Chapter 5

Nrf2 Contributes to the Poor Prognosis and Chemoresistance

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Additional information is available at the end of the chapter

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Abstract

With the increasing incidence of human cancer and continued difficulty in treating metastatic tumors, there is an urgent need to identify biomarkers for tumors with poor outcome and novel therapeutic targets. Many therapeutic targets have been found in recent years. One promising biomarker and therapeutic target that is valuable for human tumor is nuclear factor erythroid 2-related factor 2 (NFE2L2, Nrf2). In this chapter, we will discuss the regulatory mechanisms and conflicting roles of Nrf2 during different stages of tumor development as well as its involvement in the drug resistance and hypoxia-induced chemoresistance. We will also discuss various positive and negative modulators of Nrf2 as reference to their potential utility as study tools and leads for further clinical development.

Keywords: Nrf2, oxidative stress, ROS, tumor, prognosis, chemoresistance

1. Introduction

Nrf2 is the main regulator for the expression of antioxidant enzymes and the detoxification proteins. With these abilities of Nrf2, Nrf2 activation confers cells with more anti-stress capacity, thus resulting in more malignancy and chemoresistance of tumor cells. Therefore, targeting Nrf2 in tumor may offer therapeutic benefit by undermining its advantage on the proliferation, migration, metastasis, and drug resistance of tumor cells. Collectively, Nrf2 has the potential to serve as a good biomarker and therapeutic target to overcome the poor prognosis and chemoresistance associated with tumor or tumor hypoxia [1, 2].

2. Nrf2 is the key regulator of antioxidant and detoxification abilities

Organisms survive based on the normal and steady function of cell metabolism to maintain cellular homeostasis. However, the process of metabolism produces many metabolic wastes. If these wastes are not properly removed, they become harmful. One of these metabolic wastes is the reactive oxygen species (ROS). While ROS can serve the signaling function, uncontrolled ROS may lead to cellular damage and death. Many key enzymes involved in the removal of excess ROS are tightly regulated by a transcription factor, Nrf2.

Nrf2 activation is strictly regulated by an ubiquitin-proteosome system (UPS) [3]. Nrf2 is negatively regulated by Keap1 (Kelch-like ECH-associated protein 1), the most important molecular switch controlling the activation and inactivation of the Nrf2 pathway. Keap1 is an adaptor for Nrf2 as the Nrf2-Keap1 complex becomes a substrate for the Cul3-dependent E3 ubiquitin ligase for proteasomal degradation. Keap1 is a cysteine-rich protein, which can be modified by many oxidants and electrophiles. Upon exposure to oxidative stress, these cysteine residues may be altered by stresses to induce conformational changes that inhibit Keap1-dependent ubiquitin ligase activity to allow Nrf2 accumulation [4, 5].

Since Nrf2 is a transcription factor, the accumulated Nrf2 proteins translocate into the nucleus to dimerize with members of the small Maf family, and bind to the antioxidant response element (ARE or electrophile response element 5′-RTGABNNNGCR-3′) in the promoter regions of cell defense genes [6]. These Nrf2-regulated proteins include Phase II detoxification enzymes and some stress response proteins as listed below:

1. Antioxidant proteins: proteins that control the antioxidant specializing in neutralizing the reactive species and protecting organisms from oxidative damage, such as NAD(P)H: quinone oxidoreductase 1 (NQO1), epoxide hydrolase, heme oxygenase 1 (HO-1), glutathione *S*-transferase (GST), and glutathione peroxidase (GPx).

2. Glutathione producing enzymes: proteins that regulate the synthesis and metabolism of glutathione, such as glutamate-cysteine ligase (GCL), which consists of two subunits, a light regulatory subunit; glutamate-cysteine ligase modifier subunit (GCLM), and a heavy catalytic enzyme; GCL catalytic subunit (GCLC).

3. Drug-metabolizing enzymes: enzymes that regulate the metabolism of drugs, including UDP-glucuronosyl-transferase 1A1 (UGT1A), carbonyl reductase 1 (CBR1), aldo-keto reductases (AKR), and cytochrome P450 (CYPs).

4. Xenobiotic transporters (ATP-binding cassette (ABC) transporter): proteins that belong to ATP phosphohydrolase, some of them are involved in the exclusion of drugs, xenobiotics and their metabolites [7], which are named multidrug resistance proteins, such as multidrug resistance protein 1 (MRP1).

5. Numerous other stress response proteins, such as thioredoxin, ferritin subunits, and copper/zinc superoxide dismutase [8] (see **Figure 1**).

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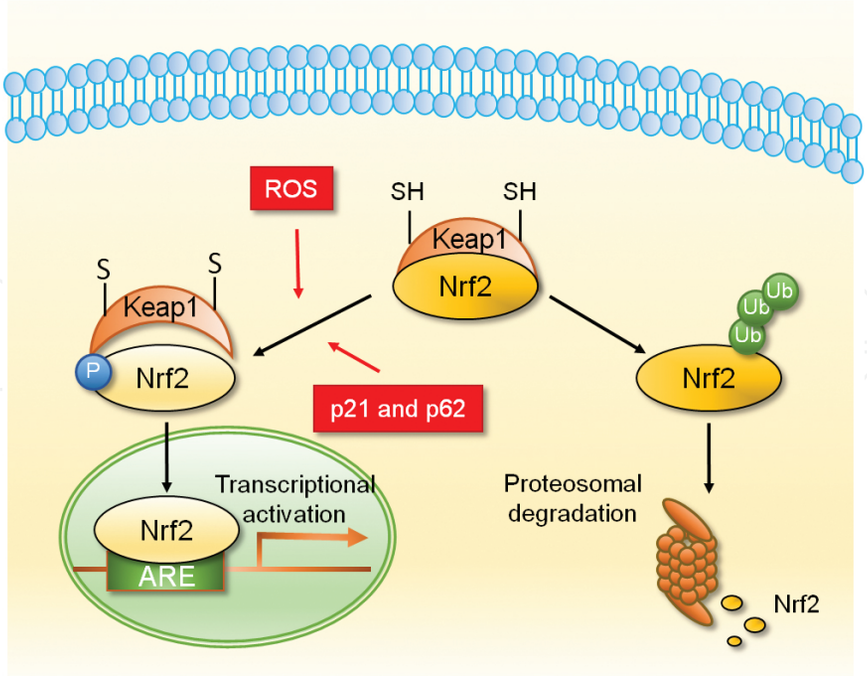

Figure 1. Regulation of Nrf2. Keap1 binds to Nrf2 and sends it to proteasomal degradation. ROS can lead to the conformational change of Keap1 and Nrf2 release. Free Nrf2 then enters the nucleus and initiate the following transcriptional process by binding to the ARE domains, P21 and P62.

3. The conflicting roles of Nrf2

Since Nrf2 is the key regulator of antioxidant capacity and detoxified proteins, the activation of Nrf2 is expected to protect cells from stresses, such as reactive oxygen species (ROS). Therefore, the Nrf2 pathway is so called oxidative stress response pathway or cellular defense pathway. Once cells or organisms are exposed to ROS induced by physical forces or chemicals, Nrf2 is activated to increase the anti-stress capacity and cope with the ROS. Nrf2 activation can stabilize the intracellular oxidant level and maintain the redox state within cells to avoid DNA damages, genomic instability, and potentially serious sabotages caused by ROS [9]. Although DNA repair mechanism can reduce slight DNA damage, higher presence of oxidizing base lesions in DNA leads to DNA mutation, which may cause aging [10], cell damage, cell death, carcinogenesis, and even cancer. Therefore, various Nrf2 activators are being pursued in chemopreventive strategies [11] to reduce tumor development. In addition, Nrf2 activators have been used to treat various human diseases, including diabetic nephropathy [12, 13] and sickle cell disease [14].

On the other hand, excess ROS may lead to numerous diseases, such as inflammation, obesity, and other metabolic diseases. For example, too much oxidative stress affects the differentiation of adipocytes and impairs the normal function of white adipose tissue [15], leading to inflammation and adipokine secretion that affect the whole organism [16, 17]. The activation of Nrf2 defense pathway can protect organisms from many metabolic diseases.

Therefore, Nrf2 can be the double edged sword in the organism. In normal cells, Nrf2 activation keeps the redox homeostasis and prevents cancer development. However, once cancer cells have established, Nrf2 activation may drive oncogenesis and confer chemoresistance. In many cancers, constitutive Nrf2 activation is an oncogenic mutation [18] and a biomarker for poor prognosis [19, 20] (**Figure 2**). In the TCGA data, mutations in the Nrf2 pathways constitute one of the major oncogenic pathways of lung cancers [21, 22]. The angel and devil roles of Nrf2 are discussed in the following sections.

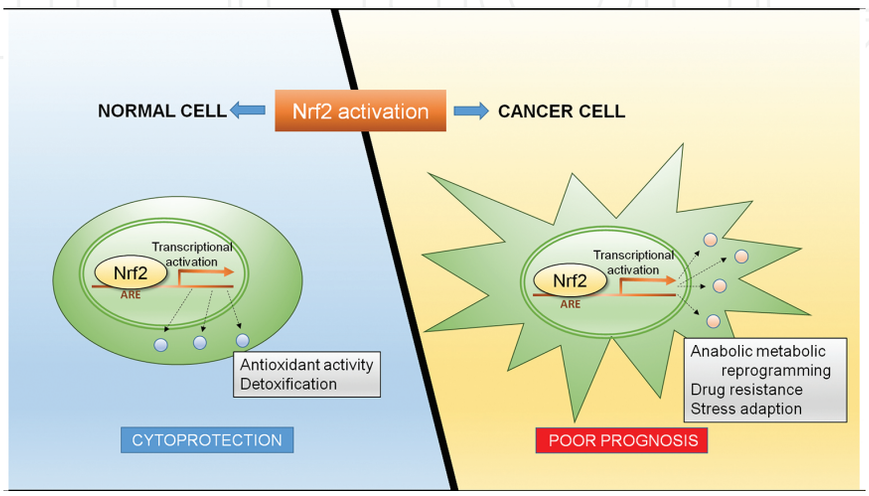

Figure 2. Nrf2 produces phase II enzymes that provide cell defense system, such as the antioxidant and detoxification, in normal cells. Once tumor is formed and cancer cells get the cytoprotective abilities of Nrf2, which triggers anabolic metabolic reprogramming, drug resistance, and stress adaption, Nrf2 leads to poor prognosis in patients.

4. The good side of Nrf2

Nrf2 activation in normal cells makes cells stronger against environmental stresses and prevents carcinogenesis. Nrf2 is able to augment a wide range of cell defense processes, thereby enhancing the overall capacity of cells to detoxify potentially harmful entities. As such, the Keap1-Nrf2 pathway is generally considered as the major cellular defense pathway that offers survival advantages.

Keap1-Nrf2 is the key cellular defense mechanism to combat oxidative stress. The activated Nrf2 protect organisms from these diseases by diminishing the ROS. Nrf2 is such a natural cytoprotective response against oxidative stress-induced inflammation. Nrf2-null mice tend to spontaneously develop various inflammatory disorders, including glomerulonephritis [23], immune-mediated hemolytic anemia [24], and multiorgan autoimmune inflammation [25]. Also, activated Nrf2 protects many body systems, including airway, liver, gastrointestinal tract and kidney, where these systems are attacked by toxic agents very often [26]. For example, Nrf2 activation via sulforaphane (Nrf2 inducer) protects kidney from chronic renal disease [27] by increasing the GCLC and glutathione level. Activation of Nrf2 also alleviates the TGF-β-

induced, increased α-SMA and repressed E-cadherin [28], which are the markers for epithelial-mesenchymal transition (EMT), through the SMUR1-SMAD7 signaling. Another Nrf2 inducer, AST120, can restore the HO-1 and NQO1 levels and decrease the production of ROS stimulated by indoxyl sulfate-induced chronic renal disease [29] Nrf2 not only protects the kidney but also protects the lungs. Nrf2 protects lungs from chronic pulmonary injury [30], fibrosis [31], and acute lung injury [32, 33]. Therefore, Nrf2 is named as the "multiorgan protector" [34].

With cytoprotective functions and the cellular defense mechanism against exogenous and endogenous insults, Nrf2 is considered as a tumor suppressor. In one hand, *in vivo* tumor development data using Nrf2-knockout mice has highlighted the tumor suppression ability of Nrf2. With treatment of chemical and physical stimuli, Nrf2-null mice are more prone to develop cancer [35]. On the other hand, Nrf2 activation can remove damaged proteins, promoting the overall survival of the cell and detoxify the cellular environment to maintain the homeostasis in the organism [36]. The abilities of Nrf2 to combat oxidative stress and inflammation, which are conducive to initiate oncogenesis, attain a result of tumor suppression [36].

5. The dark side of Nrf2

Gain of Nrf2 in cancer cells: the Nrf2 pathway is a powerful sensor for cellular redox state and is activated directly by oxidative stress and/or indirectly by stress response protein kinases. Although Nrf2 is beneficial to normal cells to fight against stresses, once tumor cells get the antioxidant and detoxificative abilities of Nrf2, things go in another direction. For example, the constitutive Nrf2 activation has redirected tumor metabolism to support the biosynthetic needs of tumor proliferation [37, 38]. In addition, Nrf2 makes cancer cells stronger against chemotherapy and leads cells to become more malignant. In this case, Nrf2 serves as a target for chemotherapy. Recent researches have highlighted that persistent accumulation of Nrf2 in cancer cells is harmful, since it can promote the survival and proliferation of cells that have acquired cancer-promoting mutations, and Nrf2 is also observed beneficial for tumorigenesis [11, 39–42]. Nrf2 orchestrates the expression of various genes that help cancer cells to resist chemotherapeutic treatment, including antioxidants (NQO1, NQO2, HO-1, and GCLC), antiapoptotic (Bcl-2), drug-metabolizing enzymes (G6PD, TKT, and PPARγ), and drug efflux transporters (ABCG2, MRP3, and MRP4) genes [43].

The activation of Nrf2-ARE pathway protects cancer cells from oxidative toxicity and H_2O_2-induced apoptosis [44, 45]. The effects of Nrf2 on tumors or cancer cells are listed below:

A. Proliferation, tumorigenesis and poor patient survival: Nrf2 contributes to the tumorigenesis, cancer proliferation in bench and poor patient survival in clinic in various tumors, including hepatocarcinoma (HCC) [46], breast tumor [47], nonsmall cell lung cancer (NSCLC) [48], glioma [49, 50], pancreatic adenocarcinoma [51], and gastric cancer [52]. Nrf2 is also found to involve in the maintenance of quiescence, survival, and stress resistance of cancer stem cells (CSCs), thus dedicating to tumor progression and recurrence [53].

B. Chemotherapeutic resistance: Nrf2 exerts the detoxification and drug export through activating multidrug resistance proteins and drug transporters. This action protects cancer cells from the damage of chemotherapy, such as 5-fluorouracil (5-FU) in gastric cancer [54] and in gallbladder cancer [55], and cisplatin (CDDP) and camptothecin in pancreatic cancer [56].

C. Epithelial-mesenchymal transition (EMT), tumor metastasis, and malignancy: cancer cells respond to some anti-diabetic drugs, which have antioxidant properties and inhibit the Kea1-dependent obstruction of Nrf2, with Nrf2 activation and result in increased migration and metastasis, such as hypoglycemic dipeptidyl peptidase-4 inhibitors (DPP-4i), saxagliptin and sitagliptin [57].

D. Hypoxia-induced drug resistance: Nrf2 contributes to the chemotherapeutic drug resistance induced by hypoxia in breast cancers [2]. Hypoxia is a natural status in the tumor center where the cancer cells outgrow the perfusion from local blood vessels for getting enough oxygen and nutrients. Hypoxia triggers the ROS unbalance and stimulates the activation of Nrf2 [2]. Following the Nrf2 nuclear translocation and ARE binding, antioxidant enzymes are produced to maintain the stability of intracellular redox state. Blocking ROS unbalance by ROS scavenger inhibits the Nrf2 activation and the following drug resistance. Inhibition of Nrf2 or the production of related enzymes with siRNA or specific inhibitor blocks the chemoresistance under hypoxia (**Figure 3**).

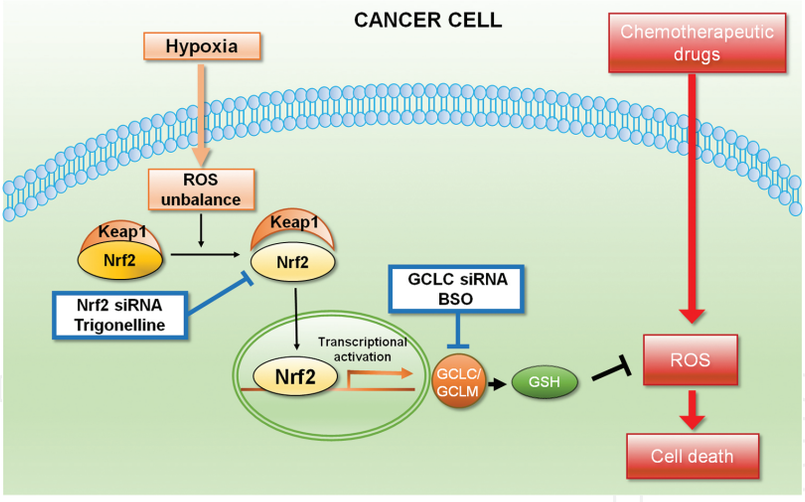

Figure 3. Nrf2, activated by hypoxia-induced ROS unbalance, starts the production of protective enzymes and contributes to the hypoxia-related chemoresistance. Specific inhibitors or siRNA targeting Nrf2 or downstream enzymes increases the cytotoxic effects of chemotherapeutic drugs.

6. Nrf2 activation in tumors

Nrf2 gets activated in malignant tumors, such as carcinomas of skin, lung, oesophagus, and larynx [58]. Many factors control the activation of Nrf2 in tumors, some are listed below.

a. The somatic mutation of Keap1 or Nrf2: the mutations in Keap1 or Nrf2 hurt the interaction of Keap1 and Nrf2, leading to a higher free Nrf2 level and activity [59].

b. The decreased level of Keap1: besides somatic mutations of Keap1, epigenetic changes, such as hypermethylation on the promoter region of Keap1, decrease the expression level of Keap1 [60]. In addition, several studies have shown that miRNAs, including mir-200A [61, 62], miR-141 [63] and mir-28 [64], also regulates the expression level of Keap1 mRNA. These events lead to the decreased level of Keap1 and the nuclear accumulation of Nrf2.

c. The increased level of Nrf2: Nrf2 can be activated by increase of some oncogenes, such as $Kras^{G12D}$ [42], or disruption of tumor suppressors, such as PTEN [37] in tumors, that lead to better cell survival and higher drug resistance.

d. Nrf2 polymorphism: in addition to varying Nrf2 expression, Nrf2 polymorphism also affects the Nrf2 activity. The Nrf2 polymorphism contributes to poor prognosis in cancers, including cholangiocarcinoma [65], lung cancer [66], and breast cancer [67]. It also contributed to diseases, such as increasing the risk of acute lung injury [68, 69] as well as blood pressure and cardiovascular mortality in patients with hemodialysis [70].

7. Regulators of Nrf2

Many molecules and chemicals are thought to regulate the Nrf2 activation; some of them are described as following (see **Figure 4**):

A. Negative regulators:

- **Endogenous**

a. Keap1: Keap1 is a natural intracellular molecule that negatively regulates the activation of Nrf2. Keap1 binds to Nrf2 in the cytoplasm, sends Nrf2 to proteosome digestion, and keeps a low Nrf2 level in cells.

b. Ubiquitin-specific processing protease 15 (USP15): USP15 deubiquitinates Keap1, stabilizes the Keap1-Cul3-E3 ligase complex, and enhances the E3 ligase activity, which leads to the binding between Keap1 and Nrf2 and the degradation of Nrf2 [71].

- **Exogenous**

c. Trigonelline: trigonelline is a coffee alkaloids that reduce nuclear accumulation of the Nrf2 protein, block expression of proteasomal genes (for example, s5a/psmd4 and α5/psma5), and reduce proteasome activity regulated by Nrf2 [72].

d. Vitamin C (ascorbic acid) [73, 74] and Vitamin E [75]: these two vitamins are water soluble vitamins with a high capacity to capture ROS. Since Nrf2 is activated via ROS imbalance, elimination of ROS by vitamins keeps low intracellular ROS and ends in low Nrf2 activity.

e. ROS scavenger: ROS scavenger is a common name for molecules that can balance the intracellular ROS, including dithiothreitol (DTT) [76], N-acetylcysteine (NAC) [77], catalase [78], 6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox) [75]. They are used as standards to check the antioxidant capacity of other molecules. Nrf2 activity remains low where these ROS scavengers keep the intracellular ROS level steady.

f. Brusatol: Brusatol is a quassinoid that provokes a rapid and transient inhibition of Nrf2 signaling. It increases the intracellular oxidative stress via inhibition of Nrf2 [79–81].

B. Activators:

♦ **Stresses**

a. ROS: ROS imbalance is the key regulator of Nrf2. Excess ROS induces the activation and nuclear translocation of Nrf2 to keep intracellular ROS balance through upregulating the level and activity of antioxidant enzymes.

b. Hypoxia: hypoxia or lack of oxygen is a prominent tumor environmental stress, and reported to induce ROS unbalance that is subsequently leading to Nrf2 activation [2, 82, 83].

♦ **Disruptor proteins and transcription factors**

c. P21 and p62: in addition to the conformational change of Keap1 to loss the bonding affinity to Nrf2, some proteins, such as p21 and p62, can directly bond to Keap1 or Nrf2, disrupting the interaction between Nrf2 and Keap1, thus ending in the nuclear accumulation and activation of Nrf2 [84–86].

d. AhR: Aryl hydrocarbon receptor (AhR), which is a ligand-dependent transcription factor by forming a heterodimer with the aryl hydrocarbon nuclear translocator (Arnt) as a nuclear partner protein. The heterodimeric protein complex regulates expression of Nrf2, and promotes the expression of phase I enzymes, phase II enzymes, and multidrug resistance-associated proteins [87–90]. Nrf2 can also regulate the activation of AhR and subsequently modulates downstream AhR signaling cascades, including increasing the expression of xenobiotic metabolism genes and inhibit the adipogenesis in mouse embryonic fibroblasts (MEFs) [91].

e. Ebselen: ebselen is a glutathione peroxidase-1 mimetic and a seleno-organic antioxidant. It attenuated cisplatin-induced oxidative stress generation through Nrf2 pathway [92].

♦ **Natural products or extracts**

f. Sulforaphane (SFN): sulforaphane, which is found in cruciferous vegetables, belongs to the isothiocyanate family (such as broccoli) and is widely used as an

antioxidant supplement and applied in cancer chemoprevention [93]. SFN reacts with Keap1 and block the binding of Keap1 and Nrf2, thus activates Nrf2 and the antioxidant function [94].

g. Curcumin: curcumin, which is a polyphenolic natural extract of turmeric [95], is reported to exhibit anti-inflammation and antitumorigenic activity and chemoprevention effect [96, 97]. To activate those protective proteins, curcumin increase the antioxidant genes through regulating the binding of Nrf2 and ARE [98, 99]. Thus, curcumin becomes one of the Nrf2 activator.

h. Resveratrol: in addition to curcumin, resveratrol is another plant extract that regulates antioxidant ability. Resveratrol, the extract from grapes, berries and peanuts, exerts antioxidant, anti-inflammation, and anti-aging effects in experimental animals. Resveratrol is also reported to upregulate Nrf2 activity in cells and organisms to elevate the protection effects toward environmental stresses [100].

i. Coffee: coffee is one of the most widely consumed beverages in the world. Coffee is noted for its antioxidant ability which protects against chronic liver disease, diabetes, and hepatocarcinoma development with the right amount. The antioxidant ability of coffee is through the activation of Nrf2 and AhR to protect organs from oxidative stress, at least in liver and stomach [101].

j. Caffeic acid phenethyl ester (CAPE): CAPE, a major component extracted from the bee product propolis in honeybee hives, is known to have antimitogenic, anticarcinogenic, anti-inflammatory activities. It activates the Nrf2 pathway to inhibit oxidative stress and inflammation [102].

k. Cinnamic aldehyde: cinnamic aldehyde, which is found in cinnamon bark, enhances Nrf2 nuclear translocation and activates Nrf2 -dependent antioxidant response to overcome stresses [103, 104].

l. Flavonoid (Chrysin, Apigenin, Luteolin): these three flavonoids can reduce the ROS level through activating Nrf2 and producing the downstream phase II enzymes [105].

♦ **Synthesized compounds**

m. Oltipraz: oltipraz is an organosulfur compound belonging to the dithiolethione class. It is also a bifunctional inducer activating both phase I and phase II drug-metabolizing enzymes via the xenobiotic responsive element [106]. It has been used as an Nrf2 activator in recent studies [107, 108].

n. Tertiary butylhydroquinone (tBHQ): tBHQ, the major metabolite of butylated hydroxyanisole, stabilizes Nrf2 and induces Nrf2 activation through mitochondrial oxidative stress induction [109, 110].

o. Other food and clinical drugs: many other foods or clinical drugs can also affect the expression and activity of Nrf2 in recent studies.

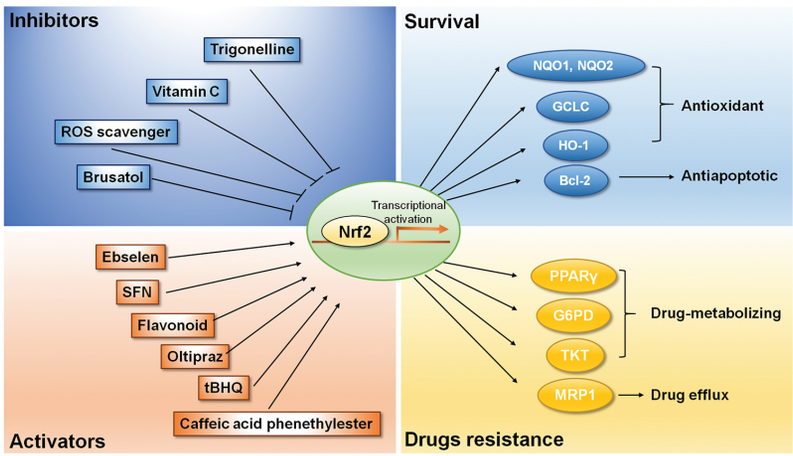

Figure 4. Positive and negative regulators of Nrf2, and the functions of enzymes and proteins produced by Nrf2 activation.

8. Conclusion

Nrf2 is powerful in the cell defense system toward oxidative stress caused by various physiological and chemical stresses. Nrf2 activation benefits the survival of not only normal cells but also cancer cells. With the anti-oxidation and detoxification abilities of Nrf2, the proliferation, tumorigenicity, migration, and metastasis of cancer cells are higher. The detoxification and drug export mechanism also give cancer cells the ability to fight against chemotherapeutic drugs. With all the characteristics of Nrf2, it is a good marker for both poor prognosis and drug resistance in tumors, both in the regular normoxic environment or under hypoxic environment [111].

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References

[1] Zhang, M., Zhang, C., Zhang, L., Yang, Q., Zhou, S., Wen, Q., and Wang, J. (2015) Nrf2 is a potential prognostic marker and promotes proliferation and invasion in human hepatocellular carcinoma. *BMC Cancer* 15, 531.

[2] Syu, J. P., Chi, J. T., and Kung, H. N. (2016) Nrf2 is the key to chemotherapy resistance in MCF7 breast cancer cells under hypoxia. *Oncotarget* 7, 14659–14672.

[3] Chapple, S. J., Siow, R. C., and Mann, G. E. (2012) Crosstalk between Nrf2 and the proteasome: therapeutic potential of Nrf2 inducers in vascular disease and aging. *Int J Biochem Cell Biol* 44, 1315–1320.

[4] Canning, P., Sorrell, F. J., and Bullock, A. N. (2015) Structural basis of Keap1 interactions with Nrf2. *Free Radic Biol Med* 88, 101–107.

[5] Vriend, J., and Reiter, R. J. (2015) The Keap1-Nrf2-antioxidant response element pathway: a review of its regulation by melatonin and the proteasome. *Mol Cell Endocrinol* 401, 213–220.

[6] Lacher, S. E., Lee, J. S., Wang, X., Campbell, M. R., Bell, D. A., and Slattery, M. (2015) Beyond antioxidant genes in the ancient Nrf2 regulatory network. *Free Radic Biol Med* 88, 452–465.

[7] Dean, M., Hamon, Y., and Chimini, G. (2001) The human ATP-binding cassette (ABC) transporter superfamily. *J Lipid Res* 42, 1007–1017.

[8] Zhang, Y., and Gordon, G. B. (2004) A strategy for cancer prevention: stimulation of the Nrf2-ARE signaling pathway. *Mol Cancer Ther* 3, 885–893.

[9] Cooke, M. S., Evans, M. D., Dizdaroglu, M., and Lunec, J. (2003) Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB J* 17, 1195–1214.

[10] Harman, D. (1956) Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11, 298–300.

[11] Kensler, T. W., and Wakabayashi, N. (2010) Nrf2: friend or foe for chemoprevention? *Carcinogenesis* 31, 90–99.

[12] Pergola, P. E., Raskin, P., Toto, R. D., Meyer, C. J., Huff, J. W., Grossman, E. B., Krauth, M., Ruiz, S., Audhya, P., Christ-Schmidt, H., Wittes, J., Warnock, D. G., and Investigators, B. S. (2011) Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* 365, 327–336.

[13] de Zeeuw, D., Akizawa, T., Audhya, P., Bakris, G. L., Chin, M., Christ-Schmidt, H., Goldsberry, A., Houser, M., Krauth, M., Lambers Heerspink, H. J., McMurray, J. J., Meyer, C. J., Parving, H. H., Remuzzi, G., Toto, R. D., Vaziri, N. D., Wanner, C., Wittes, J., Wrolstad, D., Chertow, G. M., and Investigators, B. T. (2013) Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 369, 2492–2503.

[14] Doss, J. F., Jonassaint, J. C., Garrett, M. E., Ashley-Koch, A. E., Telen, M. J., and Chi, J. T. (2016) Phase 1 study of a sulforaphane-containing broccoli sprout homogenate for sickle cell disease. *PLoS One* 11, e0152895.

[15] Castro, J. P., Grune, T., and Speckmann, B. (2016) The two faces of reactive oxygen species (ROS) in adipocyte function and dysfunction. *Biol Chem* 397, 709–724.

[16] Luperini, B. C., Almeida, D. C., Porto, M. P., Marcondes, J. P., Prado, R. P., Rasera, I., Oliveira, M. R., and Salvadori, D. M. (2015) Gene polymorphisms and increased DNA damage in morbidly obese women. *Mutat Res* 776, 111–117.

[17] Fernandez-Sanchez, A., Madrigal-Santillan, E., Bautista, M., Esquivel-Soto, J., Morales-Gonzalez, A., Esquivel-Chirino, C., Durante-Montiel, I., Sanchez-Rivera, G., Valadez-Vega, C., and Morales-Gonzalez, J. A. (2011) Inflammation, oxidative stress, and obesity. *Int J Mol Sci* 12, 3117–3132.

[18] Probst, B. L., McCauley, L., Trevino, I., Wigley, W. C., and Ferguson, D. A. (2015) cancer cell growth is differentially affected by constitutive activation of NRF2 by KEAP1 deletion and pharmacological activation of NRF2 by the synthetic triterpenoid, RTA 405. *PLoS One* 10, e0135257.

[19] Furfaro, A. L., Traverso, N., Domenicotti, C., Piras, S., Moretta, L., Marinari, U. M., Pronzato, M. A., and Nitti, M. (2016) The Nrf2/HO-1 axis in cancer cell growth and chemoresistance. *Oxid Med Cell Longev* 2016, 1958174

[20] Hintsala, H. R., Jokinen, E., Haapasaari, K. M., Moza, M., Ristimaki, A., Soini, Y., Koivunen, J., and Karihtala, P. (2016) Nrf2/Keap1 pathway and expression of oxidative stress lesions 8-hydroxy-2?-deoxyguanosine and nitrotyrosine in melanoma. *Anticancer Res* 36, 1497–1506.

[21] Cancer Genome Atlas Research, N. (2014) Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 511, 543–550.

[22] Cancer Genome Atlas Research, N. (2012) Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 489, 519–525.

[23] Yoh, K., Itoh, K., Enomoto, A., Hirayama, A., Yamaguchi, N., Kobayashi, M., Morito, N., Koyama, A., Yamamoto, M., and Takahashi, S. (2001) Nrf2-deficient female mice develop lupus-like autoimmune nephritis. *Kidney Int* 60, 1343–1353.

[24] Lee, J. M., Chan, K., Kan, Y. W., and Johnson, J. A. (2004) Targeted disruption of Nrf2 causes regenerative immune-mediated hemolytic anemia. *Proc Natl Acad Sci U S A* 101, 9751–9756.

[25] Ma, Q., Battelli, L., and Hubbs, A. F. (2006) Multiorgan autoimmune inflammation, enhanced lymphoproliferation, and impaired homeostasis of reactive oxygen species in mice lacking the antioxidant-activated transcription factor Nrf2. *Am J Pathol* 168, 1960–1974.

[26] Cho, H. Y., and Kleeberger, S. R. (2010) Nrf2 protects against airway disorders. *Toxicol Appl Pharmacol* 244, 43–56.

[27] Ryoo, I. G., Ha, H., and Kwak, M. K. (2014) Inhibitory role of the KEAP1-NRF2 pathway in TGFbeta1-stimulated renal epithelial transition to fibroblastic cells: a modulatory effect on SMAD signaling. *PLoS One* 9, e93265.

[28] Ryoo, I. G., Shin, D. H., Kang, K. S., and Kwak, M. K. (2015) Involvement of Nrf2-GSH signaling in TGFbeta1-stimulated epithelial-to-mesenchymal transition changes in rat renal tubular cells. *Arch Pharm Res* 38, 272–281.

[29] Bolati, D., Shimizu, H., Yisireyili, M., Nishijima, F., and Niwa, T. (2013) Indoxyl sulfate, a uremic toxin, downregulates renal expression of Nrf2 through activation of NF-kappaB. *BMC Nephrol* 14, 56.

[30] Cho, H. Y., Jedlicka, A. E., Reddy, S. P., Kensler, T. W., Yamamoto, M., Zhang, L. Y., and Kleeberger, S. R. (2002) Role of NRF2 in protection against hyperoxic lung injury in mice. *Am J Respir Cell Mol Biol* 26, 175–182.

[31] Cho, H. Y., Reddy, S. P., Yamamoto, M., and Kleeberger, S. R. (2004) The transcription factor NRF2 protects against pulmonary fibrosis. *FASEB J* 18, 1258–1260.

[32] Chan, K., and Kan, Y. W. (1999) Nrf2 is essential for protection against acute pulmonary injury in mice. *Proc Natl Acad Sci U S A* 96, 12731–12736.

[33] de la Vega, M. R., Dodson, M., Gross, C., Manzour, H., Lantz, R. C., Chapman, E., Wang, T., Black, S. M., Garcia, J. G., and Zhang, D. D. (2016) Role of Nrf2 and autophagy in acute lung injury. *Curr Pharmacol Rep* 2, 91–101.

[34] Lee, J. M., Li, J., Johnson, D. A., Stein, T. D., Kraft, A. D., Calkins, M. J., Jakel, R. J., and Johnson, J. A. (2005) Nrf2, a multi-organ protector? *FASEB J* 19, 1061–1066.

[35] Ramos-Gomez, M., Dolan, P. M., Itoh, K., Yamamoto, M., and Kensler, T. W. (2003) Interactive effects of nrf2 genotype and oltipraz on benzo[a]pyrene-DNA adducts and tumor yield in mice. *Carcinogenesis* 24, 461–467.

[36] Shelton, P., and Jaiswal, A. K. (2013) The transcription factor NF-E2-related factor 2 (Nrf2): a protooncogene? *FASEB J* 27, 414–423.

[37] Mitsuishi, Y., Taguchi, K., Kawatani, Y., Shibata, T., Nukiwa, T., Aburatani, H., Yamamoto, M., and Motohashi, H. (2012) Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming. *Cancer Cell* 22, 66–79.

[38] DeNicola, G. M., Chen, P. H., Mullarky, E., Sudderth, J. A., Hu, Z., Wu, D., Tang, H., Xie, Y., Asara, J. M., Huffman, K. E., Wistuba, II, Minna, J. D., DeBerardinis, R. J., and Cantley, L. C. (2015) NRF2 regulates serine biosynthesis in non-small cell lung cancer. *Nat Genet* 47, 1475–1481.

[39] Menegon, S., Columbano, A., and Giordano, S. (2016) The dual roles of NRF2 in cancer. *Trends Mol Med* 22, 578–593.

[40] Wang, X. J., Sun, Z., Villeneuve, N. F., Zhang, S., Zhao, F., Li, Y., Chen, W., Yi, X., Zheng, W., Wondrak, G. T., Wong, P. K., and Zhang, D. D. (2008) Nrf2 enhances resistance of cancer cells to chemotherapeutic drugs, the dark side of Nrf2. *Carcinogenesis* 29, 1235–1243.

[41] Homma, S., Ishii, Y., Morishima, Y., Yamadori, T., Matsuno, Y., Haraguchi, N., Kikuchi, N., Satoh, H., Sakamoto, T., Hizawa, N., Itoh, K., and Yamamoto, M. (2009) Nrf2 enhances cell proliferation and resistance to anticancer drugs in human lung cancer. *Clin Cancer Res* 15, 3423–3432.

[42] DeNicola, G. M., Karreth, F. A., Humpton, T. J., Gopinathan, A., Wei, C., Frese, K., Mangal, D., Yu, K. H., Yeo, C. J., Calhoun, E. S., Scrimieri, F., Winter, J. M., Hruban, R. H., Iacobuzio-Donahue, C., Kern, S. E., Blair, I. A., and Tuveson, D. A. (2011) Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. *Nature* 475, 106–109.

[43] Bai, X., Chen, Y., Hou, X., Huang, M., and Jin, J. (2016) Emerging role of NRF2 in chemoresistance by regulating drug-metabolizing enzymes and efflux transporters. *Drug Metab Rev*, 1–27.

[44] Qaisiya, M., Coda Zabetta, C. D., Bellarosa, C., and Tiribelli, C. (2014) Bilirubin mediated oxidative stress involves antioxidant response activation via Nrf2 pathway. *Cell Signal* 26, 512–520.

[45] Li, J., Lee, J. M., and Johnson, J. A. (2002) Microarray analysis reveals an antioxidant responsive element-driven gene set involved in conferring protection from an oxidative stress-induced apoptosis in IMR-32 cells. *J Biol Chem* 277, 388–394.

[46] Nault, J. C., Rebouissou, S., and Zucman Rossi, J. (2015) NRF2/KEAP1 and Wnt/beta-catenin in the multistep process of liver carcinogenesis in humans and rats. *Hepatology* 62, 677–679.

[47] Funes, J. M., Henderson, S., Kaufman, R., Flanagan, J. M., Robson, M., Pedley, B., Moncada, S., and Boshoff, C. (2014) Oncogenic transformation of mesenchymal stem cells decreases Nrf2 expression favoring in vivo tumor growth and poorer survival. *Mol Cancer* 13, 20.

[48] Maki, Y., Fujimoto, J., Lang, W., Xu, L., Behrens, C., Wistuba, II, and Kadara, H. (2015) LAPTM4B is associated with poor prognosis in NSCLC and promotes the NRF2-mediated stress response pathway in lung cancer cells. *Sci Rep* 5, 13846.

[49] Kanamori, M., Higa, T., Sonoda, Y., Murakami, S., Dodo, M., Kitamura, H., Taguchi, K., Shibata, T., Watanabe, M., Suzuki, H., Shibahara, I., Saito, R., Yamashita, Y., Kumabe, T., Yamamoto, M., Motohashi, H., and Tominaga, T. (2015) Activation of the NRF2 pathway and its impact on the prognosis of anaplastic glioma patients. *Neuro Oncol* 17, 555–565.

[50] Ji, X., Wang, H., Zhu, J., Zhu, L., Pan, H., Li, W., Zhou, Y., Cong, Z., Yan, F., and Chen, S. (2014) Knockdown of Nrf2 suppresses glioblastoma angiogenesis by inhibiting hypoxia-induced activation of HIF-1alpha. *Int J Cancer* 135, 574–584.

[51] Soini, Y., Eskelinen, M., Juvonen, P., Karja, V., Haapasaari, K. M., Saarela, A., and Karihtala, P. (2014) Nuclear Nrf2 expression is related to a poor survival in pancreatic adenocarcinoma. *Pathol Res Pract* 210, 35–39.

[52] Ko, H., Kim, S. J., Shim, S. H., Chang, H., and Ha, C. H. (2016) Shikonin induces the apoptotic cell death via regulation of p53 and Nrf2 in AGS human stomach carcinoma cells. *Biomol Ther (Seoul)* 2016, 1–9.

[53] Ryoo, I. G., Lee, S. H., and Kwak, M. K. (2016) Redox modulating NRF2: a potential mediator of cancer stem cell resistance. *Oxid Med Cell Longev* 2016, 2428153.

[54] Hu, X. F., Yao, J., Gao, S. G., Wang, X. S., Peng, X. Q., Yang, Y. T., and Feng, X. S. (2013) Nrf2 overexpression predicts prognosis and 5-FU resistance in gastric cancer. *Asian Pac J Cancer Prev* 14, 5231–5235.

[55] Shibata, T., Kokubu, A., Gotoh, M., Ojima, H., Ohta, T., Yamamoto, M., and Hirohashi, S. (2008) Genetic alteration of Keap1 confers constitutive Nrf2 activation and resistance to chemotherapy in gallbladder cancer. *Gastroenterology* 135, 1358–1368, 1368e1351–e1354.

[56] Hong, Y. B., Kang, H. J., Kwon, S. Y., Kim, H. J., Kwon, K. Y., Cho, C. H., Lee, J. M., Kallakury, B. V., and Bae, I. (2010) Nuclear factor (erythroid-derived 2)-like 2 regulates drug resistance in pancreatic cancer cells. *Pancreas* 39, 463–472.

[57] Wang, H., Liu, X., Long, M., Huang, Y., Zhang, L., Zhang, R., Zheng, Y., Liao, X., Wang, Y., Liao, Q., Li, W., Tang, Z., Tong, Q., Wang, X., Fang, F., Rojo de la Vega, M., Ouyang, Q., Zhang, D. D., Yu, S., and Zheng, H. (2016) NRF2 activation by antioxidant antidiabetic agents accelerates tumor metastasis. *Sci Transl Med* 8, 334–351.

[58] Sporn, M. B., and Liby, K. T. (2012) NRF2 and cancer: the good, the bad and the importance of context. *Nat Rev Cancer* 12, 564–571.

[59] Hast, B. E., Cloer, E. W., Goldfarb, D., Li, H., Siesser, P. F., Yan, F., Walter, V., Zheng, N., Hayes, D. N., and Major, M. B. (2014) Cancer-derived mutations in KEAP1 impair NRF2 degradation but not ubiquitination. *Cancer Res* 74, 808–817.

[60] Hanada, N., Takahata, T., Zhou, Q., Ye, X., Sun, R., Itoh, J., Ishiguro, A., Kijima, H., Mimura, J., Itoh, K., Fukuda, S., and Saijo, Y. (2012) Methylation of the KEAP1 gene promoter region in human colorectal cancer. *BMC Cancer* 12, 66.

[61] Liu, Q. L., Zhang, J., Liu, X., and Gao, J. Y. (2015) Role of growth hormone in maturation and activation of dendritic cells via miR-200a and the Keap1/Nrf2 pathway. *Cell Prolif* 48, 573–581.

[62] Eades, G., Yang, M., Yao, Y., Zhang, Y., and Zhou, Q. (2011) miR-200a regulates Nrf2 activation by targeting Keap1 mRNA in breast cancer cells. *J Biol Chem* 286, 40725–40733.

[63] Shi, L., Wu, L., Chen, Z., Yang, J., Chen, X., Yu, F., Zheng, F., and Lin, X. (2015) MiR-141 activates Nrf2-dependent antioxidant pathway via down-regulating the expression of Keap1 conferring the resistance of hepatocellular carcinoma cells to 5-fluorouracil. *Cell Physiol Biochem* 35, 2333–2348.

[64] Yang, M., Yao, Y., Eades, G., Zhang, Y., and Zhou, Q. (2011) MiR-28 regulates Nrf2 expression through a Keap1-independent mechanism. Breast *Cancer Res Treat* 129, 983–991.

[65] Khunluck, T., Kukongviriyapan, V., Puapairoj, A., Khuntikeo, N., Senggunprai, L., Zeekpudsa, P., and Prawan, A. (2014) Association of NRF2 polymorphism with cholangiocarcinoma prognosis in Thai patients. *Asian Pac J Cancer Prev* 15, 299–304.

[66] Ishikawa, T. (2014) Genetic polymorphism in the NRF2 gene as a prognosis marker for cancer chemotherapy. *Front Genet* 5, 383

[67] Hartikainen, J. M., Tengstrom, M., Kosma, V. M., Kinnula, V. L., Mannermaa, A., and Soini, Y. (2012) Genetic polymorphisms and protein expression of NRF2 and Sulfiredoxin predict survival outcomes in breast cancer. *Cancer Res* 72, 5537–5546.

[68] Cho, H. Y., Jedlicka, A. E., Gladwell, W., Marzec, J., McCaw, Z. R., Bienstock, R. J., and Kleeberger, S. R. (2015) Association of Nrf2 polymorphism haplotypes with acute lung injury phenotypes in inbred strains of mice. *Antioxid Redox Signal* 22, 325–338.

[69] Marzec, J. M., Christie, J. D., Reddy, S. P., Jedlicka, A. E., Vuong, H., Lanken, P. N., Aplenc, R., Yamamoto, T., Yamamoto, M., Cho, H. Y., and Kleeberger, S. R. (2007) Functional polymorphisms in the transcription factor NRF2 in humans increase the risk of acute lung injury. *FASEB J* 21, 2237–2246.

[70] Shimoyama, Y., Mitsuda, Y., Tsuruta, Y., Hamajima, N., and Niwa, T. (2014) Polymorphism of Nrf2, an antioxidative gene, is associated with blood pressure and cardiovascular mortality in hemodialysis patients. *Int J Med Sci* 11, 726–731.

[71] Villeneuve, N. F., Tian, W., Wu, T., Sun, Z., Lau, A., Chapman, E., Fang, D., and Zhang, D. D. (2013) USP15 negatively regulates Nrf2 through deubiquitination of Keap1. *Mol Cell* 51, 68–79.

[72] Arlt, A., Sebens, S., Krebs, S., Geismann, C., Grossmann, M., Kruse, M. L., Schreiber, S., and Schafer, H. (2013) Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity. *Oncogene* 32, 4825–4835.

[73] May, J. M. (2000) How does ascorbic acid prevent endothelial dysfunction? *Free Radic Biol Med* 28, 1421–1429.

[74] Wagner, A. E., Boesch-Saadatmandi, C., Breckwoldt, D., Schrader, C., Schmelzer, C., Doring, F., Hashida, K., Hori, O., Matsugo, S., and Rimbach, G. (2011) Ascorbic acid partly antagonizes resveratrol mediated heme oxygenase-1 but not paraoxonase-1

induction in cultured hepatocytes—role of the redox-regulated transcription factor Nrf2. *BMC Complement Altern Med* 11, 1.

[75] Messier, E. M., Bahmed, K., Tuder, R. M., Chu, H. W., Bowler, R. P., and Kosmider, B. (2013) Trolox contributes to Nrf2-mediated protection of human and murine primary alveolar type II cells from injury by cigarette smoke. *Cell Death Dis* 4, e573

[76] Aon, M. A., Cortassa, S., and O'Rourke, B. (2010) Redox-optimized ROS balance: a unifying hypothesis. *Biochim Biophys Acta* 1797, 865–877.

[77] Sun, S. Y. (2010) N-acetylcysteine, reactive oxygen species and beyond. *Cancer Biol Ther* 9, 109–110.

[78] Preston, T. J., Muller, W. J., and Singh, G. (2001) Scavenging of extracellular H_2O_2 by catalase inhibits the proliferation of HER-2/Neu-transformed rat-1 fibroblasts through the induction of a stress response. *J Biol Chem* 276, 9558–9564.

[79] Olayanju, A., Copple, I. M., Bryan, H. K., Edge, G. T., Sison, R. L., Wong, M. W., Lai, Z. Q., Lin, Z. X., Dunn, K., Sanderson, C. M., Alghanem, A. F., Cross, M. J., Ellis, E. C., Ingelman-Sundberg, M., Malik, H. Z., Kitteringham, N. R., Goldring, C. E., and Park, B. K. (2015) Brusatol provokes a rapid and transient inhibition of Nrf2 signaling and sensitizes mammalian cells to chemical toxicity-implications for therapeutic targeting of Nrf2. *Free Radic Biol Med* 78, 202–212.

[80] Sun, X., Wang, Q., Wang, Y., Du, L., Xu, C., and Liu, Q. (2016) Brusatol enhances the radiosensitivity of A549 cells by promoting ROS production and enhancing DNA damage. *Int J Mol Sci* 17, 997–1010.

[81] Ren, D., Villeneuve, N. F., Jiang, T., Wu, T., Lau, A., Toppin, H. A., and Zhang, D. D. (2011) Brusatol enhances the efficacy of chemotherapy by inhibiting the Nrf2-mediated defense mechanism. *Proc Natl Acad Sci U S A* 108, 1433–1438.

[82] Salminen, A., Kaarniranta, K., and Kauppinen, A. (2016) AMPK and HIF signaling pathways regulate both longevity and cancer growth: the good news and the bad news about survival mechanisms. *Biogerontology* 17, 655–680.

[83] Lee, S. L., Ryu, H., Son, A. R., Seo, B., Kim, J., Jung, S. Y., Song, J. Y., Hwang, S. G., and Ahn, J. (2016) TGF-beta and hypoxia/reoxygenation promote radioresistance of A549 lung cancer cells through activation of Nrf2 and EGFR. *Oxid Med Cell Longev* 2016, 6823471

[84] Levonen, A. L. (2014) Activation of stress signaling pathways by oxidized and nitrated lipids. *Free Radic Biol Med* 75 Suppl 1, S8

[85] Kansanen, E., Jyrkkanen, H. K., and Levonen, A. L. (2012) Activation of stress signaling pathways by electrophilic oxidized and nitrated lipids. *Free Radic Biol Med* 52, 973–982.

[86] Taguchi, K., Motohashi, H., and Yamamoto, M. (2011) Molecular mechanisms of the Keap1-Nrf2 pathway in stress response and cancer evolution. *Genes Cells* 16, 123–140.

[87] Miao, W., Hu, L., Scrivens, P. J., and Batist, G. (2005) Transcriptional regulation of NF-E2 p45-related factor (NRF2) expression by the aryl hydrocarbon receptor-xenobiotic response element signaling pathway: direct cross-talk between phase I and II drug-metabolizing enzymes. *J Biol Chem* 280, 20340–20348.

[88] Yeager, R. L., Reisman, S. A., Aleksunes, L. M., and Klaassen, C. D. (2009) Introducing the "TCDD-inducible AhR-Nrf2 gene battery". *Toxicol Sci* 111, 238–246.

[89] Lu, H., Cui, W., and Klaassen, C. D. (2011) Nrf2 protects against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced oxidative injury and steatohepatitis. *Toxicol Appl Pharmacol* 256, 122–135.

[90] Kalthoff, S., Ehmer, U., Freiberg, N., Manns, M. P., and Strassburg, C. P. (2010) Interaction between oxidative stress sensor Nrf2 and xenobiotic-activated aryl hydrocarbon receptor in the regulation of the human phase II detoxifying UDP-glucuronosyltransferase 1A10. *J Biol Chem* 285, 5993–6002.

[91] Shin, S., Wakabayashi, N., Misra, V., Biswal, S., Lee, G. H., Agoston, E. S., Yamamoto, M., and Kensler, T. W. (2007) NRF2 modulates aryl hydrocarbon receptor signaling: influence on adipogenesis. *Mol Cell Biol* 27, 7188–7197.

[92] Kim, S. J., Park, C., Han, A. L., Youn, M. J., Lee, J. H., Kim, Y., Kim, E. S., Kim, H. J., Kim, J. K., Lee, H. K., Chung, S. Y., So, H., and Park, R. (2009) Ebselen attenuates cisplatin-induced ROS generation through Nrf2 activation in auditory cells. *Hear Res* 251, 70–82.

[93] Zhang, Y., Talalay, P., Cho, C. G., and Posner, G. H. (1992) A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. *Proc Natl Acad Sci U S A* 89, 2399–2403.

[94] Wells, G. (2015) Peptide and small molecule inhibitors of the Keap1-Nrf2 protein-protein interaction. *Biochem Soc Trans* 43, 674–679.

[95] Ammon, H. P., and Wahl, M. A. (1991) Pharmacology of *Curcuma longa*. *Planta Med* 57, 1–7.

[96] Talero, E., Avila-Roman, J., and Motilva, V. (2012) Chemoprevention with phytonutrients and microalgae products in chronic inflammation and colon cancer. *Curr Pharm Des* 18, 3939–3965.

[97] Khan, S., Karmokar, A., Howells, L., Thomas, A. L., Bayliss, R., Gescher, A., and Brown, K. (2016) Targeting cancer stem-like cells using dietary-derived agents—where are we now? *Mol Nutr Food Res* 60, 1295–1309.

[98] Gao, S., Duan, X., Wang, X., Dong, D., Liu, D., Li, X., Sun, G., and Li, B. (2013) Curcumin attenuates arsenic-induced hepatic injuries and oxidative stress in experimental mice through activation of Nrf2 pathway, promotion of arsenic methylation and urinary excretion. *Food Chem Toxicol* 59, 739–747.

[99] Balogun, E., Hoque, M., Gong, P., Killeen, E., Green, C. J., Foresti, R., Alam, J., and Motterlini, R. (2003) Curcumin activates the haem oxygenase-1 gene via

regulation of Nrf2 and the antioxidant-responsive element. *Biochem J* 371, 887–895.

[100] Bonnefont-Rousselot, D. (2016) Resveratrol and cardiovascular diseases. *Nutrients* 8, 250–274.

[101] Kalthoff, S., Ehmer, U., Freiberg, N., Manns, M. P., and Strassburg, C. P. (2010) Coffee induces expression of glucuronosyltransferases by the aryl hydrocarbon receptor and Nrf2 in liver and stomach. *Gastroenterology* 139, 1699–1710.

[102] Li, M., Wang, X. F., Shi, J. J., Li, Y. P., Yang, N., Zhai, S., and Dang, S. S. (2015) Caffeic acid phenethyl ester inhibits liver fibrosis in rats. *World J Gastroenterol* 21, 3893–3903.

[103] Huang, T. C., Chung, Y. L., Wu, M. L., and Chuang, S. M. (2011) Cinnamaldehyde enhances Nrf2 nuclear translocation to upregulate phase II detoxifying enzyme expression in HepG2 cells. *J Agric Food Chem* 59, 5164–5171.

[104] Wang, F., Pu, C., Zhou, P., Wang, P., Liang, D., Wang, Q., Hu, Y., Li, B., and Hao, X. (2015) Cinnamaldehyde prevents endothelial dysfunction induced by high glucose by activating Nrf2. *Cell Physiol Biochem* 36, 315–324.

[105] Huang, C. S., Lii, C. K., Lin, A. H., Yeh, Y. W., Yao, H. T., Li, C. C., Wang, T. S., and Chen, H. W. (2013) Protection by chrysin, apigenin, and luteolin against oxidative stress is mediated by the Nrf2-dependent up-regulation of heme oxygenase 1 and glutamate cysteine ligase in rat primary hepatocytes. *Arch Toxicol* 87, 167–178.

[106] Miao, W., Hu, L., Kandouz, M., and Batist, G. (2003) Oltipraz is a bifunctional inducer activating both phase I and phase II drug-metabolizing enzymes via the xenobiotic responsive element. *Mol Pharmacol* 64, 346–354.

[107] Wajda, A., Lapczuk, J., Grabowska, M., Slojewski, M., Laszczynska, M., Urasinska, E., and Drozdzik, M. (2016) Nuclear factor E2-related factor-2 (Nrf2) expression and regulation in male reproductive tract. *Pharmacol Rep* 68, 101–108.

[108] Rao, J., Qian, X., Li, G., Pan, X., Zhang, C., Zhang, F., Zhai, Y., Wang, X., and Lu, L. (2015) ATF3-mediated NRF2/HO-1 signaling regulates TLR4 innate immune responses in mouse liver ischemia/reperfusion injury. *Am J Transplant* 15, 76–87.

[109] Imhoff, B. R., and Hansen, J. M. (2010) Tert-butylhydroquinone induces mitochondrial oxidative stress causing Nrf2 activation. *Cell Biol Toxicol* 26, 541–551.

[110] Shi, X., Li, Y., Hu, J., and Yu, B. (2016) Tert-butylhydroquinone attenuates the ethanol-induced apoptosis of and activates the Nrf2 antioxidant defense pathway in H9c2 cardiomyocytes. *Int J Mol Med* 38, 123–130.

[111] No, J. H., Kim, Y. B., and Song, Y. S. (2014) Targeting nrf2 signaling to combat chemoresistance. *J Cancer Prev* 19, 111–117.

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