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Review Article

Modulation of Nrf2/Keap1 pathway by dietary phytochemicals

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ABSTRACT

Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), also known as NFE2L2, has emerged as a transcription factor that plays a crucial role in cellular protection against free radical damage and reduce the incidence of the radical derived degenerative diseases such as cancer. Nrf2 is a basic leucine zipper transcription factor that binds to ARE leading to induction of a verity of ARE driven detoxification and antioxidant genes. In basal conditions, Nrf2 is sequestered in the cytoplasm by an inhibitory partner the cytoskeletal anchoring protein Kelch-like ECH associated protein-1 (Keap1) through extensive hydrogen bonds. Inducers dissociate this complex, allowing Nrf2 to translocate to the nucleus. A number of studies have elucidated that nutritional compounds can modulate the activation of Nrf2/Keap1 system. This review aims to discuss some of the key nutritional compounds that enhance the activation of Nrf2, with consequent antioxidant and anti-inflammatory defensive effects.

Keywords: Nrf2, Keap1, Phytochemicals

INTRODUCTION

In recent years, there has been a growing of interest, supported by a number of studies on the understanding of how phytochemicals influence the prevention and/or treatment of diverse chronic diseases. Despite prominent progress in our understanding of the carcinogenic process, the mechanisms of action of most chemopreventive phytochemicals have not been entirely explained. A number of dietary compounds have been identified as prospective chemopreventive agents. Several vegetables and fruits including; broccoli, blueberries and cacao beans, are among the most protective specifically due to an excess of active molecules such as isothiocyanates, polyphenols, and flavonoids. Together, these naturally occurring molecules are known as phytochemicals.[1] Upon entering cells, these phytochemicals can directly scavenge free radicals and can also provoke electrophilic stress signals that trigger proteins linked to diverse cellular signaling pathways.[2] This capability involves the activation of Nrf2/Keap1 complex. Nrf2 has emerged as a transcription factor that plays an important part in the maintenance of cellular homeostasis.[3] Activation of the Nrf2/Keap1 complex results in the induction of cellular defence mechanisms, including phase II detoxifying enzymes and other stress defence molecules that preserve normal cells from reactive oxygen species (ROS) and/or reactive nitrogen species (RNS).[4] Previous studies have demonstrated that nutritional components may modulate the Nrf2/Keap1 complex system, it is therefore may be of significance to elucidate the useful effects of this system in numerous chronic diseases.

Keap1/Nrf2 SYSTEM

The antioxidant-activated transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) regulates the induction of cytoprotective genes against chemical toxicity and oxidative injuries.[5] Nrf2 belongs to the basic leucine zipper transcription factor family, a member of the cap 'n' Collar family of regulatory proteins that also

includes NF-E2, Nrf1, Nrf3, Bach1, and Bach2.[6] Under basal conditions, Nrf2 is sequestered in the cytoplasm by Keap1 protein and facilitates Nrf2 degradation via the proteasome system.[7] Upon exposure to electrophilic or oxidative stress, Nrf2 dissociates from Keap1 and translocates into the nucleus, where it undergoes heterodimerization with sMaf protein and binds to the ARE sequence in the upstream promoter regions, leading to the induction of a diverse cytoprotective genes include: NAD(P)H: quinone oxidoreductase (NQO-1), glutathione-S-transferase (GST), glutamate cysteine ligase (GCL), heme oxygenase-1 (HO-1), etc.[8] This Nrf2-ARE binding complex seems to be the main mechanism for the defence strategy of the cells against oxidative stress, by inducing proteins that are involved in antioxidative responses as well as by elimination of electrophiles through conjugation by induction of detoxifying enzymes.[9] Moreover, Nrf2-null mice lack this co-ordinated genetic programme, and are susceptible to diverse oxidative stress-related diseases, including chemical carcinogenesis, acetaminophen toxicity, and diesel-exhaust induced DNA damage.[10]

Based upon the homology of cross-species orthologous, six highly conserved functional domains were identified in the primary structure of Nrf2, known as Nrf2-ECH homology (Neh) domains, Neh1 to Neh6.[5] Neh1 domain has a CNC basic leucine zipper domain which is required for its ability to dimerize with other b-Zip proteins and to bind DNA as a heterodimer.[11] Neh2 consists of the amino-terminal region of the Nrf2 and serve as a negative regulator of Nrf2.[12] Neh3 domain located at the C-terminal end of the protein and required for the transcriptional activation of Nrf2.[13] Both Neh4 and Neh5 are transactivation domains, interact with the cAMP response element-binding protein (CREB)-binding protein (CBP) to regulate the start of transcription.[14] Neh6 domain, in turn, contributes to redox-independent negative control of Nrf2.[12]

It has been elucidated that Nrf2 through its Neh2 domain interacts with the cytosolic protein Keap1, also known as inhibitor of Nrf2 (INrf2), and negatively controls Nrf2 function. The Keap1 protein consists of 624 amino acids and structurally related to Drosophila actin-binding protein Kelch.[5] Keap1 is composed of five major domains: an N-terminal region (NTR), broad complex, tramtrack, and bric-a-brac domain (BTB), a cysteine-rich intervening region (IVR), the double glycine repeat region (DGR) or Kelch domain, and a C terminal Kelch region (CTR). Keap1 forms a homodimer and each dimer binds one molecule of Nrf2 by its two Kelch domains, with one high affinity binding site (ETGF motif) and one weak affinity binding site (DLG motif). Both motifs are located in the Neh2 domain of Nrf2.[15] The ETGF motif has a higher affinity for Keap1 than the DLG motif and this is the so-called ''hinge-and-latch'' model.[16] In overall, ubiquitination of Nrf2 either by Keap1 dependent or independent means is an essential mechanism to suppress Nrf2. Activation of Nrf2 is started by the dissociation of Nrf2 from Keap1, preventing its ubiquitination, and allowing its translocation into the nucleus. Through its control by multiple kinases and proteins, Nrf2 eventually binds with ARE and triggers phase II detoxification enzymes and antioxidants.[17]

BIOLOGICALLY ACTIVE FOOD COMPONENTS AND Nrf2

Keap1, which regulates Nrf2 activity, is structurally designed to respond to oxidants and electrophiles.[18] The high cysteine content of Keap1 suggested that cysteine residues would be an excellent candidate as the sensor for inducers. Hence, chemical inducers are able to modifying cysteine residues, they are likely also able to be activators/inducers of Nrf2.[18] Following Nrf2 activation, induction of phase II and antioxidative enzymes, especially GST, NQO1, and elevated glutathione levels are characteristic cellular events.[19] Activation of Nrf2 signalling by specific chemicals can be considered as one of efficient ways for prevention of oxidative stresses. Nrf2-activating chemicals that induce ARE downstream genes have been categorized as cytoprotective agents. These include phenolic antioxidants (e.g. butylated hydroxyanisole), isothiocyanates (sulforaphane from broccoli), derivatives of 1,2-dithiole-3-thiones (oltipraz, 3H-1,2-dithiol-3-thione, D3T), derivatives of polyphenols (e.g. Resveratrol), turmeric compounds (Curcumin), and many others.[20,21] Researchers routinely use these compounds to identify Nrf2-inducible genes.

Butylated hydroxylanisole (BHA)

BHA is a synthetic phenolic antioxidant that is widely utilized as a food additive, due to its chain-breaking action during the autooxidation of lipid, and probably present in nearly all food preservatives.[23] In addition to its ability to inhibit lipid peroxidation, BHA displays a number of interesting and potentially important biological activities.[24] Dietary administration of BHA has been suggested to provide protection against chemical carcinogens,[25] possibly due to its ability to induce phase II detoxifying enzymes including; epoxide hydrolases (EH), UDP-glucuronosyltransferase (UGT), NQO-1 and GST.[26,27] Moreover, the ability of BHA to inhibit cytochrome p450 and monooxygenases that activate carcinogens has also been attributed to this effect.[28] In addition to the anticarcinogenic effects of BHA, several reports have established that BHA may also be a tumor initiator in some tissues of animals. For instance, BHA has been found to be carcinogenic to the forestomachs of rats, mice, and hamsters when fed constantly at high concentrations.[29,30] Both of anti-carcinogenic and carcinogenic effects of BHA are well described, and has been suggest to be dose- and/or tissue-dependent.[23] Studies on the metabolism of BHA describes several metabolic processes presumably occur, including dimerization, conjugation, and O-demethylation.[31] Tert-butylhydroquinone (tBHQ), one of the main metabolites of BHA, has been identified to exert anti-carcinogenic

activities in some animal models of cancer in a similar way that displayed by BHA. This implicates modulation of enzymes responsible for metabolic activation or deactivation of carcinogenic compounds.[32] Therefore, metabolic formation of tBHQ is suggested to contribute to the anticarcinogenic properties of BHA.[23]

Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane, SFN)

SFN is a naturally occurring isothiocyanate that has been isolated from broccoli as the main phase II enzyme induce found in organic solvent extracts of this vegetable. SFN has captured researchers' attention as a favourable cancer chemopreventive agent.[33] In many studies, sulforaphane can reduce the incidence of a various forms of tumor.[34] It has been suggested that the main mechanisms of chemoprotection by isothiocyanates depend on the modulation of carcinogen metabolism by inhibition of metabolic activation of phase I enzymes and the induction of phase II detoxification enzymes.[35,36] In fact, reporters from molecular studies have revealed that isothiocyanates can induce phase II enzymes by catalysing the transcription of their genes via a common antioxidant and/or electrophile promoter element placed in the upstream regulatory region of diverse phase II enzyme genes for example by activation of Nrf2 and inhibition of nuclear factor-κB (NF-κB).[37,38] Moreover, sulforaphane increased mRNA and protein expressions of Nrf2 and its downstream target gene NQO-1 in *in-vitro* experiments.[39] A number of studies have revealed the mechanism of Nrf2 activation by SFN to involve disturbed Keap1 interactions due to alterations in critical Keap1 cysteine residues.[40] The interaction of SFN with Keap1 causes the nuclear build-up of Nrf2 and the activation of its transcriptional machinery. Likewise, SFN may impact the activity of a diverse intracellular kinases to phosphorylate Nrf2 proteins, by involving in nucleocytoplasmic pathway of Nrf2 or modulation of Nrf2 protein stability.[41,42] Further, a variety of other independent mechanisms have been suggested to play a powerful role in the prevention of cancer growth by isothiocyanates such as; the activation of c-Jun NH2-terminal kinase,[36] and extracellular signal-regulated kinase-1/2.[43] Isothiocyanates could also work at the DNA level or impact signal transduction pathways leading to cell cycle arrest.[44]

Dithiolethiones (3H-1,2-dithiole-3-thiones)

Dithiolethiones including 3H-1,2-dithiole-3-thione (D3T), 4-methyl-5-pyrazinyl- 3H-1,2-dithiole-3-thione (OLT) and 5-tert-butyl-3H-1,2-dithiole- 3-thione (TBD) are class of organosulfur compounds exhibiting cancer chemopreventive activity in many target organs. These chemical compounds are known to activate the transcription factor Nrf2.[45] Administration of sulfhydryl reactive compounds such as D3T abolishes Keap1 suppression of Nrf2 activity, allowing the translocation and accumulation of Nrf2 in the nucleus.[46] The modification of protein thiol residues on Keap1 by dithiolethiones appear to be the most possible mechanism by which dithiolethiones activate Keap1/Nrf2 system. Moreover, the reaction of thiols with dithiolethiones results in generation of reactive oxygen species, which have the possibility to alter cysteine residues on Keap1.[47] Oltipraz, one of dithiolethiones, was primarily developed for the treatment of schistosomiasis and has been identified as an effective chemopreventive agent in various rodent organs such as the pancreas, lung, stomach, bladder, colon, kidney, trachea liver, mammary gland and skin.[48] It has also been demonstrated that oltipraz is effective against wide range of carcinogen, some of which are popular human carcinogens, e.g. aflatoxin B1 (AFB1), benzo[a]pyrene, and 2-amino-1-methyl-6-phenylimidazo[4,5]pyridine.[45]

Resveratrol (3, 5, 4'-trihydroxystilbene)

Resveratrol is a type of plant compounds called non-flavonoid polyphenols found in peanuts, grapes, and red wines.[49] Resveratrol thought to has antioxidant activity, which depends on the redox activities of phenolic hydroxyl groups, protecting the body against many conditions such as cancer and heart diseases.[50] Researchers reported that the antioxidant activity of resveratrol are mediated by the induction of phase II detoxification enzymes via Nrf2 including; NQO-1, GST, and superoxide dismutase (SOD), etc.[51] Corroborating these findings, Palsamy et al. also demonstrated that resveratrol treatment of diabetic rats normalized the renal expression of Nrf2/Keap1 and increased SOD, GST, glutathione peroxidase (GPx), glutathione reductase (GR) and catalase activities.[52] A number of studies have shown that resveratrol can modulate several pathways involved in cell cycle growth and apoptosis.[53] Resveratrol gained enormous significance as it possesses cancer protective as well as anticancer activities in diverse biological systems.[54] In animal studies, administration of resveratrol results in prevents the development of skin,[55] mammary,[56] prostate tumours,[57] as well as suppresses tumorigenesis in the stomach,[58] colon,[59] and liver.[60] Several mechanisms may account for the cancer preventive effect of resveratrol including inhibition of free radical formation and activities of cyclooxygenase (COX), hydroperoxidase, inducible nitric oxide synthase, cytochrome P-450 and protein kinase C, regulation of growth factors and matrix metalloproteins.[61] These multiple mechanisms participate to the comprehensive influence of resveratrol's effects against cancer cells.[62]

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)

Curcumin is the main active component of turmeric, a yellow compound isolated from the rhizomes of Curcuma longa, distributed mainly throughout tropical and subtropical regions of the world, and has been used for thousands of years in traditional medicines.[63] Curcumin exhibit various important activities such as anti-

inflammatory, antioxidant, and chemopreventive activities. All of these activities are thought to be mediated through its regulation of many transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes.[64] Curcumin shows both direct and indirect antioxidant activities by scavenging reactive oxygen species and inducing the expression of cytoprotective proteins in an Nrf2-dependent way.[65,66] In a study by Garg et al., dietary administration of curcumin in mice raised nuclear Nrf2, ARE binding activity, and target gene expression in the liver and lungs.[67] Moreover, administration of curcumin has been found to increase expression of the xenobiotic detoxifying enzymes in both liver and kidney of mice.[68]

Vitamin E

Vitamin E is well known for its strong antioxidant activity and has been suggested as the most important lipid soluble antioxidant in humans.[69] Vitamin E represent eight different isomers that belong to two classes; tocopherols (TP) and tocotrienols (T3).[70] The α-tocopherol is the main form in the human body, and it is a famous antioxidant compound that inhibits lipid peroxidation and other free radical-mediated reactions in biological systems.[71] However, tocotrienols have been suggested to possess superior antioxidant activity compared to tocopherols at preventing cardiovascular diseases and cancers.[72,73] The consumption of vitamin E for prevention and treatment of human diseases is well documented. Numerous studies revealed that vitamin E exhibited chemopreventive activity. For instance, Barve et al. studied the effects of a diet contain a mix of γ-tocopherol and α-tocopherol on prostate carcinogenesis in a murine model of prostate cancer, and they found that Nrf2 was significantly upregulated following treatment.[74] Hsieh et al. demonstrated the ability of tocotrienol to induce Nrf2 expression, as evidenced by decrease in Keap1 levels in estrogen receptor-negative MDA-MB-231 cells but not in estrogen receptor-positive MCF-7 cells. Tocotrienols represent distinguished and selective activity in controlling the Nrf2-Keap1 system, in coordination with the induced expression of genes that modulate cytoprotective oxidative stress and regulation of proliferation in breast cancer cells.[75] Moreover, tocotrienols was found to induce various Nrf2 regulated enzymes such as γ-glutamyltransferase (GGT), UDP-Glucuronyltranferase (UDP-GT) and GST.[76,77] Although tocopherol have been found to increases the expression of Nrf2, a recent study conducted by Li et al. elucidated that the antioxidant activity of the tocopherols in mice are independent of the Nrf2 pathway using Nrf2-knockout mice.[78] Therefore, more studies are needed to confirm the activity of vitamin E on Nrf2 gene expression.

CONCLUSION

As discussed above, a compelling data demonstrating the transcription of Nrf2 is influenced by nutritional compounds. Most of the dietary component evaluated above shows protective effect against many diseases by modulation of the Nrf2/Keap1 system leading to coordinated up-regulation of ARE driven detoxification enzymes. Taking together all the studies that have been discussed in this review, it is not yet possible to provide safe and efficient doses for supplementation since most studies are performed in *in-vitro* or in animals and it is unclear how far these doses can be extrapolated to be influential in humans.

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