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Review

The role of nuclear factor erythroid 2-related factor 2 in hepatoprotective activity of natural products: A review

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ABSTRACT

Internal metabolism and environmental toxicant exposure can be caused to generate reactive oxygen species in human organelles which lead to oxidative stress. The nuclear factor erythroid 2–related factor 2 (Nrf2), a basic leucine zipper (bZip) transcription factor, controls the expression of antioxidant response element (ARE)–dependent genes to regulate cellular resistance to oxidants. Nrf2 is an essential factor for hepatoprotection against drugs and xenobiotics. The key role of Nrf2 in hepatoprotection has been highlighted since Nrf2 knockout mice showed high sensitivity to xenobiotic-induced hepatotoxicity. Some natural products including polyphenols, terpenoids and alkaloids can induce Nrf2 expression as a key protein in the antioxidant defense system of hepatocytes. This review outlines natural product activators of Nrf2 that protect the liver from toxicity induced by xenobiotics.

1. Introduction

The liver is one of the most important organs in the human body with vital functions from its role in glucose hemostasis and lipids metabolism to immunological and vascular functions (Mitra and Metcalf, 2012). One of the most critical and differentiated functions of the liver is its detoxifying role that like a barrier between the gastrointestinal tract and drug targets throughout the body eliminating toxicants via reducing lipophilicity of almost every foreign toxicant that absorbed from lumen. Hepatocytes carry out this activity using specific enzymes called cytochrome P450 enzymes that do the most in metabolizing xenobiotics through changes in the chemical structures of the foreign substances (Guengerich, 2001). However, these changes in chemical structures of xenobiotics in some cases produce toxic substances that can lead to toxicity in hepatocytes and ultimately cause hepatotoxicity in humans (Zimmerman, 1999).

Hepatotoxicity is a life-threatening toxicity that can be induced by several xenobiotics including drugs and toxins. Even, substances that are normally considered safe for human, in higher doses can cause severe hepatotoxicity (e.g. over-the-counter drug acetaminophen and ethanol) and lead to liver transplantation or death. Many drugs are withdrawn from the market owing to this toxicity (Lee, 2003). Therefore, hepatoprotection with natural (silymarin) and synthetic compounds (acetylcysteine) is a practical way that has been frequently used to alleviate xenobiotics hepatotoxicity (Vargas-Mendoza et al., 2014a; Smilkstein et al., 1988).

The nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) is a transcription factor, that regulates antioxidant response elements (ARE)-mediated gene expression (Itoh et al., 1999). The researches were especially focused on the role of Nrf2 in cancer (somehow controversial) (Sporn and Liby, 2012), oxidative stress and toxicity (Ma, 2013). In normal conditions, Nrf2 is mainly inhibited by Kelch-like ECH-associated protein 1 (Keap1). Oxidative and electrophilic stresses antagonize Keap1 inhibitory effects (Itoh et al., 1999) and following activation, Nrf2 binds to ARE on DNA and can regulate more than 100 genes (Sporn and Liby, 2012). The final result will be detoxification of exogenous and some endogenous chemicals from the cell (Venugopal and Jaiswal, 1996). Any alteration or aberration in the activity of Nrf2

Abbreviations: Antioxidant response element, (ARE); Kelch-like ECH-associated protein 1, (Keap1); Glutathione S-transferase, (GST); NAD(P)H:quinone oxidoreductase 1, (NQO1); Nuclear factor erythroid 2 (NFE2)-related factor 2, (Nrf2); Heme oxygenase-1, (HO-1); Carbon tetrachloride, (CCl4); c-Jun N-terminal kinase, (JNK); Glutathione peroxidase, (GPx); Superoxide dismutase, (SOD); Nuclear factor-κB, (NF-κB); Natural product, (NP); Thioredoxin-1, (TRX1); Heat shock factor 1, (HSF1); Natural products, (NPs)

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can lead to the susceptibility of the affected cell to oxidative compounds (Motohashi and Yamamoto, 2004).

The role of Nrf2 in hepatoprotection was highlighted when Nrf2 knockout mice showed high sensitivity to acetaminophen-induced hepatotoxicity (Enomoto et al., 2001). Since then, many other research groups reported the vital role of Nrf2 for hepatoprotection against drugs and xenobiotics (Wu et al., 2012; Liu et al., 2010a; Li et al., 2014a).

According to these strong evidence, one rational approach for defense against hepatotoxic xenobiotics could be the activation of Nrf2 as a key protein in antioxidant defense systems of hepatocytes.

Since the identification of Nrf2, many natural products (NPs) have shown modulatory activity on Nrf2 (Kumar et al., 2014). In fact, proven detoxifying and protective effects of some NPs (e.g. sulforaphane) against oxidative stress is now related to activation of Nrf2 (Gao et al., 2001; Shinkai et al., 2006). The role of Nrf2 in the hepatoprotective activity of NPs was also subject to extensive researches (Gao et al., 2001; Cho et al., 2011; Choi et al., 2016). In this review, we summarize NP activators of Nrf2 that protect the liver from toxicity induced by xenobiotics. We also discussed the future perspectives of this research area.

Scopus, Pubmed, Web of Science, and Science Direct were searched for the terms “Nrf2″or “nuclear factor erythroid 2 (NFE2)-related factor 2”, “hepatoprotection” or “hepatotoxicity” or “liver injury” and “natural products” without any limitation in search criteria.

2. Role of Nrf2 in the cellular antioxidant defense system of the cells

The nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) is a transcription factor, structurally related to basic region leucine zipper (bZip) transcription factors subfamily (Ma, 2013). Nrf2 is encoded by the *NFE2L2* gene and has a highly conserved region that is different from the other members of bZip transcription factors like c-Jun and c-Fos (Chan et al., 1995). Nrf2 was first identified in 1994 as a protein that binds to the NF-E2 binding site of human β-globin genes (Moi et al., 1994). Only a few years later, Itoh et al. discovered its role as a regulator of ARE-mediated gene expression (Itoh et al., 1999).

In a cell with normal condition, attachment of Nrf2 to Keap1 prevents localization from cytoplasm into nuclei and cullin 3 can degrade Nrf2 via ubiquitination. Thereby, the cytoplasmic half-life of Nrf2 under normal conditions is only 20 min (Kobayashi et al., 2004). Oxidative and electrophilic stresses in the cell detach Nrf2 from Keap1, and free Nrf2 can translocate into the nucleus and combine with small Maf proteins (MAFF, MAFG, MAFK) (Yamamoto et al., 2008; Itoh et al., 1997). The resulting heterodimer then will bind to ARE and regulate expression of more than 100 genes which some of them encode proteins involved in antioxidant defense system of the cells (Sporn and Liby, 2012). As it is shown in Fig. 1, heme oxygenase 1 (HO-1), catalase (CAT), glutathione peroxidase (GPx), NAD(P)H: quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), glutathione S-transferase (GST), sulfiredoxin 1 (SRXN1), thioredoxin reductase 1 (TXNRD 1), UDP-glucuronosyltransferase (UGT) and multidrug resistance-associated proteins (MRP) are some of the proteins that their gene expression will alter after activation of Nrf2 (Ma, 2013). These enzymes and many others that are not listed above, work together to alleviate the effects of toxicants and eliminate them from the cell (see Fig. 2).

Nrf2 is distributed ubiquitously in human tissues, with the greatest accumulation in the kidney, muscle, lung and liver, showing the importance of Nrf2 as an universal guardian against oxidative and electrophilic stresses induced by toxicants in several tissues (22). According to these strong evidence, one rational approach for defense against different stresses could be the activation of Nrf2 as a key protein in antioxidant defense systems of the cells. However, a serious concern was raised when studies revealed that in many cancer cells Nrf2 is overactivated. It is now obvious that the cells exposed to oxidative and electrophilic stresses can benefit from transient activation of Nrf2 by pharmacological agents without risk of making the cells cancerous, whereas constitutive activation of Nrf2 via genetic mutations can lead to cancer (Sporn and Liby, 2012).

Nrf2 attracted much attention for its pivotal role in prevention of degenerative and chronic diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) (Joshi and Johnson, 2012; Al-Sawaf et al., 2015). Dimethyl fumarate (Tecfidera®) is a successful example of Nrf2 activators that was approved by FDA in 2013 for treatment of relapsing–remitting MS. Dimethyl fumarate showed protective activity in glial cells and immune regulatory effects mainly through activation of Nrf2 (Bomprezzi, 2015).

3. Role of Nrf2 in xenobiotics-induced toxicity

The importance of Nrf2 against toxicity of xenobiotics was highlighted when Nrf2 knockout mice showed higher sensitivity to BHT-induced acute pulmonary injury more than normal mice (Chan and Kan, 1999). In Nrf2 knockout mice, 23% survival was observed after i.p. injection of 600 mg/kg BHT, while at the same dose, 67% of wild-type mice survived. LD_{50} of BHT for wild-type mice was above 1500 mg/kg, while for null mice was 530 mg/kg (Chan and Kan, 1999). Similar results were observed in hepatotoxicity induced by acetaminophen in Nrf2 knockout mice. LD_{50} of acetaminophen in the male null mice was 235 mg/kg, while for male wild-type mice LD_{50} was increased to 400 mg/kg (Chan et al., 2001). Another study also proved the higher sensitivity of Nrf2 knockout mice to the hepatotoxic effects of acetaminophen and linked this hypersensitivity to decreased expression of ARE-regulated drug metabolizing enzymes (Enomoto et al., 2001). Other studies on Nrf2-null mice also documented the importance of Nrf2 as a guardian against xenobiotics-induced toxicity in several organs (Hu et al., 2006; Liu et al., 2010b; Jiang et al., 2009; Aoki et al., 2001; Li et al., 2014b). Nrf2-null mice are more sensitive to nephrotoxicity of cisplatin, pulmonary toxicity of bleomycin, cardiac toxicity of doxorubicin and neurotoxicity of 6-hydroxy dopamine (Ma, 2013). Nrf2-null mice are also more susceptible to carcinogens and more easily bear tumors in most of the tissues (Ramos-Gomez et al., 2001). These and many other examples highlight the importance of Nrf2 in universal protection against toxicity of drugs and toxins in several organs.

In parallel to these studies on Nrf2-null mice, the other groups studied the activation of Nrf2 by natural and synthetic small molecules as a possible strategy for protection against xenobiotics-induced toxicity and tumorigenesis in several organs. Oltipraz (a dithiolethione organosulfur compound) and sulforaphane (an isothiocyanate) were among the first Nrf2 activators tested for the protection against carcinogens (Iida et al., 2004; Xu et al., 2006). Oltipraz showed anti-tumorigenic activity in experimental models and entered clinical trials to inhibit the hepatocarcinogenesis induced by aflatoxin (Wang et al., 1999). Oltipraz could protect against carcinogenic effects of aflatoxin on hepatocytes via induction of phase 2 enzymes (Wang et al., 1999). Anti-carcinogenic activity of sulforaphane, an organosulfur natural inducer of Nrf2, was also proved in animal studies (Zhang and Gordon, 2004).

In many experimental models of xenobiotics-induced toxicity, induction of Nrf2 could successfully prevent from toxicity or at least reduced the severity of toxicity in targeted organs (Gao et al., 2013; Lu et al., 2018; Tsai et al., 2018). In a study by Liu et al., the activation of Nrf2 protected against hepatotoxicity of acetaminophen, cadmium, CCl_4, furosemide, lithocholic acid, microcystin and phalloidin (Liu et al., 2013). These studies not only uphold the importance of Nrf2 as key guardian against xenobiotics-induced toxicity, but also confirm the activation of Nrf2 as a possible way for protection against the toxicity in different organs, especially liver.