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Review Article

Regulation of Nrf2—an update

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ABSTRACT

Nrf2:INrf2 (Keap1) are cellular sensors of oxidative and electrophilic stress. Nrf2 is a nuclear factor that controls the expression and coordinated induction of a battery of genes that encode detoxifying enzymes, drug transporters, antiapoptotic proteins, and proteasomes. In the basal state, Nrf2 is constantly degraded in the cytoplasm by its inhibitor, INrf2. INrf2 functions as an adapter for Cul3/Rbx1 E3 ubiquitin ligase-mediated degradation of Nrf2. Chemicals, including antioxidants, tocopherols including α-tocopherol (vitamin E), and phytochemicals, and radiation antagonize the Nrf2:INrf2 interaction and lead to the stabilization and activation of Nrf2. The signaling events involve preinduction, induction, and postinduction responses that tightly control Nrf2 activation and repression back to the basal state. Oxidative/electrophilic signals activate unknown tyrosine kinases in a preinduction response that phosphorylates specific residues on Nrf2 negative regulators, INrf2, Fyn, and Bach1, leading to their nuclear export, ubiquitination, and degradation. This prepares nuclei for unhindered import of Nrf2. Oxidative/electrophilic modification of INrf2 cysteine 151 followed by PKC phosphorylation of Nrf2 serine 40 in the induction response results in the escape or release of Nrf2 from INrf2. Nrf2 is thus stabilized and translocates to the nucleus, resulting in a coordinated activation of gene expression. This is followed by a postinduction response that controls the "switching off" of Nrf2-activated gene expression. GSK3β, under the control of AKT and PI3K, phosphorylates Fyn, leading to Fyn nuclear localization. Fyn phosphorylates Nrf2 Y568, resulting in nuclear export and degradation of Nrf2. The activation and repression of Nrf2 provide protection against oxidative/electrophilic stress and associated diseases, including cancer. However, deregulation of INrf2 and Nrf2 due to mutations may lead to nuclear accumulation of Nrf2 that reduces apoptosis and promotes oncogenesis and drug resistance.

Contents

Abbreviations: Nrf2, NF-E2 related factor 2; INrf2, inhibitor of Nrf2, also known as Keap1; ARE, antioxidant-response element; ROS, reactive oxygen species

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Oxidative stress

Cells are constantly challenged by environmental (xenobiotics, drugs, and UV light) and endogenous (reactive oxygen species, hydroperoxides, and quinone) stressors [1,2]. If unchecked, these lead to oxidative stress and diseases of many organs (Fig. 1). Oxidative stress-related diseases include skin (dermatitis, psoriasis, and burn), kidney (renal graft and glomeruloneph), eye (retinal damage and cataract), cardiovasculature (heart and vessel diseases including atherosclerosis), lung (hyperoxia, asthma, and acute respiratory distress syndrome (ARDS)), joints (rheumatoid arthritis), liver (injury and ischemic bowel), brain (trauma, Parkinson and Alzheimer diseases), and multiorgan diseases, including diabetes, aging, and cancer [1,2].

Chemical protection against oxidative stress

Phenolic antioxidants, vitamins, and naturally occurring phytochemicals are known to reduce oxidative stress leading to protection of cells against its adverse effects [3–6]. Many of these compounds

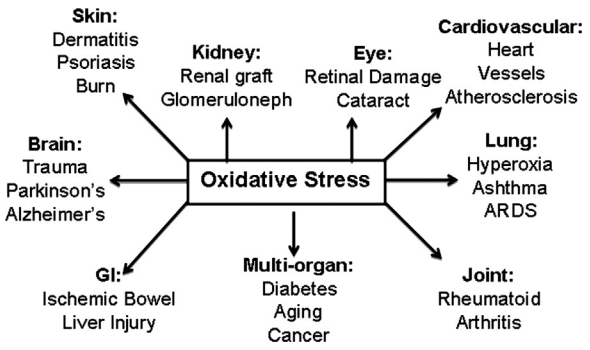

Fig. 1. Oxidative stress-related diseases. The information in this figure was obtained from oxidative stress resource web link (www.oxidativestressresource.org) and modified.

are well-known drugs in prevention and cure of cancer. The chemical structures of a few representative phenolic antioxidants, vitamins, and phytochemicals are shown (Fig. 2). The phenolic antioxidants BHA (*tert*-butyl-4-hydroxyanisole) and BHT (3,5-di-*tert*-butyl-4-hydroxytoluene) inhibit chemical carcinogenesis [7,8]. Vitamins are essential for the normal growth and development of organisms. Vitamin E among the various vitamins has demonstrated antioxidant properties. Vitamin E is a group of tocopherols and tocotrienols. However, only α-tocopherol functions as the vitamin E in vivo. Each tocopherol contains a chromanol ring system and a 16-carbon phytyl chain (Fig. 2). Depending on the positions and numbers of methyl groups they exist as α-, β-, γ-, and δ-tocopherols (Fig. 2). All tocopherols are antioxidants. However, γ- and δ-tocopherols are stronger antioxidants than the others because of their unmethylated carbon 5 [9]. Epidemiological studies have shown cancer preventive activity of vitamin E (α-tocopherol) [4]. However, its role in cancer prevention is controversial. More recent studies suggest that γ- and δ-tocopherols are cancer preventive, whereas α-tocopherol is not [4]. Phytochemicals include a large number of many varieties of compounds produced from plants [10]. Some phytochemicals are sulforaphane, silibinin, honokiol, (−)-epigallocatechin gallate (EGCG), and quercetin. Sulforaphane, a product of broccoli sprouts, retarded prostate tumor growth in TRAMP mice and suppressed the growth of prostate cancer PC-3 cells in nude mice [11,12]. Silymarin and its major constituent, silibinin, are extracts from the medicinal plant *Silybum marianum* (milk thistle) and have traditionally been used for the treatment of liver diseases [13]. Recently, these orally active, flavonoid agents have also been shown to exert significant antineoplastic effects in a variety of in vitro and in vivo cancer models, including skin, breast, lung, colon, bladder, prostate, and kidney carcinomas [13]. Honokiol is a product of *Magnolia officinalis* that restarted growth of PC-3 xenografts in nude mice [14]. EGCG reduced tumor size and completely abrogated tumors in both androgen-repressed prostate cancer LNCaP and androgen-refractory PC3 tumor xenograft in athymic nude mice [15]. Quercetin from vegetables and fruits suppressed development of preneoplastic lesions and proliferation of azoxymethane-induced aberrant crypt

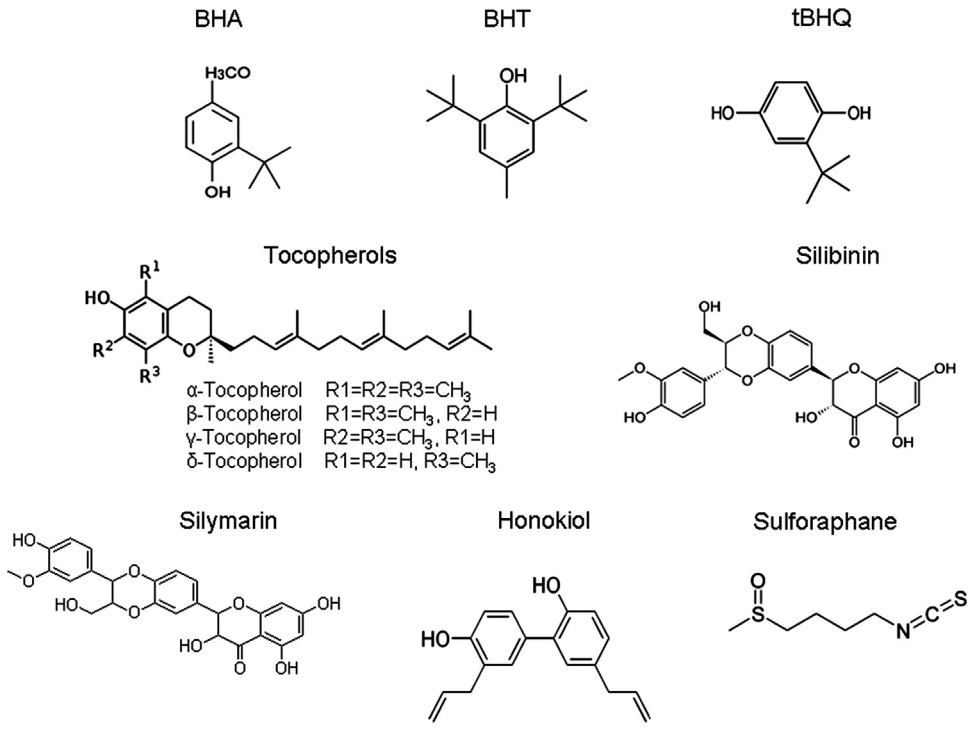

Fig. 2. Structures of a few representative antioxidants, tocopherols including α-tocopherol (vitamin E), and phytochemicals.