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REVIEW PAPER

Therapeutic Approaches to Alzheimer's Disease Through Modulation of NRF2

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Abstract

The nuclear factor erythroid-derived 2-related factor 2 (NFE2L2/NRF2) is a master transcription factor that regulates oxidative stress-related genes containing the antioxidant response element (ARE) in their promoters. The damaged function and altered localization of NRF2 are found in most neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis. These neurodegenerative diseases developed from various risk factors such as accumulated oxidative stress and genetic and environmental elements. NRF2 activation protects our bodies from detrimental stress by upregulating antioxidative defense pathway, inhibiting inflammation, and maintaining protein homeostasis. NRF2 has emerged as a new therapeutic target in AD. Indeed, recent studies revealed that NRF2 activators have therapeutic effects in AD animal models and in cultured human cells that express AD pathology. This review will focus on the NRF2 pathway and the role of NRF2 in AD and suggest some NRF2 inducers as therapeutic agents for AD.

Keywords NRF2 · NRF2 activator · Alzheimer's disease · Amyloid-β · Oxidative stress · ROS · Neurodegenerative disease

Introduction

Reactive oxygen species (ROS) are chemically reactive molecules that contain oxygen (Zuo et al. 2015). ROS are generated as a natural by-product in the biological metabolism, and they play important roles in cell signaling and stress responses. However, ROS concentrations are dramatically elevated under stress conditions (e.g., environmental stress), and high levels of ROS lead to damage in cell structure and oxidative stress. The primary risk factor for neurodegenerative disease is aging, which is a result of high levels of oxidative stress (Johnson and Johnson 2015). The accumulation of misfolded proteins such as amyloid-β (Aβ), tau phosphorylation (p-Tau), and α-synuclein are linked with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Karuppagounder et al. 2009; Sherman and Goldberg 2001). The misfolded and aggregated proteins induce mitochondrial fragmentation and dysfunction that lead to an increase of in the levels of aberrant ROS (Cho et al. 2009; Liu et al. 2017; Baek et al. 2017). Including oxidative stress, unrelenting stress contributes to aging and age-related neurodegenerative diseases including AD, PD, and amyotrophic lateral sclerosis. Aβ and p-Tau have long been considered widely accepted AD-causing risk factors. ROS-triggered oxidative stress plays a crucial role in the generation and accumulation of Aβ in AD brains (Jo et al. 2010; Bonda et al. 2010; Gwon et al. 2012; Liu et al. 2017). Aβ induces neuroinflammation by activating microglia, which leads to the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) and subsequently contributes to synaptic damage and neuronal loss (Smith et al. 2012). Increased oxidative stress also affects tau hyperphosphorylation through increasing the activity of p38 MAPK (Giraldo et al. 2014). In this regard, the strategy of antioxidant therapy is attractive for AD as well as other neurodegenerative disorders (Uttara et al. 2009; Feng and Wang 2012; Liu et al. 2017).

The nuclear factor erythroid 2-related factor 2 (NFE2L2/NRF2) pathway possesses great potent in AD treatment. In

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basal conditions, kelch ECH associating protein 1 (KEAP1), a Cullin3-based E3 ligase, sequesters NRF2 in cytoplasm, which poly-ubiquitinates NRF2 and subsequent proteasomal degradation (Kobayashi et al. 2004; Keleku-Lukwete et al. 2017). In contrast, ROS and NRF2 activators disrupt KEAP1/NRF2 interaction through reaction with KEAP1 cysteine residues (Saito et al. 2016; Keleku-Lukwete et al. 2017). The accumulation of NRF2 protein is followed by nucleus translocation and interaction with binding partners, which drives the transcription of detoxifying and antioxidant genes (Sykiotis and Bohmann 2010). In this article, we discuss NRF2 roles and the effects of NRF2 activators in AD.

NRF2/ARE Signaling Pathway

As aforementioned, NRF2 is a master regulator of a prominent antioxidant and phase II detoxification genes, which protect the cells from electrophilic and oxidative stress. In normal conditions, KEAP1, a cytoplasmic inhibitor of NRF2, associates with NRF2 and keeps facilitating its proteasomal degradation through poly-ubiquitination. Under oxidative stress, KEAP1-NRF2 association is stalled, NRF2 translocates the nucleus, and then it binds to the antioxidant response element (ARE; 5′-TGANNNNGC-3′) sites in target genes through forming a heterodimer with one of the small musculoaponeurotic fibrosarcoma oncogene (MAF) proteins.

NRF2 Protein Structure

NRF2 protein comprises seven functional NRF2-ECH homologous (Neh) domains (Fig. 1). Neh1 domain is necessary for the formation of a heterodimer with small MAF, and it mediates binding to the ARE sequence in the promoter of its target genes (Moi et al. 1994). NRF2 binds to KEAP1 through the N-terminal Neh2 domain, where it is responsible for the cytoplasmic localization of NRF2 and is the major regulatory domain (Kobayashi et al. 2004; Zhang et al. 2004). The C terminus Neh3 is a transactivation domain that recruits chromo-ATPase/helicase DNA-binding protein 6 (CHD6) (Nioi et al. 2005). Neh4 and Neh5 are other transactivation domains that recruit transcription factors and other canonical proteins such as cAMP response element-binding (CREB)-binding protein (CBP) and/or receptor-associated co-activator 3 (RAC3) (Katoh et al. 2001; Kim et al. 2013b). NRF2 can be regulated by Hrd1 and GSK-3β/β-transducin repeat-containing protein (β-TrCP)-dependent mechanisms. Hrd1 is an E3 ubiquitin ligase that resides in the endoplasmic reticulum (ER) membrane. NRF2 interacts with Hrd1 in the Neh4 and Neh5 domains (Wu et al. 2014). GSK-3β phosphorylates NRF2 at the Neh6 domain by facilitating interaction with β-TrCP and NRF2 (McMahon et al. 2004; Rada et al. 2011; Chowdhry et al. 2013). Retinoid X receptor α, a negative regulator of NRF2, binds to the Neh7 domain of NRF2 (Wang et al. 2013).

NRF2 Binding Partner

NRF2 requires dimerization with a binding partner that contains a basic-leucine zipper (bZip) DNA-binding domain such as small MAFs (Fig. 2a) (Itoh et al. 1997). However, small MAF proteins have DNA-binding domains (Fujiwara et al. 1993) but no transactivation domains, which suggests the possibility that the NRF2/small MAF complex demands other partners for ARE-mediated transcription. Several studies suggested that CBP interacts with NRF2/small MAF (Katoh et al. 2001). CBP has histone acetyltransferase activity, remodeling chromatin to relax promoters including ARE and thereby recruiting RNA polymerase 2. In addition to small MAFs, other transcription factors have been identified as interacting with NRF2 including c-Jun, activating

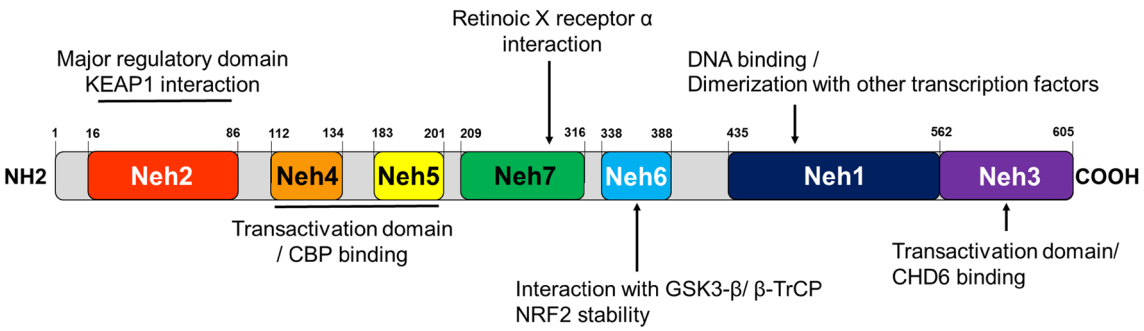

Fig. 1 Schematic representation of NRF2 protein domains. NRF2 has seven domains called Neh1–7. Neh2 is a major regulatory domain and interacts with KEAP1. Neh4 and Neh5 domains are transactivation domains and bind to the transcriptional co-activator CBP. NRF2 interacts with RXRα through the Neh7 domain. NRF2 stability is regulated through the Neh6 domain in which NRF2 interacts with β-TrCP and GSK-3β. Through Neh1 domain, NRF2 binds to DNA and dimerizes with other transcription factors. Neh3 domain is another transactivation domain as well as Neh4–5 and NRF2 binds to CHD6 through this domain

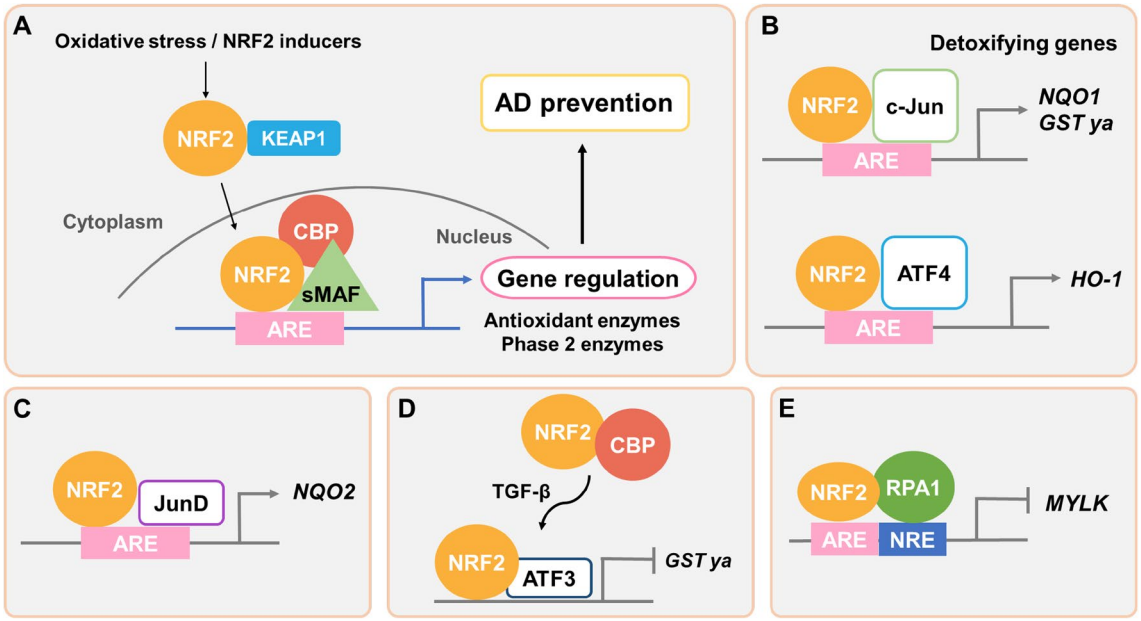

Fig. 2 NRF2 functions as transcriptional activator and repressor. **a** Under stress conditions or the treatment of NRF2 activators, NRF2/KEAP1 interaction is disrupted and NRF2 translocates to the nucleus. NRF2 interacts with bZip transcription factors (e.g., small MAF; sMAF) and co-activators such as CBP and binds the ARE sites of NRF2 target genes. NRF2 induces cytoprotective genes and phase II detoxifying enzyme genes, ultimately prevents AD pathology. **b, c** Aside from sMAF, NRF2 interacts with other transcription factors such as c-Jun, ATF4 (**b**), and JunD (**c**) and regulates the transcription of detoxifying genes (*NQO1, GST Ya, HO-1*, and *NQO2*). **d** In TGF-β stimuli, ATF3 interacts with NRF2 by competing with CBP and NRF2/ATF3 negatively regulates the transcription of NRF2 target gene, *GST Ya*. **e** RPA1 competes with small MAF for NRF2 interacting, followed by NRF2/RPA1 complex binding to ARE-NRE and repressing many genes with diverse functions (e.g., *MYLK*)

transcription factor 4 (ATF4), JunD, ATF3, runt-related transcription factor 2 (Runx2), YY1 and replication protein A1 (RPA1) (Fig. 2)(Venugopal and Jaiswal 1998; Wang and Jaiswal 2006; He et al. 2001; Brown et al. 2008; Hinoi et al. 2006; René et al. 2010; Liu et al. 2018).

NRF2 in association with c-Jun regulates the ARE-mediated expression of detoxifying genes such as *NAD(P)H:quinon oxidoreductase 1* (*NQO1*) and *glutathione S-transferase* (*GST*) *Ya* (Fig. 2b) (Venugopal and Jaiswal 1998). ATF4 forms a heterodimer with NRF2, thereby upregulating NRF2 target gene *heme oxygenase-1* (*HO-1*) by directly binding to the ARE in *HO-1* promoter (Fig. 2b) (He et al. 2001). JunD, an AP1 family bZip transcription factor, is another binding partner of NRF2 and upregulates *NQO2* gene expression with NRF2 in an ARE-dependent manner (Fig. 2c) (Wang and Jaiswal 2006). ATF3 expression increases are mediated by transforming growth factor (TGF)-β. ATF3 as an NRF2-binding partner competes with CBP. The ATF3-NRF2 complex binds to the AREs located in the promoter of the NRF2 target gene *GST Ya* and represses target gene expression (Fig. 2d) (Brown et al. 2008). Runx2 plays a critical role in cellular differentiation processes in osteoblasts. NRF2 down-regulates Runx2-dependent transcription of *Osteocalcin* by inhibiting Runx2 recruitment to ARE-like motif in the *Osteocalcin* promoter, but NRF2 physically interacts with Runx2 and represses Runx2-dependent transcription activity (Hinoi et al. 2006). Cystic fibrosis transmembrane conductance receptor (CFTR) is an epithelial Cl^- channel, and its loss of function induces cystic fibrosis. René et al. identified ARE-like motif located downstream the transcriptional start site of *CFTR* promoter. NRF2 negatively regulates CFTR expression by binding the ARE-like site in CFTR promoter with YY1. NRF2 promotes YY1 nuclear translocation and cooperates with YY1 to repress CFTR transcriptional activity (René et al. 2010). Recently, Liu et al. discovered that NRF2 can act as a transcriptional repressor as well as activator by interacting with RPA1. The NRF2-RPA1 complex directly binds to the ARE and an adjacent 7 bp negative regulatory sequence (AACTTCA), which is referred to as NRF2-RPA1 element (NRE) and located at the 3′ flanking region of ARE in the *MYLK* promoter (Fig. 2e). Research for this paper revealed that NRE is required for NRF2-dependent *MYLK* gene repression and the NRF2-RPA1-ARE-NRE complex reduces other genes as well via genome-wide and RNA-seq datasets (Liu et al. 2018).

NRF2 in Alzheimer's Disease

Aging is a risk factor of Alzheimer's disease characterized by mitochondrial damage, synaptic and neuronal loss, cognitive dysfunction, accumulation of Aβ, and neurofibrillary tangle (NFT) of hyperphosphorylated tau (Alzheimer's Association 2018). Oxidative stress in the nervous system contributes greatly toward AD progression (Lin and Beal 2006), and Aβ plays a key role in AD pathophysiology. Aβ peptide is generated following cleavage of amyloid-β precursor protein (APP) by two enzymes, β site APP cleaving enzyme 1 (BACE1) and γ-secretase (Woo et al. 2009; Zhang et al. 2011), and it is believed that Aβ oligomers cause neuronal toxicity in AD.

NRF2 Effects on Amyloidopathy

NRF2 has been shown to be a protective factor against AD pathology, and NRF2 expression is low in aged AD animal models and AD patient brains. NRF2 was attenuated in an APP/PS1 transgenic mouse brain at the time of Aβ deposition. NRF2 reduction was observed in 16-month old APP/PS1 mice concomitant with aging (Kanninen et al. 2008). Ramsey et al. found that NRF2 localization is affected in AD brains via immunohistochemistry. In both nucleus and cytoplasm, NRF2 is found in the normal hippocampus, but it is primarily present in cytoplasm in AD (Ramsey et al. 2007). NRF2 activation is reduced and its target gene expression is decreased in AD, consistent with NRF2 level changes (Kanninen et al. 2008). However, some researchers have demonstrated that the levels of NRF2 target gene are up-regulated in AD relative to control brains: NQO1, p62, HO-1, and glutamate cysteine ligase modifier subunit (GCLM) (Raina et al. 1999; Wang et al. 2000; SantaCruz et al. 2004; Tanji et al. 2013). These paradoxical results could be affected by the disease stage or region of brain collection (Johnson and Johnson 2015).

NRF2-related genetic and pharmaceutical approaches have been suggested for developing drugs for AD. NRF2 activation plays a protective role against AD-related pathophysiology. Gene delivery using lentiviral vector (LV) to code human *NRF2* into the hippocampus of an APP/PS1 mouse significantly ameliorated cognitive deficits. NRF2 induction displaces the balance between soluble and insoluble Aβ toward an insoluble Aβ pool, could possibly reduce the levels of toxic soluble Aβ peptides. In addition, LV-NRF2 treatment efficiently reduces astrocytosis in morphology via regulating GFAP expression level (Kanninen et al. 2009).

Nrf2 deficiency leads to increased sensitivity to 3-NP, which is a mitochondrial toxin, in primary neurons and in vivo. *Nrf2*-KO primary cortical neurons are protected by *Nrf2*-overexpressing astrocytes (Calkins et al. 2009). NRF2 modulates autophagy by upregulating p62. *Nrf2*-deficient APP/PS1 (APP/PS1/$Nrf2^{-/-}$) mouse showed increasing levels of APP, Aβ1–40, Aβ1–42, and polyubiquitin conjugated proteins in inflammatory response. Autophagic dysfunction is also increased in APP/PS1/$Nrf2^{-/-}$ mice. *Nrf2* deficiency exacerbated AD pathology in APP/PS1 mice (Joshi et al. 2015). Furthermore, cognitive impairment in APP/PS1/$Nrf2^{-/-}$ mice was linked to increased interferon-gamma (IFNγ), and microgliosis without altering gross motor function (Branca et al. 2017).

NRF2 Effects on Tauopathy

Under normal conditions, tau stabilizes microtubules and contributes to intracellular trafficking (Dixit et al. 2008; Vershinin et al. 2007). In AD, however, the function of tau is destroyed, thereby leading to cytoskeletal disruption and the development of NFT pathology (Congdon and Sigurdsson 2018). The post-translational modification of tau leads to loss of microtubule binding and elevating tau aggregation (Lindwall and Cole 1984), and aggregated tau was discovered to be hyperphosphorylated (Grundke-Iqbal et al. 1986). NRF2 reduces the phosphorylated tau by inducting autophagy adaptor protein NDP52. NRF2 strongly up-regulated the NDP52 expression by binding AREs in its promoter, and NDP52 induction facilitates autophagy-mediated degradation of phosphorylated tau (Jo et al. 2014). Lastres-Becher et al. demonstrated that human TAU p301 mutant expresses CX3CL1, which activates AKT (p-AKT^{Ser473}), inhibits GSK-3β (p-GSK-$3β^{Ser9}$), and upregulates NRF2 by blocking degradation. The CX3CL1/NRF2/HO-1 axis attenuates tauopathy-induced microgliosis. In this paper, CX3CL1 and NRF2 expressions were unexpectedly upregulated in AD and progressive supranuclear palsy patients, which could be compensational effects and interpreted as a "help me" signal (Lastres-Becker et al. 2014). Rojo et al. revealed through microarray analysis that $Nrf2^{-/-}$ mice brains reproduce the alternation of transcriptional pathways in human elderly and AD brains. Then, *Nrf2*-deficient mice with amyloidopathy and tauopathy (AT-NRF2-KO) were generated. AT-NRF2-KO mice presented marked increases in oxidative stress and inflammation as well as amyloidopathy- and tauopathy-related markers and exhibited deficits in spatial learning and memory (Rojo et al. 2017).

NRF2 Activators as Therapeutics for Alzheimer's Disease

Numerous chemical compounds and natural products have been identified as NRF2 inducers. Among NRF2 activators, several compounds that disrupt KEAP1/NRF2 interaction or

activate NRF2 have been verified in AD animal models with ameliorating AD pathology (Table 1).

NRF2 Activators Affecting Aβ

CDDO-methylamide (CDDO-MA, synthetic triterpenoids) induces HO-1 gene expression via NRF2/ARE pathway (Liby et al. 2005). When Tg19959 mice were fed CDDO-MA or control chow for 3 months, CDDO-MA ameliorated spatial memory retention, reduced SDS-soluble plaque Aβ42 without affecting APP processing, and decreased plaque burden in the hippocampus (Dumont et al. 2009). Puerarin is a phytoestrogen derived from the root of *Pueraria*. Puerarin markedly ameliorated cognitive impairment

Table 1 NRF2 inducers tested in animal models

Compound	AD model	Behavior test	Protective mechanism	References
Aβ reduction				
CDDO-MA	Tg19959	MWM	Oxidative stress, microgliosis ↓	Dumont et al. (2009)
Puerarin	APP/PS1	MWM	Oxidative stress, lipid peroxidation ↓ (No effects on Aβ)	Zhou et al. (2014)
β-Hydroxybutyrate	Aβ-injected rat	–	Oxidative stress, apoptotic protein ↓	Xie et al. (2015)
Orientin	Aβ-injected mouse	MWM	Oxidative stress, Mitochondrial dysfunction and apoptosis ↓	Yu et al. (2015)
Antroquinonol	hAPP-J20	MWM	Oxidative stress, inflammatory cytokine ↓	Chang et al. (2015)
Dl-3-*n*-butylphthalide ide	APP/PS1	MWM, Y-maze, NOR	Oxidative stress	Wang et al. (2016)
Sodium hydrosulfide (NaHS)	APP/PS1	MWM	Antioxidant effects ↑, APP and BACE1 levels ↓	Liu et al. (2016)
Carnosic acid	hAPP-J20, 3xTg-AD	MWM	Synaptic loss, astrocytosis ↓	Lipton et al. (2016)
Vanillic acid	Aβ-injected mouse	MWM, Y-maze	Antioxidant effects ↑, neuroinflammation, apoptosis, synaptic deficits ↓	Amin et al. (2017)
Methysticin	APP/PS1	MWM	Oxidative stress, neuroinflammation ↓ (Aβ deposits not altered)	Fragoulis et al. (2017)
3H-1,2-dithiole-3-thione	Tg2576	MWM	Oxidative stress ↓, neurogenesis ↑	Cui et al. (2018) and Wang et al. (2017)
Cocaine- and amphetamine-regulated transcript peptide (CART)	Aβ-injected rat	MWM, OF	Oxidative stress, neuronal apoptosis ↓	Jiao et al. (2018)
Amanita caesarea polysaccharides	D-gal and $AlCl_3$-injected mouse	MWM, OF	Oxidative stress ↓, cholinergic system ↑	Li et al. (2018)
p-Tau reduction				
Fisetin	–	–	Autophagy ↑	Kim et al. (2016)
Benfotiamine (BFT)	P301S	CFC, EPM	Oxidative stress, mitochondrial dysfunction and inflammation ↓	Tapias et al. (2018)
Dimethyl fumarate (DMF)	P301L	–	Neuronal impairment, inflammation ↓	(Cuadrado et al. 2018)
Both Aβ and p-Tau reduction				
Sulforaphane	Aβ-injected rat, tunicamycin-injected rat	MWM, Y-maze, PA	ER stress, oxidative stress ↓	Kim et al. (2013a) and Zhu et al. (2015)
Allicin	Tunicamycin-injected rat	MWM	ER stress, oxidative stress ↓	Zhu et al. (2015)
Mini-GAGR	3xTg-AD	Barnes Maze	Oxidative stress ↓	Murphy et al. (2018)

MWM Morris Water Maze test, *NOR* novel object recognition test, *CFC* contextual fear conditioning test, *EPM* Elevated Plus Maze, *OF* open field test, *PA* passive avoidance test

(–) indicates that the effects of compounds were not verified in vivo or through behavioral test

and activated AKT/NRF2/HO-1 axis in APP/PS1 but did not affect Aβ burden (Zhou et al. 2014). Among the components of ketone bodies, β-hydroxybutyrate activated the NRF2 pathway and prevented Aβ aggregation in Aβ-injected rat hippocampus and in Aβ-treated PC-12 cells (Xie et al. 2015). Orientin, which is a flavone, reduced Aβ levels and alleviated impaired cognitive function and oxidative stress by upregulating NRF2 in Aβ1–42-induced C57B/6 mice (Yu et al. 2015). Antroquinonol, a ubiquinone derivative isolated from *Antrodia camphorata*, improved learning and memory, reduced Aβ levels, and mitigated astrogliosis in hAPP-J20 mice (APP transgenic mice). Antroquinonol increased NRF2 but decreased histone deacetylase 2 (Chang et al. 2015). Dl-3-*n*-butylphthalide (Dl-NBP) is a small-molecule compound derived from a Chinese herb that upregulates the NRF2 signaling pathway. Dl-NBP increased LTP, alleviated cognitive deficits, and reduced synaptic loss of neurons in APP/PS1 mice. In Dl-NBP-treated AD mice, soluble Aβ1–40 and 1–42 decreased, unlike insoluble Aβ fibrillar levels and Aβ burden (Wang et al. 2016). H_2S up-regulated NRF2, HO-1, and GST levels in sodium hydrosulfide (a H_2S donor)-injected APP/PS1 mice. H_2S ameliorated cognitive impairment and decreased the number of senile plaques through NRF2 activation (Liu et al. 2016). Carnosic acid (CA) is a low-molecular electrophilic compound in rosemary that promotes NRF2 activation. CA rescued spatial learning deficits and reduced Aβ accumulation and astrocytosis in hAPP-J20 mice. In 3xTg-AD mice, CA decreased p-Tau levels as well as GFAP signal (Lipton et al. 2016). Vanillic acid (VA) is a flavoring agent found in the root of *Angelica sinensis*. VA attenuated Aβ accumulation and cognitive impairment in an Aβ1–42 injected mouse model. VA abrogated oxidative stress via increasing p-AKT^{ser473}, p-GSK-3β^{ser9}, and NRF2 levels (Amin et al. 2017). Methysticin is one of the six major kavalactones found in the kava plant. Methysticin activated the NRF2 pathway and reduced neuroinflammation, hippocampal oxidative damage, and long-term memory impairment in APP/PS1 mice. However, the Aβ deposition in brains of methysticin-treated APP/PS1 mice was not altered relative to vehicle mice (Fragoulis et al. 2017). 3H-1,2-dithiole-3-thione (D3T) is a cyclic sulfur-containing dithiolethione that is derived from cruciferous vegetables. D3T treatment alleviated cognitive impairment, reduced insoluble Aβ levels in hippocampus, and promoted neurogenesis in Tg2576 mice. D3T activated the SIRT1/NRF2 pathway and markedly reduced the protein level of acetylated-NRF2 (Cui et al. 2018; Wang et al. 2017). Cocaine- and amphetamine-regulated transcript (CART) peptide attenuated Aβ accumulation and improved cognition and locomotor activity in Aβ1–42-treated rats. CART peptide activated NRF2/HO-1 pathway and attenuated neuronal apoptosis in rat hippocampus (Jiao et al. 2018). *Amanita caesarea* polysaccharides (ACPS), a polysaccharide obtained from *Amanita caesarea* aqueous extract, enhanced the nuclear levels of NRF2 by suppressing KEAP1 expression. ACPS suppressed the deposition of Aβ, ameliorated oxidative stress, and improved AD-like behaviors in d-gal and $AlCl_3$ treated AD mice (Li et al. 2018).

NRF2 Activators Affecting p-Tau

Fisetin, 3,7,3′,4′-tetrahydroxyflavone, is an organic flavonoid obtained from fruits and vegetables such as strawberries and cucumbers. Fisetin induced autophagic degradation of p-Tau by activating TFEB and NRF2 transcription factors; however, Fisetin did not demonstrate therapeutic effect in AD mice model (Kim et al. 2016). Benfotiamine (BFT) is a synthetic S-acyl derivative of thiamine (vitamin B1) with an open-ringed structure. BFT treatment ameliorated behavioral deficits and reduced tau pathology in P301S mice. BFT stimulated the activation of NRF2 target genes as well as the NRF2/ARE pathway, but no effect was seen in *Nrf2*-KO mouse embryonic fibroblasts, thus showing BFT's effects in an NRF2-dependent manner (Tapias et al. 2018). Dimethyl fumarate (DMF), a simple molecule derived from fumaric acid, is an approved drug for relapsing–remitting multiple sclerosis as an oral formulation termed BG-12 (Bomprezzi 2015). DMF showed protective effects against α-synuclein toxicity in PD (Lastres-Becker et al. 2016). In a tauopathy model, DMF modulated tau hyperphosphorylation and neuronal impairment. DMF attenuated tau-related neurodegeneration by disrupting the KEAP1/NRF2 interaction and through the GSK-3β/NRF2 signaling pathway. DMF attenuated astrogliosis and microgliosis in an NRF2-dependent manner, as these effects were not observed in $Nrf2^{-/-}$ mice (Cuadrado et al. 2018). Aside from BFT and DMF, no NRF2 activators were verified in $Nrf2^{-/-}$ mice.

NRF2 Activators Affecting Both Aβ and p-Tau

Sulforaphane is a phytochemical obtained from cruciferous vegetables such as broccoli. NRF2 is activated via sulforaphane disrupting KEAP1 and NRF2 interaction. Sulforaphane showed neuroprotective effects against AD in an animal model. Some papers revealed that sulforaphane ameliorated cognitive deficits in acute AD (Kim et al. 2013a) or tunicamycin-infused rat models (Zhu et al. 2015). Also, sulforaphane prevented Aβ aggregation and tau phosphorylation via NRF2 activation. Allicin, which is obtained from garlic, improved endoplasmic reticulum (ER) stress-related cognitive retention by activating PERK/NRF2 pathway. Allicin decreased tau phosphorylation and Aβ deposit in a tunicamycin-induced rat model (Zhu et al. 2015). Recently, Murphy et al. discovered Mini-GAGR, a 0.7 kD cleavage product of low-acyl gellan gum, which is able to pass through the blood brain barrier (BBB). Mini-GAGR, a NRF2-activating

polysaccharide, decreased ROS in mouse cortical neurons and reduced p-Tau and Aβ in 3xTg-AD mouse model (Murphy et al. 2018).

NRF2 Activators for Therapeutic Agents

Although thousands of scientists and health care experts have tried to develop drugs for AD, no therapeutic agents targeting Aβ or p-Tau in AD have been approved or shown significant effects in clinical trials (Selkoe and Hardy 2016). Several phase III clinical trials with small molecules or immunotherapy are ongoing. Because discovery and development of de novo drugs takes a very long time, drug repositioning is a very attractive approach and has a great advantage. As shown in Table 1, the effects have been verified for numerous NRF2 inducers in AD animal models. No inducers have been tested for clinical trials of AD; however, some of NRF2 inducers are candidates for clinical trials (Fig. 3). DMF, also known as BG-12, was approved for treating adults with relapsing multiple sclerosis by the U.S. Food and Drug Administration (FDA) (Biogen Idec 2013) and the European Medicines Agency (EMA) in 2013 (European Medicines Agency 2013). The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) also approved DMF as a disease-modifying drug for multiple sclerosis in 2017 (Niino et al. 2018). In addition to multiple sclerosis, DMF has proved effective in animal models for tauopathy and PD (Jing et al. 2015; Cuadrado et al. 2018).

Sulforaphane, a phytochemical contained in broccoli sprouts in relatively high concentration, is formed from glucoraphanin as a consequence of myrosinase activity when various vegetables are cut or chewed. In order to enhance any neuroprotective effects on the brain, any phytochemicals must cross the BBB. Jazwa et al. revealed that sulforaphane can penetrate the BBB and accumulate in cerebral tissues such as the ventral midbrain and striatum in mice. Sulforaphane concentration reached maximum level at 15 min and still presented after 2 h in the striatum (Jazwa et al. 2011). Three cysteine residues (Cys151, Cys273, and Cys288) of KEAP1 protein are essential for disrupting KEAP1-mediated NRF2 inhibition (Fig. 3) (Saito et al. 2016; Sun et al. 2017). Sulforaphane preferentially reacts with Cys151 of KEAP1 and induces the conformational change of KEAP1 (Hu et al. 2011). Several clinical trials of sulforaphane have been completed or are ongoing for several diseases. In a phase II clinical trial for prostate cancer, 20 patients who had recurrent prostate cancer were treated with 200 μmoles/day of sulforaphane-rich extracts (Alumkal et al. 2015). While this treatment did not decrease prostate-specific antigen (PSA), the treatment safety and the effects on PSA doubling time modulation may warrant further studies.

CDDO compound has been tested for non-neurodegenerative diseases. While CDDO methyl (bardoxolone methyl) was tested in phase III clinical trials for type 2 diabetes and stage 4 chronic kidney disease, bardoxolone methyl did not reduce the risk of end-stage renal disease or high rate of death from cardiovascular causes (De Zeeuw et al. 2013; Chin et al. 2014). However, the investigators found the causes of failure and studies are continuing without identified risk factors (Chin et al. 2018). A new CDDO derivative (RTA 408) was entered in clinical trial for Friedreich's ataxia, an autosomal recessive inherited disease that neurodegenerative movement disorder (ClinicalTrials.gov Identifier: NCT0225543).

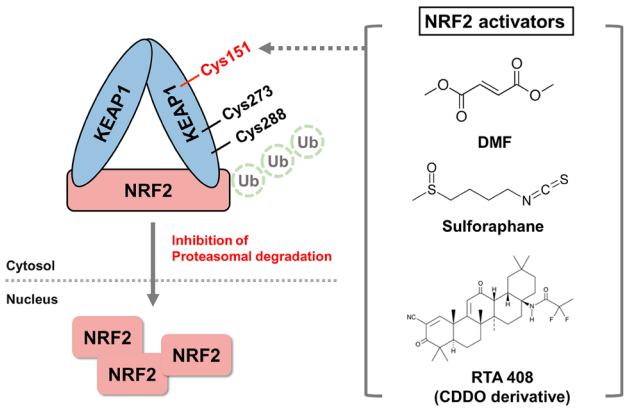

Fig. 3 NRF2 activators modify the cysteine 151 of KEAP1 protein. The modifiers of three cysteine residues 151, 273, 288 of KEAP1 regulate NRF2 accumulation in nucleus. Among NRF2 activators, DMF, sulforaphane, and RTA408 (CDDO derivative) modify cysteine 151 residues of KEAP1. Three compounds are already in use or clinical trials. NRF2-activation molecules interrupt NRF2/KEAP1 interaction, thereby the proteasomal degradation of NRF2 is inhibited. An accumulated NRF2 translocates to the nucleus

Conclusion

While human life span is extended due to advances in medical science, the incidence of age-related neurodegenerative disorders is increasing. Aging is the primary risk factor for various diseases including neurodegenerative diseases. With aging, considerable oxidative stress contributes to the progression of neurodegeneration. NRF2 is a major transcription factor activated in stress conditions, and it transcriptionally upregulates the genes of antioxidant enzymes to defend cells against damage. Several studies have shown that NRF2 is closely related to aging. The levels of NRF2 target genes are reduced in aged rat, with the reduced NRF2 expression levels and its activity (Suh et al. 2004). Kubben et al. discovered that repressed NRF2 signaling contributes to the premature aging phenotype of Hutchinson-Gilford progeria syndrome (HGPS) while reactivation of NRF2 decreases ROS

and restores cellular HGPS defects (Kubben et al. 2016). The KEAP1/NRF2 pathway has emerged as an attractive target for AD, and NRF2 inducers exhibit advantages as potent AD therapeutic agents. Numerous NRF2 activators have been verified in preclinical models in AD, and now it is essential to verify the safety and efficacy of these compounds in clinical trials. Because DMF has been FDA-approved, if its efficacy for AD is proven, it may be another successful drug repositioning. Based on the evidence suggested in this paper, we propose that NRF2-targeted approaches are an alternative strategy for AD drug development. However, in order to develop the successful NRF2 activators with AD therapies, more detailed and in-depth mechanistic studies should be conducted on how the NRF2 pathway regulates AD pathophysiology.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interests.

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