimulation of genes such as PR and Bcl2. ER-positive breast cancers would exhibit suppressed expression of these estrogen-inducible genes during oxidative stress.

Redox Status in Cancer Stem Cells

Studies have shown that redox balance plays an important role in the maintenance of stem cell self-renewal and in differentiation. Very little is known about the redox status in cancer stem cells. Normal haemopoietic stem cells and normal mammary epithelial stem cells maintained lower levels of ROS than their mature progeny to prevent cellular differentiation and maintain long-term self-renewal.⁵⁷⁻⁵⁹ A newly identified subpopulation of cells, known as ‘cancer stem cells’, are responsible for the reoccurrence of tumor following chemotherapy. These cells are highly drug resistance and one can hypothesize that these cells use redox regulatory mechanisms to escape the cell death by several anticancer agents.⁶⁰⁻⁶⁵ Cancer stem cells actually maintain both the stemness nature and cancer cell characteristics for growth and survival and probably they share some very common characteristics like normal stem cells in redox regulation. Evidences are that subsets of cancer stem cells in human and murine breast tumors contain lower ROS levels, similar to normal stem cells, than the corresponding non-tumorigenic cells.⁵⁷ This low level of ROS seems to be associated with elevated expression of ROS-scavenging molecules, which may contribute to tumor radioresistance. We believe BRCA1 has a role in modulating cancer stem cells. The major transcription factor responsible for the stemness nature of the cells is the Forkhead Box Os (FoxOs) that upregulates the expression of SOD and catalase.^{66,67} Biological properties of the cancer stem cells renders that these cells might have an elevated antioxidation enzymes pool to maintain reduced levels of ROS like normal stem cells. On the other hand, this high antioxidant capacity also favors the survival of the cancer stem cells and drug resistance. Moreover, some stem cells reside in a relatively low oxygen microenvironment that might also limit the endogenous ROS production. Thus cancer stem cells in a hypoxic microenvironment may be relatively resistant to radiotherapy and chemotherapy with redox-cycling agents since their cytotoxicity requires the availability of local oxygen. It is thus crucial to first determine the redox status in cancer stem cells compared with normal stem cells and with cancer cells in tumors.^{57,68} Discovery of the main molecular signaling pathway that maintains the redox nature in cancer stem cells might provide a possibility to abrogate the survival mechanisms in these cancer stem cells and allow the eradication of the root of cancer.

Targeting Redox Mediated Signaling Cascade Leading to Cell Death in Cancer

Cancer cells have been found to be in a state of redox imbalance, an alteration in the homeostasis between oxidants and antioxidants, resulting in increased oxidants within the cell. Oxidative stress due to the chronic over-exposure to ROS is thought to contribute to a variety of processes, including aging, degenerative diseases, and cancer.¹²⁻¹⁶ On the other hand, ROS also play an essential role as secondary messengers in the normal regulation of a variety of physiological processes, suggesting that their production is a double-edged sword. Oxidative stress can induce positive responses such as cellular proliferation or activation, as well as negative responses such as growth inhibition or cell death. Cellular redox status is maintained by several intracellular redox-regulating molecules, including thioredoxins (TRX).⁶⁹ TRX is one of the key regulators of signaling in the cellular responses against various stresses. TRX demonstrates a cytoprotective action against oxidative stress-induced apoptosis as well as induces growth-promoting effect as an autocrine growth factor. Moreover, TRX is involved in the regulation of protein-protein or protein–nucleic acid interactions through its redox nature of the cysteine residues. TRX translocates from the cytosol into the nucleus due to a variety of cellular stresses, to regulate the expression of various genes through the redox factor-1 (Ref-1/APEX1).⁷⁰ Glutathione (GSH)/Glutaredoxin (GRX) system also maintains the redox homeostasis in the cells but it is dependent on the TRX redox regulation.⁷¹ GRX is a small dithiol protein involved in various cellular functions, including the redox regulation of certain enzyme activities via its disulfide exchange reaction. Overexpression of GRX, protect cells from hydrogen peroxide (H₂O₂)-induced apoptosis by regulating the redox state of the cell. Thus molecules or enzymes that can penetrate the redox environment of the cancer cells will be beneficial for killing the same. Incidentally stress levels in some tumor cells are actually masked by the activation of anti-oxidation/anti-apoptotic signaling. If this molecular shield can be removed in the cancer cells, death signals can be reinstated by inducing stress and cells can be forced to undergo apoptosis again. A number of examples imply that this can be achieved. For example, non-small-cell lung carcinoma cells become more resistant to cytotoxic agents such as cisplatin, doxorubicin and etoposide due to the elevated levels of Her-2/neu expression but when Her-2/neu signaling was inhibited, these cells become re-sensitized to these agents.⁷² Similarly, the ectopic expression of a mutated EGFR, in advanced glioma, exhibit resistance to cisplatin due to reduced apoptosis. Blocking EGFR signaling in these cells restores their cisplatin sensitivity.⁷³ Blocking Her-2 with Herceptin (Trastuzumab) sensitizes highly drug-resistant breast cancer cells to cytotoxic drugs.⁷⁴ In fact, the combination of chemotherapy with cellular redox system modifiers has shown promising results in clinical trials. How these combined therapies modulate ROS and stress kinase pathways at the cellular level has not been determined yet. The study of stress signaling has proved to be instructive in explaining recent advances in cancer therapy and should facilitate the development of improved anticancer strategies.

Phytochemicals as Anti-Cancer Chemopreventive Compounds that Targets Redox Regulations

Considering the burden of health-care cost as a major global concern, dietary chemoprevention provides an inexpensive, readily applicable and easily accessible approach to cancer control and management and at present it is a hot area of research. Strengthening of cellular defense mechanism or restoration of stress-response signaling by administering dietary phytonutrients provides an important strategy for cancer chemoprevention. Currently antioxidant activity is the most common *in vitro* parameter used to assess or predict potential benefits of plant derived compounds. However, correlations between *in vitro* antioxidant activity and actual health benefits are unknown. Such *in vitro* antioxidant data ignore other potentially beneficial or harmful effects of phytochemicals like modification of enzyme activity and/or cell signaling pathways. There are several compounds we are working with, that target the redox system of the cancer cells either by inducing ROS-mediated apoptosis or prevent the cells from exogenous or endogenous sources of ROS by upregulating cellular defense system and inhibiting the cancerous growth.

Indole-3-carbinol (I3C), a phytochemical from cruciferous vegetables, is of interest because a diet rich in cruciferous vegetables is associated with a reduced risk of several tumor types, such as breast cancer. In the acidic environment of the stomach, I3C undergoes hydrolysis to a number of products, including a dimeric product, 3,3'-diindolylmethane (DIM), its major active metabolite.⁷⁵ Both these phytochemicals stimulate BRCA1 in breast and prostate cancer cells and has been shown to protect cells against oxidative stress mediated by H₂O₂ and γ -radiation.^{75,76} Genistein (4,5,7-trihydroxyisoflavone) was identified as the predominant isoflavone in soybean enriched foods, which comprises a significant portion of the Asian diet, has been shown to inhibit prostate carcinogenesis in animal models. Genistein has antioxidant effects and protects cells against ROS by scavenging free radicals, inhibiting the expression of stress-response related genes.⁷⁶ Furthermore, genistein is a powerful inhibitor of NF κ B, Akt and PTK signaling pathways, all of which are important for cell survival.⁷⁷ Curcumin, on the other hand, is a diferuloylmethane, derived from the rhizomes of turmeric. Curcumin targets the Nrf2-ARE signaling pathway to induce phase II detoxifying enzymes on an event of oxidative stress.^{38,78} Addition of curcumin disrupts the Nrf2-Keap1 complex, leading to elevated Nrf2 binding to ARE and subsequent increase in the expression and activity of HO-1 in porcine renal epithelial proximal tubule (LLC-PK₁) cells and/or rat kidney epithelial (NRK-52E) cells via activation of p38 MAP kinase. UDP-glucuronosyltransferase (UGT) isozymes catalyze detoxification of numerous chemical toxins present in our daily diet and environment, which give rise to ROS, by conjugation to glucuronic acid. Curcumin modulates the activity of cellular UGT1A7 and UGT1A10 and increases the bioavailability of other compounds such as Genistein or Diadzein in the cells that has an inhibitory effect on cancer.⁷⁹⁻⁸¹

Whole food and spices demonstrate excellent source of mixture of compounds that targets the redox system of the cells and

are known for their high therapeutic potential for ages. Spices are now receiving increasing attention as many of them have been shown to have anti-carcinogenic properties. Saffron, Clove, Cardamom and Cinnamon are highly aromatic spices, commonly used in Asian, Arab and some Scandinavian cuisines. We and others have demonstrated several anti-carcinogenic activities of these spices against several cancers by upregulating several phase II detoxification enzymes, antioxidants and reducing the lipid peroxides in the cells.⁸²⁻⁸⁷ Additionally, garlic, which is whole food used all over the world demonstrates a formidable prophylactic and therapeutic medicinal property.⁸⁵ Garlic extracts inhibits the oxidative modification of lipids induced by DMBA, thus protecting cells from injury by the oxidized molecules.⁸⁵ Oral administration with aqueous infusion of garlic and cardamom in addition to the DMBA treatment to the swiss albino mice demonstrate downregulation of COX2 and p53 (tumor suppressor) expression when compared to the DMBA treated mice only indicating reduction of inflammation related abnormalities in the phytochemicals treated mice. These phytochemicals delayed the formation of skin papillomas in animals and simultaneously decreased the size and number of papillomas demonstrating their beneficial effects.^{84,85}

Redox Sensitive Transcription Factors Involved in Oxidative Stress

The concept of "Redox Regulation" in the field of cancer prevention is emerging to understand the mechanisms behind the pathogenesis of several disorders including tumor initiation and malignant transformation.^{88,89} Redox sensitive transcription factors are the key players in regulating several pathways that lead to carcinogenesis. Transcription factors/activators are a group of proteins that bind to specific consensus sequences (cis elements) in the promoter regions of downstream target/effector genes and either transactivate or repress effector gene expression. The change in the expression of the effector genes eventually leads to several biological modifications such as proliferation, growth suppression, differentiation or senescence. Furthermore, redox-induced biochemical alterations sometimes lead to change in the biological functions of these proteins. Therefore, differential regulation of these transcriptional activators, which in turn, regulate many target/effector genes, may provide an additional mechanism by which small antioxidant molecules play protective roles in anti-cancer processes and thus have an important impact on drug discovery and therapy for the inhibition of cancer. This section will focus on the redox regulation of transcription factors/activators with emphasis on Nrf2 and NF κ B that modulate during oxidative stress.

Nrf2

The role of the activation of Nuclear factor-erythroid-2-related factor 2 (Nrf2) transcription factor and its repression by Kelch-like ECH-associated protein 1 (Keap1) during oxidative stress has been well established.⁹⁰⁻⁹² The basal expression as well as the induction of genes encoding phase II enzymes are mediated

by means of the antioxidant response element (ARE).⁹³ ARE is a cis-acting enhancer sequence that transcriptionally regulates these genes, to maintain the cellular redox status and to protect against oxidative damage. Several studies have demonstrated that Nrf2 is involved in the regulation of ARE-mediated gene expression.^{90,94} Nrf2 is a member of basic leucine zipper transcription factors and is essential for the coordinated induction of genes that encodes stress-responsive or cytoprotective enzymes and related proteins, such as NQO1, SODs, GSTs, GPx, HO-1, glutamate cysteine ligase (GCL), catalase and thioredoxin. Nrf2 plays an essential role in maintaining cellular homeostasis and hence represents a critical target for prevention of oxidative stress- or inflammation-associated carcinogenesis. Under normal physiological conditions, Nrf2 forms an inactive complex with the negative regulator, Keap1 which controls the subcellular localization and steady-state levels of Nrf2. Cysteine residues present in Keap1 function as redox sensors. Oxidation or chemical modification of some of the highly reactive cysteine residues facilitates the dissociation of Nrf2 from Keap1 and subsequent nuclear translocation.⁹⁵⁻⁹⁷ Therefore, Nrf2 constitutes a unique redox regulator that can be modulated in response to redox imbalance caused by oxidative and electrophilic stresses. Evidences gathered from the *Nrf2*-deficient mice, demonstrate a strong redox imbalanced system that failed to induce genes responsible for carcinogen detoxification and protection against oxidative stress.⁹⁸ In addition, levels of pro-inflammatory mediators, such as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukin (IL)-1 β , IL-6, and tumor necrosis factor alpha (TNF α), were significantly elevated in the colonic tissues of *Nrf2*^{-/-} mice as compared to their wild-type counterparts.⁹⁹ All of these conditions described above induce generation of ROS in the cells. Thus, it would be highly advantageous to explore the cytoprotective gene expression induced by anti-cancer compounds with the Nrf2-Keap1 system as a prime molecular target.

In breast cancer cells (MCF-7, T47D and MCF-10A), Nrf2 plays an important role in suppressing oxidative stress rendered by either paraquat or H₂O₂ by upregulating several phase II detoxification enzymes. On the other hand ectopic expression of wtBRCA1 also stimulate the expression of Nrf2 in the same cells thus indicate an important function of Nrf2 in breast cancer.^{34,75,100} Additionally, retinoic acid (RA), which is an analogue of Vitamin A, has been shown to inhibit breast cancer cell growth¹⁰¹ although it is clinically hindered by toxicity possibly related to oxidative stress. At relatively low concentrations RA inhibits Nrf2 and the expression of its target antioxidation enzymes, thus possibly raises the toxicity. Nrf2 enhancement as a therapeutic target of retinoid toxicity awaits further investigation.¹⁰² Gamma-tocopherol (γ -T) alone or in combination with alpha-tocopherol diet to mice [murine prostate cancer model (TRAMP)] has been shown to suppress prostate carcinogenesis by significantly upregulating the expression of Nrf2 and its related detoxifying and antioxidant enzymes, thereby suppressing prostate intraepithelial neoplasia (PIN) and tumor development.⁷ More evidences of Nrf2 involvement in prostate cancer is demonstrated by multiple human prostate cancer microarray data sets that revealed that

Nrf2 and members of the glutathione-S-transferase (GST) mu family are extensively decreased in human prostate cancer. Loss of Nrf2 initiates a detrimental cascade of reduced GST expression, elevated ROS levels and ultimately DNA damage associated with initiation of cellular transformation in the prostate gland.¹⁰³

NF κ B

The NF κ B family of redox transcription factors has been activated in many malignancies including breast, prostate, pancreas, colon, leukemia, lymphoma etc. NF κ B activation results in development and/or progression of cancer by regulating the expression of genes involved in cell growth and proliferation, anti-apoptosis, angiogenesis and metastasis.¹⁰⁴⁻¹⁰⁸ The NF κ B transcription factors are composed of homodimers or heterodimers of Rel proteins, which interact with inhibitory proteins, members of the I κ B family. As a consequence of binding to cytoplasmic I κ Bs, the nuclear localization signal of the NF κ B dimer is masked and NF κ B is sequestered in the cytoplasm. In response to pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), bacterial lipopolysaccharide (LPS) or viral double-strand RNA (dsRNA), the I κ Bs are rapidly phosphorylated and then undergo ubiquitination and proteolysis by the 26S proteasome, resulting in release and translocation of NF κ B to the nucleus, where it activates transcription of specific target genes. It is suggested that NF κ B activity is regulated by intracellular ROS levels, but the exact molecular mechanism involved in this regulation remains to be elucidated.^{25,109,110} For example it was shown that ROS overproduced by 4-OHE₂ increased the nuclear translocation of NF κ B and its DNA binding through induction of I κ B kinase alpha and IKK β activities that contribute to neoplastic transformation of human mammary epithelial cells (MCF-10A).¹¹⁰ Similar effect has been observed with sodium arsenite that mimics the effects of estradiol and induces cell proliferation in the estrogen responsive breast cancer cell line MCF-7. Sodium arsenite stimulate ROS generation followed by oxidative DNA damage. It also induces HO-1 and c-Myc proteins as well as NF κ B activation and cell proliferation in human breast cancer MCF-7 cells.¹¹¹

In certain cell types, such as Wurzburg subclone of T cells, L6 skeletal muscle myotubes, human breast MCF-7 and 70Z/3 pre-B cells, hydrogen peroxide (H₂O₂) was shown to be an effective inducer of NF κ B activation, but in other cell types it does not.^{112,113} Intracellular level of reduced glutathione (GSH), which may differ from one cell type to another, may be crucial for H₂O₂-induced NF κ B response during oxidative stress. GSH is the major intracellular thiol and an excellent ROS scavenger. N-acetyl-L-cysteine (NAC) is a nontoxic compound that protects cells from oxidative damage and Buthionine-Sulfoximine (BSO) is a drug that causes GSH depletion since it selectively inhibits glutamylcysteine synthetase, the enzyme responsible for GSH synthesis. Preincubation with NAC abolished H₂O₂-induced NF κ B activation in the Wurzburg T cells, while preincubation with BSO demonstrate detectable H₂O₂-induced NF κ B activation in HeLa cells.^{114,115} Several indirect lines of evidence suggest a role for ROS as a common and critical intermediate for various

NFκB-activating signals.^{25,109,110,116} This conclusion is based largely on the inhibition of NFκB activation by a variety of antioxidants and by overexpression of antioxidant enzymes.¹¹⁷ These reagents have been reported to block NFκB activation in many instances, although the extent of inhibition appears to vary depending on cell type and duration of the stimulus. Overexpression of manganese superoxide dismutase (MnSOD) or GPx abolished NFκB activation induced by TNF, LPS, PMA and H₂O₂. AP-1 activity, JNK activation and apoptosis induced by TNF were also suppressed by overexpression of MnSOD.¹¹⁸ Molecularly, oxidative stress stimulate the formation of the slow migrating ubiquitinated forms of the NFκB subunit, IκBα, in SDS-polyacrylamide gel, which rapidly degrades unless cells were treated with the proteasome inhibitor.¹¹⁹ Addition of antioxidants or overexpression of peroxidases in the same stressed cells blocked IκBα degradation induced by TNF, PMA and LPS. Taken together, these data suggested that post translational modification of IκBα and subsequent degradation might be the step that is responsive to oxidative stress.

In prostate cancer cells, a constitutive NFκB activity was reported either due to increase in activity of IκB kinase complex or by regulating the expression of c-myc, cyclin D1 and IL6 in the same cells that deregulate the redox homeostasis in the cells. Additionally, expression of androgen receptor was found to be inversely proportional with the activity of NFκB. Several natural products have been successfully tested against prostate cancer progression but the most effective ones are the soy isoflavones such as, genistein and daidzein. Genistein acts as antioxidant and simultaneously inhibits the TNFα induced activation of the redox-sensitive transcription factor, NFκB, in these cells as well as in human lymphocytes. Surprisingly both anti apoptotic and pro apoptotic function of NFκB have been reported in prostate cancer cells that make it difficult to understand the role of NFκB in prostate cancer cells. Similarly, activation of NFκB signaling is responsible in ROS mediated pancreatic cancer progression. Pancreatic stellate cells (PSC) play a pivotal role in the development of pancreatic fibrosis, which is a characteristic feature of chronic pancreatitis and of desmoplastic reaction associated with pancreatic cancer. PSCs activation is important for the development of anti-fibrosis therapy. Recent studies have identified key mediators of stimulatory and inhibitory signals such as peroxisome proliferator-activated receptor-gamma (PPAR-γ), Rho/Rho kinase, NFκB, MAP kinases, phosphatidylinositol 3 kinase (PI3K) and reactive oxygen species (ROS) might be candidates for the development of anti-fibrosis therapy targeting PSCs.¹²⁰ In human leukemic cells (HL-60) and colon adenocarcinoma cells (LS-174 and WiDr), β-carotene alone or in combination with α-tocopherol or NAC, is associated with significant increase in ROS production and in oxidized glutathione (GSSG) content. These effects were always accompanied by a sustained elevation of NFκB and by a significant inhibition of cell growth that suggests that NFκB induced by β-carotene is involved in the growth-inhibitory and proapoptotic effects of the carotenoid in leukemia and colon adenocarcinoma cells.¹²¹ Moreover, diallyl sulfide (DAS), an organosulfur component of garlic, induces apoptosis in colon cancer cells by stimulating the expression of NFκB

and Caspase 3. It also suppresses the expression of extracellular regulatory kinase-2 (ERK-2) and inhibits the expression of ROS in the same colon cancer cells.¹²² Isothiocyanates that are found in cruciferous vegetables such as broccoli, brussels sprouts, cauliflower and cabbage, suggest that cruciferous vegetable intake may lower overall cancer risk generated during oxidative stress, including colon and prostate cancer due to inactivation of NFκB signaling pathway.

Oxidative Stress Signaling through MAP Kinases

Mitogen-activated protein kinases (MAPKs) are the key players of kinase cascades that connect extracellular signals to specific transcription factors, thereby converting these signals into cellular responses. In mammalian systems, there are three subgroups of MAPKs: ERKs (extracellular signal-regulated kinases), JNKs (c-Jun N-terminal kinases) and p38 MAPKs. Growth factors and mitogens use the Ras/Raf/MEK/ERK signaling cascade to transmit signals from their receptors to regulate gene expression and prevent apoptosis in normal condition.^{123,124} The MAPK signaling cascade is activated by a wide variety of receptors involved in growth and differentiation including receptor tyrosine kinases (RTKs), integrins and ion channels. This pathway has been reported to be activated in over 50% of acute myelogenous leukemia, acute lymphocytic leukemia and are frequently activated in breast, prostate cancers and other cancer types.¹²⁴⁻¹²⁶ Under optimal growth conditions, transiently elevated ROS levels confer a growth advantage to tumor cells. However, exposure of these cells to anticancer agents induces a prolonged increase in ROS levels resulting in potentiation of apoptosis. Thus ROS modulates the ability of stress kinases to stimulate cell growth or cell death and it depends on signal intensity and signal duration.^{127,128} This idea has been nurtured to explain the complex nature of ERK signaling in cell cycle regulation and in stress activated protein kinase signaling (SAPK). Transient, reduced activity of SAPK promotes cell proliferation, whereas persistent, increased activity results in cell killing.^{129,130} Conversely, in drug-resistant tumors, phase II enzymes or other antioxidant defenses are often upregulated, shielding cells from apoptosis. ASK1, an upstream regulator of SAPKs, is inhibited in normal cells through its association with thioredoxin, which is an antioxidant capable of metabolizing ROS. Increased levels of ROS lead to the dissociation of this complex and thereby facilitate the activation of ASK1 and subsequently SAPKs.^{131,132} A similar redox control has been identified for JNK where increased level of ROS triggers the detachment of JNK associated glutathione-S-transferase-π (GSTp) and thereby facilitating JNK activation.¹³³ Moreover, ROS-dependent activation of JNK may also lead to knock down of a JNK phosphatase via an unknown mechanism linking ROS and stress induced kinases an important player in cancer cell growth. Recently it was demonstrated that mammalian stanniocalcin-1 (STC1), which is a glycoprotein, has been implicated in various biological processes including angiogenesis and its aberrant expression has been reported with hormone responsive cancers such as breast, prostate and ovarian cancer. During oxidative stress

the expression of STC1 increased several folds that are associated with decrease in ERK1/2 activation in mouse MEFs.¹³⁴

Several natural phytochemicals exploit the signaling cascades of MAP kinases to exert its effects on the modulation of cancer initiation and progression. Kaempferol is a flavonoid that reduces the cell viability of breast cancer cells by inducing ROS mediated apoptosis and ERK activation as demonstrated by 3D culture conditions.^{135,136} On the other hand, Acacetin, which is a natural flavone, and stimulate apoptosis in MCF-7, breast cancer cells that is mediated by activation of caspases, ROS generation, mitochondria-mediated cell death signaling and the induction of SAPK/JNK1/2-c-Jun signaling pathway.¹³⁷ Exposure of MCF-7 and MDA-MB-231 breast cancer cells to kotomolide A (KTA), a new butanolide constituent, resulted in cellular GSH reduction and ROS generation, accompanied by JNK activation and apoptosis.¹³⁸ When comes to pancreatic cancer, it is very aggressive and unresponsive to treatments due to its resistance to apoptosis. Growth inhibition of pancreatic cells is dependent on the efficiency of scavenging ROS as well as effective inhibition of ERK1/2 signaling pathway activation as demonstrated by using the free radical scavenger NAC or the MEK/ERK1/2 inhibitor (PD98059). Moreover, ERK1/2 induction is dependent on ROS production as demonstrated by a complete removal of ERK1/2 phosphorylation by NAC.¹³⁹ Thus ROS act as prosurvival, anti-apoptotic factor in pancreatic cancer cells. Moreover, treatment of SW620 (colon cancer cells) with berberine, which is a major constituents of *Coptidis Thizoma*, resulted in activation of apoptosis by phosphorylation of JNK and p38 MAPK, as well as generation of the ROS.¹⁴⁰ Furthermore, proline oxidase (POX), that often considered as a 'housekeeping enzyme', induce apoptosis through both intrinsic and extrinsic pathways and is involved in nuclear factor of activated T cells (NFAT) signaling and regulation of the MEK/ERK pathway in colon cancer cells. It is suggested that, as a nutrition factor, POX may modulate apoptosis signals induced by p53 or other anti-cancer agents and enhance apoptosis in stress situations.¹⁴¹

Activating Map kinase pathways in prostate cancer cells is often beneficial to stimulate apoptosis and inhibition of growth. Melatonin, the main secretory product of the pineal gland, inhibits the growth of prostate cancer cells (LNCaP) and promotes apoptosis via MAPKs, which are closely associated with apoptosis and survival. Melatonin also activates JNK and p38 kinase whereas extracellular signal-regulated kinase (ERK) was not responsive to melatonin. Thus, melatonin may be of promise for anti-prostate cancer strategies that will utilize the MAP kinase pathways.¹⁴² Moreover the well known AKT/mammalian target of rapamycin (AKT/mTOR) and ERK MAPK signaling pathways have been shown to participate in prostate cancer progression. A combinatorial therapy using rapamycin, an inhibitor of mTOR, and PD0325901, an inhibitor of MAPK kinase 1 (MEK; the kinase directly upstream of ERK), inhibits cell growth in cultured prostate cancer cells. Furthermore, analyses of human prostate cancer tissue microarrays demonstrated that AKT/mTOR and ERK MAPK signaling pathways are often deregulated during prostate cancer progression in humans.¹⁴³ In androgen-independent prostate cancer (PC-3) cells, natural

phytochemical, Capsaicin, originated from Red Pepper that has anticarcinogenic, antimutagenic or chemopreventive properties, inhibits cell growth and induces apoptosis through ROS generation. Capsaicin also stimulated the MAP kinase cascades, ERK, JNK and p38 MAPK, to demonstrate its antiproliferative effect but it does not activate p38 MAPK.¹⁴⁴ Lastly a new ionic Pd(II) complex, with the metal center coordinated to two different chelating ligands, the pure curcumin (from turmeric) and the 4,4'-dinonyl-2,2'-bipyridine, has been shown to inhibit both cell growth and apoptosis in several human prostate cancer cells, (LNCaP, PC3, and DU145) through the production of ROS and JNK phosphorylation associated with GSTp1 downregulation.¹⁴⁵ Thus exploiting the MAP kinase pathway could be an important step towards inhibition of the occurrences of prostate cancer.

On the basis of what discussed above in regards to the role of oxidative stress in carcinogenesis with emphasis to breast, prostate, colon and pancreatic cancer we generated a pictorial model (Fig. 2) using Motifolio Tool kit (www.motifolio.com). We tried to demonstrate the crosstalk between the molecular mechanisms that occur during the anti-carcinogenic actions of several compounds by exploiting Nrf2, NFκB or MAP kinase pathways when the cells are under oxidative stress.

Concluding Remarks and Future Perspectives

Redox adaptation is an important concept that cancer cells undertake to survive, under persistent endogenous ROS stress and become resistant to certain anticancer agents. Redox-modulating strategies to target these biochemical properties of cancer cells will be a feasible therapeutic approach that may enable therapeutic selectivity and to overcome drug resistance. One of the best strategies is to increase the ROS metabolizing capacity of the agents (antioxidants and antioxidation enzymes) that subsequently suppress the tumor growth. But, there are reports that using antioxidants in clinical trials are associated with increased cancer incidences, probably due to the inhibition of ROS mediated apoptosis of cancer cells. In addition, there is experimental evidence that antioxidants (e.g., paclitaxel and bortezomib) and radiation therapy, could actually decrease the ROS-mediated anti-tumor activity of the anticancer agents.^{146,147} An alternative approach is to treat cancer cells with pharmacological agents that have pro-oxidant properties, which increase ROS generation or abrogate the cellular antioxidant systems in the tumor itself. Cancer stem cells are highly resistant to anticancer drugs and might use the same redox adaptation as normal stem cells, for their survival. An approach that can break this redox adaptation by depleting the main antioxidant pool from the cells might be beneficial to eliminate the cancer stem cells. Studies showing that a compound known as TDZD-8 (4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione) can induce the depletion of thiols, leading to a rapid accumulation of ROS and selectively kill leukaemic cells expressing stem-cell markers with minimal toxicity to normal haemopoietic stem cells,¹⁴⁸ highlights this as an important research direction.

Molecularly, it has become clear that cancer results from alterations and aberrations in several hundred genes, indicating that a tumor cell uses multiple pathways to survive and thrive.

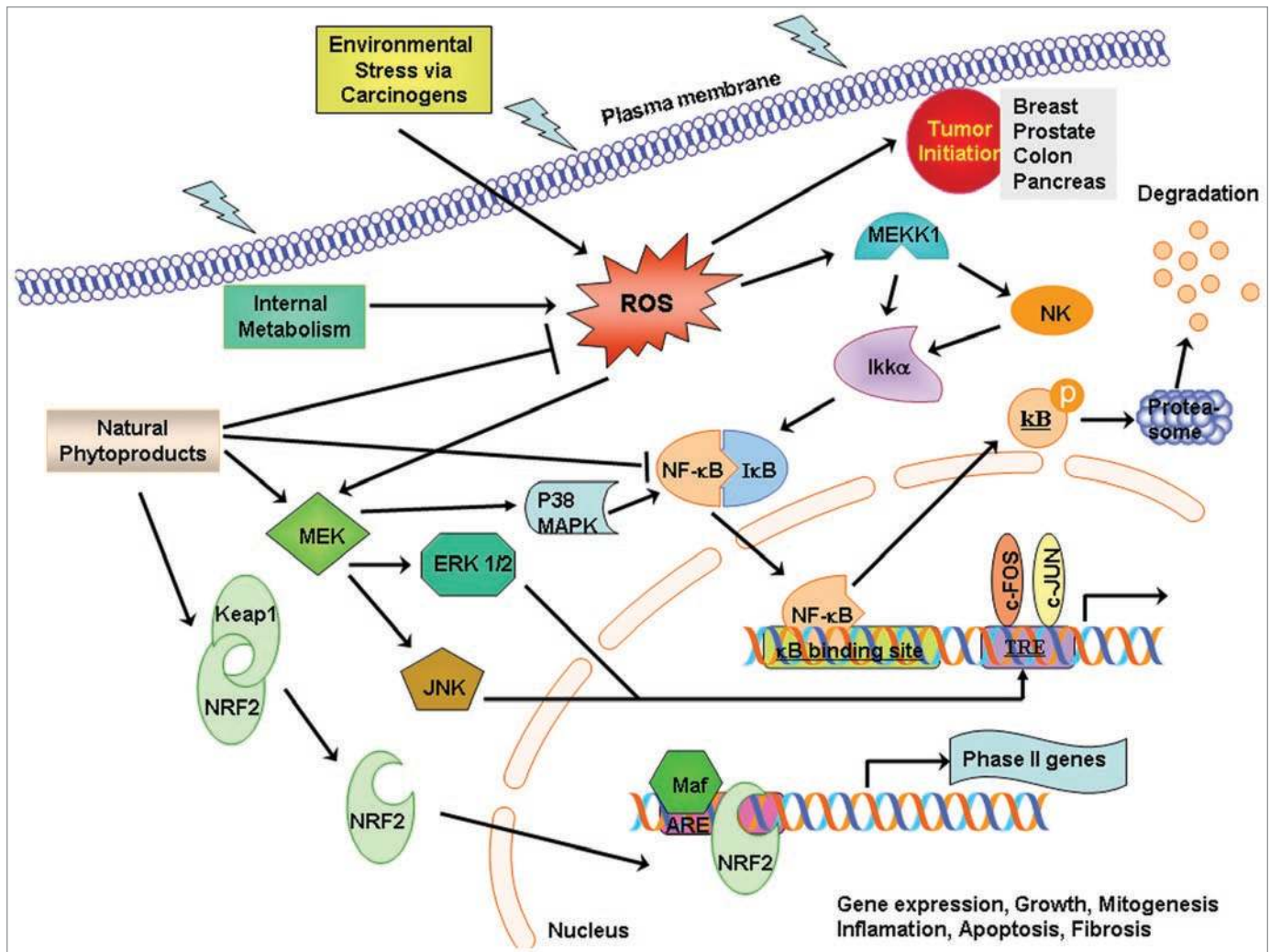


Figure 2. A putative model for oxidative stress induced interactions in carcinogenesis. Reactive oxygen species (ROS) mediated oxidative stress either by environmental carcinogens such as UV and ionizing radiation or by mitochondrial metabolism exerts several effects on DNA damage and generation of oxidative lesions, gene expression, growth regulation mitogenesis, inflammation, apoptosis and fibrosis leading to genomic instability and cancer progression. Chemical signals generated by dietary chemopreventive agents, anticancer agents, antioxidants and antioxidation enzymes, cause Nrf2 nuclear translocation that sets in motion a dynamic machinery of coactivators and corepressors that might form a multimolecular complex with Nrf2 for modulating transcriptional response through the antioxidant response element, ARE producing several phase II detoxification enzymes as stimulation of cellular defense system during stress. Oxidative stress might also cause release of NFκB from IκB and stimulate NFκB nuclear translocation to modulate transcriptional response through the NFκB response element. Several members of the MAPK family may act in concert with Nrf2 and NFκB with multiple interactions between the members of the putative complex to elicit the chemopreventive and pharmacotoxicological events against carcinogenesis.

A definitive role of selected dietary naturally occurring products for prevention and treatment of cancer is now getting high popularity. The challenge is how best to use this information for cancer prevention in populations with differing cancer risk. One way to address this problem is to design potent mixture of several phytochemicals from plant and fruit sources that could have an additive and synergistic effect to inhibit several molecular pathways required by cancer cells to survive. Such cocktails will have greater likelihood for producing cancer chemopreventive effects in humans than individual components. Bioavailability is one of the critical issues to be discussed even before considering the beneficial effects of several phytochemicals because metabolism of the dietary

phytochemicals and their biological properties depends on their presence at the time and site of the damage. Another issue of concern is whether purified phytochemicals have the same protective effects, as do the whole food or mixture of foods in which these compounds are present. The current knowledge base teaches us that they are generally more effective when consumed as whole foods.

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