



Review

Shaping the Nrf2-ARE-related pathways in Alzheimer's and Parkinson's diseases

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ABSTRACT

A failure in redox homeostasis is a common hallmark of Alzheimer's Disease (AD) and Parkinson's Disease (PD), two age-dependent neurodegenerative disorders (NDD), causing increased oxidative stress, oxidized/damaged biomolecules, altered neuronal function and consequent cell death. Activation of nuclear factor erythroid 2-related factor 2 (Nrf2), a redox-regulated transcription factor, results in upregulation of cytoprotective and antioxidant enzymes/proteins, protecting against oxidative stress. Nrf2 regulation is achieved by various proteins and pathways, at both cytoplasmatic and nuclear level; however, the elaborate network of mechanisms involved in Nrf2 regulation may restrain Nrf2 pathway normal activity. Indeed, altered Nrf2 activity is involved in aging and NDD, such as AD and PD. Therefore, understanding the diversity of Nrf2 control mechanisms and regulatory proteins is of high interest, since more effective NDD therapeutics can be identified. In this review, we first introduce Keap1-Nrf2-ARE structure, function and regulation, with a special focus on the several pathways involved in Nrf2 positive and negative modulation, namely p62, PKC, PI3K/Akt/GSK-3β, NF-κB and p38 MAPK. We then briefly describe the evidences for oxidative stress and Nrf2 pathway deregulation in different stages of NDDs. Finally, we discuss the potential of Nrf2-related pathways as potential therapeutic targets to possibly prevent or slowdown NDD progression.

1. Introduction

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are physiologically formed as byproducts of normal metabolism and have important roles in cell signaling, homeostasis, autophagy and cell division (Obuobi et al., 2016). Under physiological conditions, low levels of ROS are fastly produced and eliminated, and tightly regulated

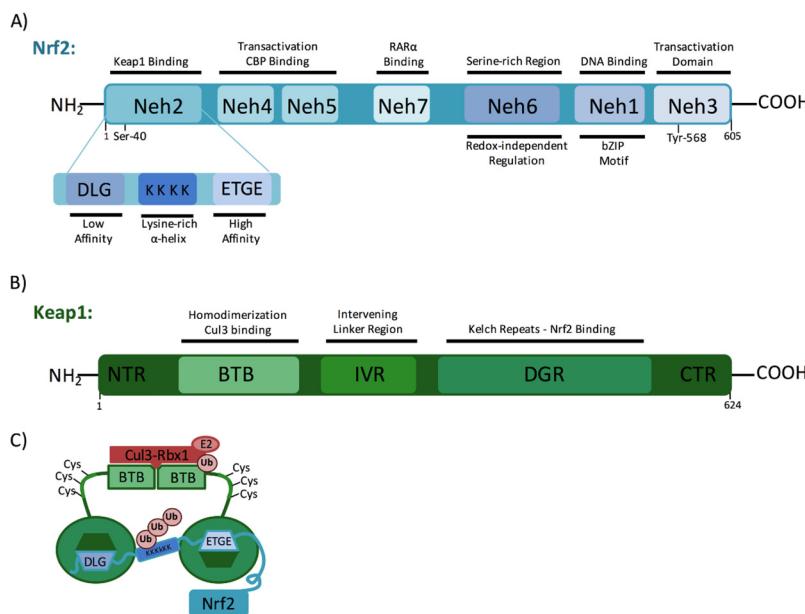
through a process designated as "redox homeostasis" (Droge, 2002). However, several risk conditions, such as aging, genetic or environmental factors may impair this homeostasis, leading to oxidative/nitrosative stress through increased ROS/RNS formation and failure of repair and detoxifying systems (Barnham et al., 2004). This causes impaired DNA structure, membrane disturbance and altered protein structure and function, leading to cellular damage (Schieber and

Abbreviations: α-Syn, α-Synuclein; β-TrCP, β-Transducin repeat-containing protein; Aβ, Amyloid-beta peptide; 6-OHDA, 6-Hydroxydopamine; 8-OHdG, 8-Hydroxy-2'-deoxyguanosine; AD, Alzheimer's disease; APP, Amyloid precursor protein; ARE, Antioxidant Response Element; bZIP, basic leucine zipper; CHD6, Chromo-ATPase/helicase DNA-binding protein; CNC, cap-n-collar; CK2, Casein kinase II; CREB, cAMP response element-binding protein; CBP, CREB-binding protein; CTR, C-terminal region; Cul3, Cullin3; DA, Dopamine; ECH, Erythroid cell-derived protein with CNC homology with chicken Nrf2; G6PD, Glucose-6-phosphate dehydrogenase; GSH, Reduced glutathione; GSSG, Oxidized glutathione; GSH-Px, Glutathione peroxidase; GSH-R, Glutathione reductase; GSH-Ts, Glutathione S-transferase; GCLc, Glutamate-cysteine ligase catalytic subunit; GCLM, Glutamate-cysteine ligase modifier subunit; GSK-3β, Glycogen synthase kinase-3β; HO-1, Heme oxygenase-1; Keap1, Kelch-like ECH-associated protein 1; LC3, microtubule-associated protein 1A/1B-light chain 3; Maf, musculoaponeurotic fibrosarcoma; MAPK, Mitogen-activated protein kinase; MCI, Mild Cognitive Impairment; NDD, Neurodegenerative disorders; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Neh, Nrf2-ECH homology; NFT, neurofibrillary tangles; Nrf2, Nuclear factor erythroid 2-related factor 2; NQO1, NAD(P)H:quinone dehydrogenase 1; PD, Parkinson's disease; PERK, Protein kinase RNA-like endoplasmic reticulum kinase; PI3K, Phosphoinositide 3 kinase; PKC, Protein kinase C; Prdx1, Peroxiredoxin 1; RARα, Retinoic acid receptor α; ROS, Reactive Oxygen Species; SNpc, *Substantia nigra pars compacta*; SOD, Superoxide dismutase; SULFs, Sulfotransferases; TR, Thioredoxin reductase; UGDH, UDP-glucose dehydrogenase

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Chandel, 2014).

In the brain, redox signaling is involved in memory consolidation, neuronal differentiation and plasticity (Bórquez et al., 2016). Neurons, in particular, are recognized to easily undergo oxidation due to their high oxygen consumption, low levels of antioxidants, high levels of iron and auto-oxidizable catecholamines in certain brain areas, high levels of membrane polyunsaturated fatty acids, as well as the fact that these are post-mitotic cells, accumulating non-degradable oxidized molecules. Indeed, large amounts of ROS lead to neuronal death and altered brain function, as observed in neurodegenerative disorders (NDD) (Anderson and Maes, 2014). Thus, increased oxidative markers and deficient enzymatic antioxidant systems are common pathological hallmarks in NDD as Alzheimer's disease (AD) (Aslan and Ozben, 2004) and Parkinson's disease (PD) (Jenner, 2003). One of the main (neuro) protective mechanism is the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), a ubiquitous transcription factor that modulates oxidative stress response. Nrf2 regulates antioxidant, anti-inflammatory and detoxifying genes, through binding to the Antioxidant Response Element (ARE), enhancer sequences present in the regulatory regions of Nrf2 target genes (Gan and Johnson, 2014; Yamazaki et al., 2015). Moreover, Nrf2 has been described to be an important regulator of normal mitochondrial structure and function, with a significant role under stress conditions (Dinkova-Kostova and Abramov, 2015); in this respect, Nrf2 has been described to control mitochondrial membrane potential and respiration, oxidative phosphorylation and ATP synthesis, also improving mitochondrial fatty acid oxidation. Additionally, Nrf2 has an essential role in mitochondrial biogenesis, mitophagy and mitochondrial integrity (Dinkova-Kostova and Abramov, 2015).

Several evidences show Nrf2 expression both in glial cells and neurons in humans and mice brain. Although Nrf2 is more commonly expressed in astrocytes, endogenous Nrf2 expression and activation are evident in neurons in aging and neurodegeneration (Liddell, 2017). Nrf2 activation protects against mitochondrial toxins in primary neuronal cultures (Lee et al., 2003), while Nrf2 knockout mice showed increased susceptibility to common neurotoxins, general neurodegeneration and astrogliosis (Hubbs et al., 2007) and dopaminergic neuronal dysfunction (Rojo et al., 2010).

2. The Keap1-Nrf2-ARE pathway

Nrf2 belongs to the basic leucine zipper (bZIP) transcription factor family retaining a cap-n-collar (CNC) structure (Itoh et al., 1995; Toki

et al., 1997). Structurally, Nrf2 is formed by seven functional regions, also known as Nrf2-ECH homology (Neh) domains, from Neh1 to Neh7 (ECH, erythroid cell-derived protein with CNC homology with chicken Nrf2). The Neh1 domain belongs to the C-terminal half of Nrf2 and encloses the CNC-bZIP region, which allows the dimerization with a small musculoaponeurotic fibrosarcoma (Maf) proteins (MafF, MafG or MafK, in vertebrates) in the nucleus and the binding of Nrf2 to DNA (Hirotsu et al., 2012; Motohashi et al., 2004). Neh2 domain, at the N-terminal region, contains two degrons commonly known as the DLG (Leu23 to Arg43, low affinity) and ETGE (Gln73 to Ile86, high affinity) motifs (Fukutomi et al., 2014), which allows the interaction with Keap1 protein, mainly responsible for Nrf2 regulation in the cytosol (Tong et al., 2006a). The Neh3 domain, present in the extremity of Nrf2 C-terminal, can recruit the chromo-ATPase/helicase DNA-binding protein (CHD6) and modulates its transcriptional activation (Nioi et al., 2005). Neh4 and Neh5 domains are involved in transactivation activity, allowing the recruitment of cAMP response element-binding protein (CREB)-binding protein (CBP) (Katoh et al., 2001; Kwok et al., 1994). The Neh6 domain has the DSGIS (Asn329 to Ser342) and DSAPGS (Ser363 to Glu379) motifs (Chowdhry et al., 2013), involved in recruitment of β-transducin repeat-containing protein (β-TrCP), which negatively controls Nrf2 (Rada et al., 2012, 2011). Recently, Wang and colleagues, identified the Neh7 domain as a region that interacts with the retinoic acid receptor α (RARα), responsible for reducing the expression of Nrf2 target genes (Wang et al., 2013) (Fig. 1A).

Keap1 is a cytosolic protein (Watai et al., 2007) that regulates Nrf2 activity. Keap1 is a five-domain protein composed by a C-terminal region (CTR) and a N-terminal region (NTR) combined with three functional domains: a Kelch domain (DGR) (Li et al., 2004), an intervening region (IVR) (Mai et al., 2004) and a bric-a-brac domain (BTB) (Zipper and Timothy Mulcahy, 2002). Ubiquitin, a 76 amino acid protein, tag proteins to degradation by proteolytic activity, which depends upon three enzymes, ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-ligase (E3) (Finley, 2009). By using BTB domain, Keap1 can form homodimers to bind Cullin3 (Cul3), an adaptor to Cul3-type E3 ubiquitin ligase complex, resulting in Nrf2 ubiquitination (Cullinan et al., 2004), while by using the DGR domain, two Keap1 proteins can bind one Nrf2 protein (Tong et al., 2006b) (Fig. 1B,C).

Under physiological conditions, Nrf2 is mostly located in the cytosol due to its interaction with Keap1 protein (Itoh et al., 1999). Under oxidative stress conditions, as excessive ROS production, Nrf2 disconnects from Keap1 and migrates to the nucleus, as described in

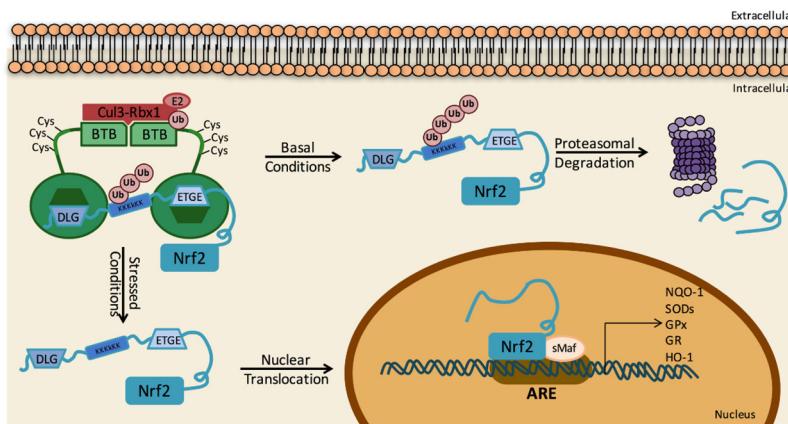


Fig. 2. Simplistic schematic representation of Nrf2 activation. Under basal/unstressed conditions Nrf2 is constantly ubiquitinated by Keap1-Cul3 complex resulting in Nrf2 recruitment for proteasomal degradation. Under stress conditions, Nrf2 can dissociate from Keap1, translocates into the nucleus and promotes the transcription of antioxidant enzymes after binding to ARE.

section 2.1 and 2.2, where it can dimerize with small Maf family members and bind to ARE (Itoh et al., 1997) (Fig. 2). When Nrf2 levels are increased in the nucleus, the Nrf2-Maf heterodimer can bind to ARE and recruit transcriptional co-activators, such as CBP or p300 (Zhu and Fahl, 2001), to promote transcription by intrinsic histone acetyltransferase activity (Kalkhoven, 2004) (Fig. 2).

ARE is defined as a cis-acting DNA enhancer motif and is positioned in the promoter of antioxidant genes, responsible for cell defense (Nioi et al., 2003), as well as metabolic genes (Hirotsu et al., 2012) and enzymes that metabolize xenobiotics (Malhotra et al., 2010). Thus, binding of Nrf2 to ARE regulates the transcriptional activation of important antioxidant enzymes such as NAD(P)H:quinone dehydrogenase 1 (NQO1), superoxide dismutase 1 (SOD1, Cu/Zn-SOD), glutathione peroxidase (GSH-Px), glutathione reductase (GSH-R), glutathione S-transferase (GSH-T), heme oxygenase-1 (HO-1), glucose-6-phosphate dehydrogenase (G6PD), glutamate-cysteine ligase catalytic subunit (GCLc), glutamate-cysteine ligase modifier subunit (GCLM), sulfo-transferases (SULFs), thioredoxin reductase (TR) or UDP-glucose dehydrogenase (UGDH) (Keum and Choi, 2014; Loboda et al., 2016). Of relevance, Nrf2 basal activity, as well as Keap1 detachment and nuclear accumulation are tightly controlled and regulated by different chemical and molecular mechanisms in accordance with the cell environment.

2.1. Keap1-dependent regulation of Nrf2

Keap1-Nrf2 interaction restricts the transcription factor in the cytosol and regulates Nrf2 levels by promoting its ubiquitin-mediated proteolysis, as described previously (Itoh et al., 1999). The BTB domain of Keap1, which facilitates the interaction with Cul3, is an adaptor to Cul3-type E3 ubiquitin ligase complex, driving Nrf2 to ubiquitination (Cullinan et al., 2004). This system allows the poly-ubiquitination in the sequence of lysine (Lys, K) residues located in the ETGE-DLG intervening region of Nrf2's Neh2 domain (Furukawa and Xiong, 2005). Therefore, the poly-ubiquitinated Nrf2 can be degraded by the 26S proteasome (Kobayashi et al., 2004), dissociating from Keap1, which can further be re-use to bind newly-translated Nrf2, thus regulating basal cellular levels of this transcription factor (Fig. 3). In the context of oxidative stress, Keap1, a cysteine-rich protein, is capable to sense oxidative stress through the possible oxidation of its 27 cysteine residues, particularly the 8 cysteine residues in the IVR region, further leading to conformational changes and release of Nrf2 (Miseta and Csutora, 2000). Moreover, many Nrf2 inducers are electrophilic, being able to react with nucleophilic thiols, including Keap1 cysteine sulfhydryl groups, forming direct covalent adducts (Dinkova-Kostova et al., 2002; Prestera et al., 1993). Thus, cysteine modifications are important mechanisms for Nrf2 activation, responsible for sensing electrophilic or oxidant conditions (Holland et al., 2008).

Besides the regulation of Keap1 through oxidation (Kobayashi et al., 2004), under certain chemical and oxidative stress conditions, Keap1

itself can be poly-ubiquitinated by modification of the Keap1 central linker domain (Hong et al., 2005; Zhang et al., 2005). In addition, under stress situations, Nrf2's DLG motif can disconnect from Keap1, allowing the binding of a polyubiquitination binding protein, p62 or substrate adaptor sequestosome-1, which targets substrates for autophagy (Copple et al., 2010; Komatsu et al., 2010). The binding of p62 to Keap1 occurs through a ETGE motif (Hancock et al., 2012) and further leads to the binding of microtubule-associated protein 1A/1B-light chain 3 (LC3) associated to the autophagosome membrane, leading to Keap1 degradation and consequent Nrf2 accumulation (Komatsu et al., 2010). Interestingly, Jain and colleagues showed that Nrf2 can mediate the induction of p62 gene expression, by binding directly to a conserved ARE in p62 promoter/enhancer, and in turn, p62 favors Nrf2 activation, creating a positive feedback loop (Jain et al., 2010).

2.2. Keap1-independent regulation of Nrf2

Besides Keap1, several proteins can regulate the Nrf2-ARE pathway, mainly by phosphorylation. In fact, Nrf2 comprises several sites for phosphorylation (Rojo et al., 2012) described as important regulators of both Nrf2 nuclear accumulation or nuclear exclusion and degradation. Next, we summarize some proteins and pathways that directly or indirectly regulate Nrf2 activity, in a Keap1-independent way, and that are involved in NDD (Fig. 3).

Hrd1 is an endoplasmic reticulum (ER) membrane E3 ubiquitin ligase (also called synoviolin) that is important for ER-associated degradation (ERAD) and for turnover control of non-ERAD substrates, namely p53 and inositol-requiring enzyme 1 (IRE1), and can negatively regulate Nrf2 (Yamasaki et al., 2007). Wu and coworkers showed that Hrd1 interacts directly with Neh4-5 domains of Nrf2, favoring its ubiquitination, thus leading to Nrf2 degradation (Gao et al., 2008; Wu et al., 2014).

The glycogen synthase kinase 3 β (GSK-3 β) is a serine/threonine protein kinase involved in apoptosis, cell proliferation, glycogen metabolism, stem cell renewal and development, and which activity is regulated through an inhibitory phosphorylation at Ser9 (Cuadrado, 2015, for review). Several evidences showed that GSK-3 β regulates Nrf2 activity. Indeed, activation of the PI3K/Akt pathway can indirectly regulate Nrf2 through the negative regulation of GSK-3 β (Chowdhry et al., 2013), while inactive GSK-3 β increased Nrf2 stability and Nrf2-related gene expression (Hayes et al., 2015). AMP-activated protein kinase (AMPK), involved in cell survival in response to stress stimuli, also inactivates GSK-3 β , favoring Nrf2 activation; AMPK can directly phosphorylate Nrf2 at Ser558 residue (Ser550 in mouse) inserted in the nuclear export signal, favoring Nrf2 nuclear accumulation (Joo et al., 2016). Once activated, GSK-3 β phosphorylates Fyn kinase, a Src family member, at threonine residues leading to its nuclear accumulation, which in turn favors Nrf2 nuclear export (Jain and Jaiswal, 2007). GSK-3 β can also phosphorylate Nrf2's Neh6 region at serine residues

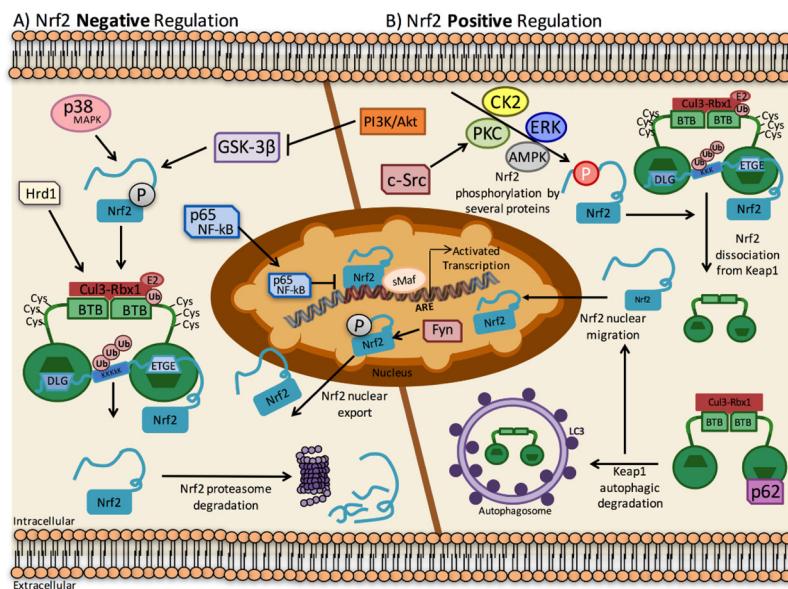


Fig. 3. Mechanisms of Nrf2 positive and negative regulation. (A) Nrf2 Negative Regulation; under basal conditions Nrf2 is ubiquitinated by Keap1–Cul3 complex and degraded by the proteasome. Additionally, p38 MAPK and GSK-3 β , which is downregulated by the PI3K/Akt pathway, can phosphorylate Nrf2 at Ser215, Ser408 and Ser577 and at Ser334–338 in the Neh6 domain, respectively, favoring its degradation. In the nucleus, the NF- κ B p65 subunit can compete with Nrf2 binding, downregulating its transcriptional activity. Nrf2 nuclear phosphorylation at Tyr-568, by Fyn kinase, is linked to its nuclear export. (B) Nrf2 Positive Regulation; after stress conditions, Keap1 reactive cysteine residues can bind covalently, allowing Nrf2 dissociation and p62 binding, which further leads to LC3 interaction associated to the autophagosome membrane, leading to Keap1 degradation and consequent Nrf2 accumulation. Additionally, PKC, CK2 and ERK can phosphorylate Nrf2 at different residues favoring its dissociation from Keap1 and consequent nuclear migration. Once in the nucleus, dimerization of transcriptional co-activator Mafs with Nrf2 facilitates stable Nrf2-ARE interaction and enhances gene transcription.

(334–338), creating a structural motif that is recognized by β -TrCP E3 ligase, leading to Nrf2 degradation (Rada et al., 2011; Rojo et al., 2008b).

Nrf2 can be also regulated through phosphorylation of serine or threonine residues by protein kinase C (PKC), which is involved in apoptosis, survival, growth and differentiation (Numazawa et al., 2003); PKC can be also activated by oxidative stress (Jung et al., 2004). Huang and colleagues demonstrated that PKC can phosphorylate Nrf2 in its Neh2 domain, at Ser40, inducing dissociation from Keap1 and consequent Nrf2 nuclear translocation (Huang et al., 2002). Interestingly, Nrf2 phosphorylation at Ser40 is necessary for its translocation, but not for its nuclear accumulation (Bloom and Jaiswal, 2003), suggesting that other mechanisms are necessary for Nrf2 stabilization and accumulation in the nucleus, besides Keap1 decoupling. Recently, we demonstrated the essential involvement of c-Src kinase in Nrf2 regulation, through PKC δ , after an oxidant stimulus. We showed that Nrf2 phosphorylation at Ser40, its nuclear accumulation and transcriptional activity involving heme oxygenase-1 (HO-1) expression were dependent on c-Src kinase activation, through PKC δ phosphorylation at Tyr311, in HT22 mouse hippocampal neural cells exposed to H_2O_2 (Fão et al., 2019).

Casein kinase II (CK2), a protein involved in replication, gene transcription and transduction processes, also controls Nrf2 activity through Nrf2 phosphorylation (Pi et al., 2007). Apopa and colleagues identified Nrf2's transcription activation domains, Neh4 and Neh5, as CK2 targets and demonstrated the role of Nrf2 phosphorylation by CK2 for Nrf2 nuclear accumulation (Apopa et al., 2008).

Moreover, mitogen-activated protein kinases (MAPK) are involved in gene expression (Turjanski et al., 2007), cell survival and apoptosis (Lu and Xu, 2006); p38 MAPK phosphorylates Nrf2 in three serine residues (Ser215, Ser408 and Ser577), which promotes decreasing Nrf2 nuclear accumulation (Keum et al., 2006; Sun et al., 2009). Additionally, protein kinase RNA-like endoplasmic reticulum kinase (PERK), a critical protein for cell survival, can phosphorylate Nrf2, triggering its dissociation from Keap1 and consequently favoring Nrf2 activity (Cullinan et al., 2003).

2.3. Nrf2 nuclear regulation

Nrf2 contains nuclear localization sequences (NLSs) in the basic region (Theodore et al., 2008), and nuclear export sequences (NESs) in the leucine zipper domain (Li et al., 2005). Thus, Nrf2's NLS motifs are recognized by adaptor proteins (such as importins) forming a protein

complex that possibly allows Nrf2 transition to the nucleus through the nuclear pore (Theodore et al., 2008). On the other hand, in the nucleus, Nrf2 can be phosphorylated at Tyr568 by Fyn kinase, a Src family member, allowing the interaction with Crm1, also known as exportin1, leading to its nuclear exportation (Jain and Jaiswal, 2007, 2006). Moreover, once in the nucleus, Nrf2 activity may be regulated by the nuclear factor- κ B (NF- κ B) complex containing the subunit RelA (p65) (Baldwin, 1996), an important transcription factor involved in bacterial and viral infection responses, inflammation and cell proliferation (Smale, 2011). Liu and colleagues reported that NF- κ B p65 subunit represses Nrf2 target genes expression, independently of its transcription activity (Liu et al., 2008) by competition of p65 with Nrf2 for the binding to CBP and by the recruitment of histone deacetylase 3 (HDAC3) by p65, resulting in local histone hypo-acetylation and consequent decreased Nrf2-ARE binding (Liu et al., 2008).

Overall, both Keap1-dependent and independent mechanisms are important ways to regulate the Nrf2-ARE pathway. Furthermore, ARE is situated in the promoter region of genes that codify for Nrf2 regulation proteins, such as Keap1 and Cul3 (Kaspar and Jaiswal, 2010), i.e. Nrf2 regulate the expression of proteins that coordinate its own degradation, acting as an auto-regulatory process of the Nrf2-ARE pathway.

3. The Nrf2-related pathways in neurodegenerative disorders

NDD share increased generation of ROS/RNS as common features of pathological progression. In this section, we briefly review the evidences for oxidative stress and Nrf2 pathway deregulation in AD and PD, the most common age-dependent neurodegenerative diseases. Moreover, we describe in detail the evidences for Nrf2-regulator pathways as potential therapeutic targets in these diseases.

3.1. Alzheimer's disease and oxidative stress

AD is an age-related progressive neurodegenerative disease and the most common cause of dementia worldwide, affecting 10% of the population over the age of 65, and 30–50% of the population over the age of 85 (Li et al., 2016). AD is characterized by a failure in neuronal and synaptic integrity, leading to memory impairment and generalized cognitive decline (Cummings, 2004). The major histological hallmarks in AD are the accumulation of extracellular amyloid plaques, i.e. amyloid beta peptide (A β) that deposits outside neurons, and intracellular neurofibrillary tangles (NFT), which consist in the accumulation of abnormal hyperphosphorylated tau protein in nerve cells,

largely affecting hippocampus and the cortex (Irvine et al., 2008; Selkoe and Hardy, 2016). A β peptide results from the processing of amyloid precursor protein (APP) by β -secretase (BACE) and γ -secretase (Weidemann et al., 2002) and has the ability to aggregate and form oligomers, participating in neuronal death (Klein et al., 2001) and ROS production (Andersen, 2004). The most common A β fragments have 40 and 42 amino-acids, with A β ₁₋₄₀ isoform being the most prevalent, followed by the hydrophobic A β ₁₋₄₂ that aggregates in a faster way and tends to form stable trimeric and/or tetrameric oligomers than A β ₁₋₄₀ (Barage and Sonawane, 2015). Inherited missense mutations directly in the A β region of APP increase the propensity of the peptide to aggregate (Haass and Selkoe, 2007). The A β ₁₋₄₂/A β ₁₋₄₀ ratio increases in mutations in the three different genes, APP, presenilin-1 (PS-1 for *PSEN1* gene) and presenilin-2 (PS-2 for *PSEN2* gene) (Haass and Selkoe, 2007). Different forms of A β have been extracted in AD brains: aggregates termed oligomers or protofibrils (depending on their complexity) and mature amyloid fibrils based on their appearance by electron or atomic force microscopy or based on the separation of soluble and insoluble fractions (Thal et al., 2015).

There are several evidences of increased oxidative stress in AD. Sultana and colleagues observed higher levels of oxidized proteins in AD human brains when compared to age-matched controls, the increase being higher in AD-affected areas (Sultana et al., 2006). Furthermore, DNA oxidation biomarkers, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), indicate that both nuclear and mitochondrial DNA are more oxidized in AD patients when compared with controls (Mecocci et al., 1994; Wang et al., 2005). AD human brains showed increased levels of 4-hydroxyalkenals (e.g. 4-HNE, 4-hydroxynonenal), the major product of polyunsaturated fatty acids (PUFA) oxidation, when compared with control subjects (Markesberry and Lovell, 1998), revealing extensive lipid peroxidation (Esterbauer et al., 1991; Lovell et al., 1997). AD brains also showed enhanced levels of neurotoxic trace elements such as iron (Ehmann et al., 1986; Thompson et al., 1988), aluminum (Xu et al., 1992), mercury (Ehmann et al., 1986, 1984) and copper (Deibel et al., 1996), which may induce the formation of free radicals. Furthermore, elevated levels of A β can contribute to oxidative stress in AD brain (Huang et al., 1999). Interestingly, there are evidences of oxidative stress already in early stages of the disease in peripheral tissues. Thus, oxidative changes found in mild AD patients are already present in Mild Cognitive impairment (MCI) group, as suggested by decreased vitamin E levels in the plasma of mild AD patients and increased oxidized glutathione (GSSG) levels in the plasma of both MCI and mild AD patients (Baldeiras et al., 2008). In addition, we previously observed ER stress-mediated Ca²⁺ dyshomeostasis and ER-associated ROS generation in peripheral blood mononuclear cells (PBMCs) from MCI patients concomitant with increased Nrf2 phosphorylation at Ser40, a residue reported to target Nrf2 nuclear translocation (Mota et al., 2015).

3.1.1. Nrf2-ARE pathway in Alzheimer's disease

In the last decades, several studies have reported different patterns of Nrf2 expression and related antioxidant proteins in AD models. In human studies, a significant decrease in nuclear Nrf2 levels and a confinement within cytoplasm in AD hippocampus was observed when compared to age-matched control individuals, suggesting a decrease in Nrf2 activity (Ramsey et al., 2007). Accordingly, the activity of anti-oxidant enzymes regulated by Nrf2, namely SOD1 and GSH-Px, were shown to be decreased in hippocampal AD tissues when compared with controls (Omar et al., 1999), although NQO1 activity was increased in AD hippocampal pyramidal neurons (Wang et al., 2000). Moreover, catalase and SOD1 activities appeared to be decreased in frontal and temporal cortex of AD brains (Marcus et al., 1998), whereas expression of HO-1 was enhanced in AD patients inferior parietal brain (Calabrese et al., 2006). As a reflection of what is happening in the central nervous system, changes in Nrf2 pathway have also been observed in peripheral tissues. Thus, although GSH was decreased in AD patient's plasma, AD lymphocytes showed enhanced expression of HO-1 and GCLM

(Calabrese et al., 2006) and increased SOD1 protein levels (Mota et al., 2015). Despite an apparent contradiction in some results obtained in human samples, it is important to highlight the fact that changes in Nrf2 pathways and/or downstream proteins may dependent in the stage of the disease and the brain area assessed.

Using AD animal models, several studies described altered Nrf2 activity. The 3xTg-AD mouse model, containing 3 genetic mutations, in presenilin-1 (*PSEN1*), amyloid precursor protein (APP), and microtubule-associated tau, that never co-exist in human AD familial forms or, in the case of tau, is not AD-related, develops an age-dependent and progressive neuropathological phenotype, including A β plaques and neurofibrillary tangles similarly to AD patients (Oddo et al., 2003). In the 3xTg-AD mouse brain cortex, we previously observed increased Nrf2 nuclear levels at 3 months of age; however this was accompanied by a decrease in SOD1 mRNA and protein levels (Mota et al., 2015), suggesting a failure in Nrf2 activation pathway. Moreover, in the same model, NQO1 levels were increased in the cortex and hippocampus at 2 months of age, followed by a decrease at older ages (Torres-Lista et al., 2014). Reduced GSH and vitamin E levels, as well as increased GSH-Px activity were also reported in the 3xTg-AD mice at 3 to 5 months of age (Resende et al., 2008). Importantly, as in human MCI PBMCs, 3 month-old PBMCs from 3xTg-AD showed increased p(Ser40)Nrf2, concordantly with Nrf2 nuclear translocation signal (Mota et al., 2015). Similar results were observed in the APP/PS1 AD mouse model, which contain human transgenes for both APP and *PSEN1* mutations. These transgenic mice evidenced reduced levels of GCLM and NQO1 mRNA at 6 months of age (Kanninen et al., 2008), as well as decreased GCLC mRNA and protein levels (Joshi et al., 2015), suggesting dysregulated Nrf2-ARE pathway in neurons of this mouse model, resulting in decreased related enzyme expression, when A β plaques become visible (Kanninen et al., 2008).

Recent studies show the importance of Nrf2-ARE activation in AD context. The use of Nrf2 inducer, sulforaphane in the AD mouse model PS1_{V97L}-Tg, with mutation in *PSEN1* gene, promoted increased cerebral Nrf2 expression and Nrf2/ARE pathway activation, ameliorated oxidative stress, amyloid pathology and improved cognitive function (Tian et al., 2018). Importantly, by crossing Nrf2^{-/-} and APP/PS1 mice, Joshi and colleagues observed increased intracellular A β , APP fragments and full-length APP in CA1 neurons from APP/PS1/Nrf2^{-/-} mice, when compared with APP/PS1 mice (Joshi et al., 2015). Branca and co-workers further described that the APP/PS1/Nrf2^{-/-} mice has exacerbated cognitive deficits and increased neuroinflammation (Branca et al., 2017). More recently, an AD model that combines amyloidopathy and tauopathy with NRF2-deficiency (AT-NRF2-KO) died prematurely and showed intensified astrogliosis and microgliosis, when compared to wild type mice (AT-NRF2-WT) (Rojo et al., 2018).

Altogether, existing results suggest that Nrf2-ARE pathway activation may occur very soon (at MCI stage) during disease progression, related with augmented ROS production and A β oligomerization. Thus, Nrf2 activation may be protective in neuronal and cognitive dysfunction, making this transcription factor a potential target for AD treatment.

3.1.2. Targeting the Nrf2 pathway as a potential therapeutic target in Alzheimer's disease

Considering the role of Nrf2 in moderate oxidative injuries and its altered regulation during AD progression, Nrf2 pathway has been suggested as a relevant therapeutic target for AD treatment. Indeed, some studies have evidenced Nrf2 targeting as being effective in AD treatment, as described next. Lentiviral vector delivering of human Nrf2 into 9 month-old APP/PS1 mouse hippocampus improved spatial learning deficits (Kanninen et al., 2009). Moreover, some studies have shown that Nrf2 activator compounds, such as curcumin (Caesar et al., 2012; Kitani et al., 2007), resveratrol (Du et al., 2014; Porquet et al., 2013), sulforaphane (Lee et al., 2013), a sulforaphane derivate, the ITH12674 compound (Egea et al., 2015), β -hydroxybutyrate (Xie et al., 2015),

orientin (Yu et al., 2015), antroquinonol (Chang et al., 2015), methysticin (Fragoulis et al., 2017) and methylene blue (methylthionium chloride) (Stack et al., 2014) have positive effects in AD models, by reducing cognitive deficits, inflammation and oxidative stress or protect against A β -mediated toxicity. As referred above, several pathways involved in Nrf2 regulation have been described to be altered in AD. In this section, we evidence the potential of targeting Nrf2-regulatory proteins in AD treatment.

The polyubiquitination binding protein, p62, can favor Nrf2 activity through Keap1 target for degradation by autophagy (Komatsu et al., 2010). The relationship between Keap1, p62 and Nrf2 in AD has been evidenced in different studies and suggest that lower levels of p62 protein in AD may be associated with decreased Keap1 degradation and consequent lower Nrf2 activity. Thus, A β injection into rat hippocampus induced increased autophagy proteins, such as LC3-II and beclin1, and further Keap1, while p62 and Nrf2 levels were decreased in the hippocampus and cortex (Zheng et al., 2012). Moreover, in the frontal cortex of AD patients, p62 levels were also decreased (Du et al., 2009a). In contrast, mRNA and protein levels of p62 as well as Nrf2 target genes were shown to be increased in the cortex of AD brains (Tanji et al., 2013). Contradictory results may be explained by the different AD stages at which the analysis was done.

PKC can phosphorylate Nrf2, favoring its dissociation from Keap1 and consequent nuclear migration. In AD context, some studies already evidenced a positive effect of PKC activation on amyloid pathology (Etcheberrigaray et al., 2004; Garrido et al., 2002; Han et al., 2004) and tau pathology (Isagawa et al., 2000), although with no direct relation with the Nrf2 pathway. AD brains presented reduced PKC protein levels and activity, as well as attenuated translocation of the enzyme to the cell membrane (Wang et al., 1994). Similarly, in *in vitro* studies, A β induced direct PKC inhibition (Lee et al., 2004), whereas PKC activation prevented hippocampal neuronal death induced by A β (Tyszkiewicz and Yan, 2005). Hypothetically, decreased PKC activity may be related with decreased Nrf2 phosphorylation and nuclear migration (Fig. 4). Thus, and considering that PKC is involved in memory processes, activation of PKC should be a potential therapeutic strategy for treating AD pathogenesis. In fact, Murphy and colleagues, developed a BBB-bypassing Nrf2-activating polysaccharide, Mini-GAGR, a cleavage

product of low-acyl gellan gum. Mini-GAGR induced increased levels and activity of Nrf2-dependent antioxidant enzymes, such as HO-1, SOD1 and GSH-Px, reduced ROS formation and protected mitochondria from oxidative insults, in cultured mouse cortical neurons, when compared to vehicle treated neurons (Murphy et al., 2018). The effect of Mini-GAGR was dependent on PKC activation, consequently Nrf2 dissociation from Keap1 and nuclear migration. When tested in the 3xTg-AD mice model, the Mini-GAGR BBB-bypassing polysaccharide increased nuclear Nrf2 levels, augmented HO-1 and SOD1 expression and reduced p-tau and A β peptide-stained neurons, in hippocampus, which resulted in improved mouse memory (Murphy et al., 2018). Recently, Talman and colleagues reviewed a list of several PKC activators as potential drug candidates for AD, describing the compounds already tested in different AD models and how they modulate PKC activity (Talman et al., 2016). Importantly, PKC activators compounds, as benzolactams and bryostatin-1, were tested in AD transgenic mouse models (APP, APP/PS1 and Tg2576). Benzolactam significantly increased sAPP α and reduced A β ₁₋₄₀ in the brains of APP transgenic mice, whereas similar results were found in APP/PS1 after bryostatin-1 treatment, with improved behavioral outcomes (Etcheberrigaray et al., 2004). Tg2576 mice, which overexpress a human mutant form of APP, treated with bryostatin-1 showed cognitive improvement, decreased A β accumulation in the brain and reduced hippocampal synapse loss (Hongpaisan et al., 2011). Although none of these studies analysed Nrf2 levels after treatment, results obtained are promising and deserved to be more thoroughly investigated.

GSK-3 β protein kinase is involved in Nrf2 regulation through phosphorylation of Nrf2 Ser334-338 residues, leading to its degradation in a Keap1-independent manner (Rada et al., 2011; Rojo et al., 2008b). In human AD brains, GSK-3 β activation is increased (Leroy et al., 2007; PEI et al., 1997) and participates in tau hyperphosphorylation (Pei et al., 1999). Mature cortical neurons, derived from induced pluripotent stem cell (iPSC) lines of patients with familial and sporadic AD, also presented increased levels of active GSK-3 β (Ochalek et al., 2017). Moreover, genetic overexpression of GSK-3 β in mouse hippocampal and cortical neurons led to neuronal loss and memory deficits (Engel et al., 2006; Hernández et al., 2002), and in the AD transgenic mice model Tg2576, GSK-3 β inhibition delayed A β accumulation and decreased

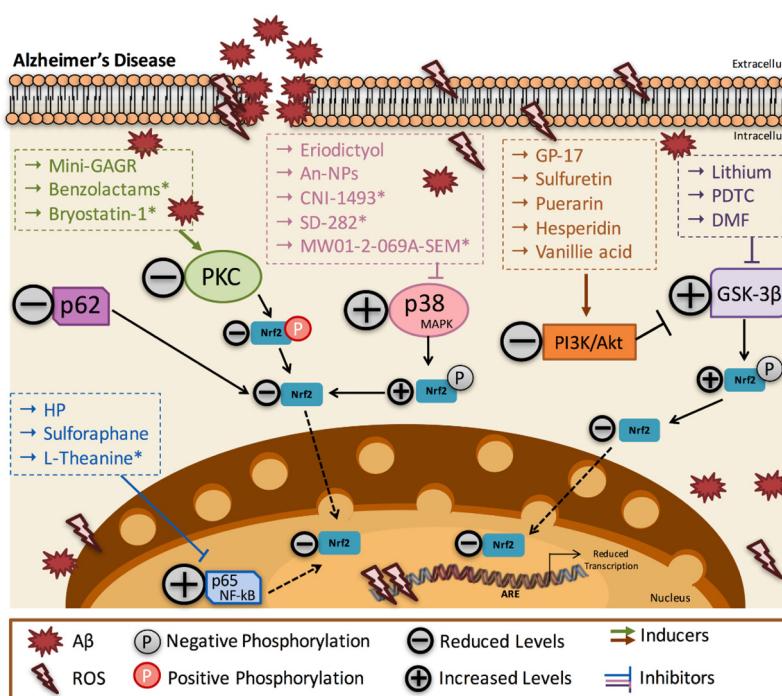


Fig. 4. Altered mechanisms of Nrf2 regulation in AD and some drugs shown to be protective in AD. Nrf2 activity and related proteins are decreased in AD. PKC and PI3K/Akt were shown to be diminished in AD, whereas inducer agents referred in the dashed boxes, in green and orange, respectively, were shown to have positive effects in different AD models, most of them through augmented Nrf2 activity. Conversely, p38 MAPK, GSK-3 β and NF- κ B p65 are increased in several AD models. Thus, their inhibition through the agents presented, significantly improved AD features in different AD models.

* Induced positive effects in AD models, through the indicated pathways, without Nrf2 direct evaluation.

plaque burden in cortical neurons (Phiel et al., 2003). In this way, considering that increased GSK-3 β activity is directly involved with Nrf2 phosphorylation and consequent degradation, and further related with Nrf2 nuclear export, through Fyn phosphorylation at Tyr568, GSK-3 β inhibition may be a possible therapeutic strategy for AD treatment (Fig. 4). Lithium, a GSK-3 β inhibitor, was shown to promote Nrf2 transcription activity in N2A neuroblasts (Rojo et al., 2008a) and also decreased A β accumulation in mice brain overexpressing APP (Phiel et al., 2003). Moreover, pyrrolidine dithiocarbamate or PDTc, a small molecule with antioxidant properties that inhibits GSK-3 β , was also shown to induce Nrf2-ARE activation and further prevented cognitive impairment in APP/PS1 mice (Malm et al., 2007). The Nrf2 inducer dimethyl fumarate (DMF) alleviated tauopathy in mice. DMF inhibited GSK-3 β activity in the hippocampus of a mouse model of tauopathy, modulating tau phosphorylation, neuronal impairment, brain-derived neurotrophic factor (BDNF) expression and inflammatory processes involved in astrogliosis, microgliosis and pro-inflammatory cytokines production (Cuadrado et al., 2018). Additionally, PI3K/Akt pathway, which downregulates GSK-3 β and favors Nrf2 activity (Kang et al., 2002), was reduced in AD patient brains (Mercado-Gómez et al., 2008). Importantly, increased PI3K/Akt pathway activation by *Gypenoside XVII* (GP-17), a novel phytoestrogen, inhibited GSK-3 β activity and enhanced Nrf2 translocation into the nucleus with consequent up-regulation of target genes in A β ₂₅₋₃₅-treated PC12 cells (Meng et al., 2014), although this form of amyloidogenic and neurotoxic A β fragment is not naturally formed in AD. Similar results were obtained with sulfuretin, an antioxidant flavonoid with several pharmacological effects (Pariyar et al., 2017), in A β ₂₅₋₃₅-treated hippocampal neurons (Kwon et al., 2015). Moreover, the antioxidant puerarin, described to have anti-hypertension, antiarrhythmic, antioxidant, antiapoptotic, and neuro-protective properties (Cheung et al., 2016), caused increased PI3K/Akt pathway activation, reduced GSK-3 β activity, increased Nrf2 activation and HO-1 gene expression in APP/PS1 mice hippocampus, with further cognitive improvement (Zhou et al., 2014). Hesperidin, a flavonoid abundant in citrus (Hong and An, 2015), the natural dietary supplementation of anthocyanins, extracted from Korean black bean (Ali et al., 2018) in the same AD mouse model (APP/PS1) (Hong and An, 2015), and vanillic acid, an antioxidant key aromatic volatile compound of vanilla beans, showed similar results after intracerebroventricular injection of A β ₁₋₄₂ into the mouse brain (Amin et al., 2017b). Altogether, results suggest GSK-3 β and/or PI3K/Akt pathways modulation as useful AD therapeutic strategies through the indirect manipulation of Nrf2 pathway.

On the other hand, the MAP kinase member, p38 MAPK, phosphorylates Nrf2, favoring its interaction with Keap1 and consequent inhibition of Nrf2 nuclear translocation (Keum et al., 2006). Importantly, p38 MAPK may be activated A β through oxidative stress, as shown in rat cortical neurons (Giraldo et al., 2014); and p38 MAPK signaling pathway was shown to be up-regulated in AD brain during early stages of neurofibrillary degeneration (Hensley et al., 1999; Sheng et al., 2001; Sun et al., 2003) and in several AD animal models (Gulbert et al., 2006; Giovannini et al., 2002; Savage et al., 2002). Thus, development of p38 inhibitors has been considered as potential therapeutics for AD (Fig. 4). Eriodictyol, a flavonoid isolated from the Chinese herb *Dracocephalum rupestre*, decreased the p38 MAPK apoptotic signaling pathway and enhanced Nrf2 protein levels with subsequent activation of ARE pathway genes, in cortical primary neurons exposed to A β ₂₅₋₃₅ (Jing et al., 2015). Additionally, Amin and colleagues used anthocyanins loaded nanoparticles (An-NPs) (a subfamily of flavonoids with antioxidant, anti-inflammatory and neuroprotective properties) in SH-SY5Y cells after A β ₁₋₄₂ exposure and reported neurotoxicity and oxidative stress reduction through decreased p38 expression and increased Nrf2 and HO-1 protein levels (Amin et al., 2017a). These data highlight the beneficial effect of p38 inhibition, and consequent Nrf2 activation, as potential AD therapeutic target. In the same line, CNI-1493 (or semapimod), a tetravalent guanylhydrazone

inhibitor of p38 MAPK, enhanced cognitive function and reduced plaque load in TgCRND8 mice, an APP mouse model (Bacher et al., 2008); and prevented A β -induced interleukin 6 and tumor necrosis factor (TNF- α) release in primary microglia cells, reducing neuroinflammation and consequent neurodegeneration (Bach et al., 2011). Other p38 MAPK inhibitors, such as SD-282 (indole-5-carboxamide) and MW01-2-069A-SRM, suppressed the increased neuronal vulnerability in APP751 transgenic mice (Koistinaho et al., 2002) and reduced proinflammatory cytokine production after A β ₁₋₄₂ injection in mouse brain (Munoz et al., 2007), respectively. Although these studies did not assess the Nrf2 pathway, it is wise to think that positive effects may be linked to further Nrf2 regulation.

In the nucleus, altered NF- κ B levels and NF- κ B-dependent repression of Nrf2 target genes expression, in AD models, suggest the relevance of this protein as an important target for AD treatment (Fig. 4). Importantly, human AD brain showed increased staining for NF- κ B-p65 in hippocampal and cortical neurons (Terai et al., 1996). A β ₁₋₄₂ exposure induced the activation of NF- κ B subunit p65 in primary neuronal cultures (Srinivasan and Lahiri, 2015) and in NG108-15 neural cells (Lin et al., 2013). A β ₁₋₄₀ also induced increased NF- κ B binding activity in primary neurons of cerebellar granule cells and in NT2N cells (Valerio et al., 2006). Thus, NF- κ B inhibitors were studied as AD therapeutic strategies. L-theanine is an amino acid present in green tea that was shown to suppress NF- κ B activity. Thus, A β ₁₋₄₂-infused mouse model treated with this compound attenuated A β ₁₋₄₂-induced memory impairment and decreased A β ₁₋₄₂ levels in the cortex and hippocampus (Kim et al., 2009). Nevertheless, in this study, Nrf2 activity or genes target levels were not measured. Sulforaphane, a well-known Nrf2 activator, upregulated Nrf2 expression and increased Nrf2 nuclear translocation through reduced DNA methylation levels of the Nrf2 promoter in the N2a cells stably expressing human Swedish mutant amyloid precursor protein (N2a/APPswe cells) (Zhao et al., 2018). Sulforaphane decreased the levels of A β ₁₋₄₂ and ROS formation, and reduced pro-inflammatory cytokines expression and p65 activation, resulting in augmented NQO1 and HO-1 protein expression levels (Zhao et al., 2018). Additionally, Hong and colleagues studied the effect of hesperidin (HP), an antioxidant present in citrus, in APP/PS1 mice (Hong and An, 2015). Interestingly, HP reduced activity of NF- κ B and enhanced the expression of Nrf2 related proteins, such as HO-1, catalase, and GSH-Px, whereas cognitive impairment was attenuated (Hong and An, 2015), suggesting that NF- κ B signaling inhibition confers neuroprotection in AD.

Regarding the proteins and pathways referred above, which positively regulate Nrf2 activity, the PI3K/Akt/GSK-3 β pathway appears to be the most studied (Table 1). Since all GSK-3 β -inhibitors and PI3K/Akt-activators compounds were very encouraging in alleviating AD features, enhancing Nrf2 activity through this pathway regulation should be seriously considered. Although studies using PKC activators revealed to be promising, there is a lack of knowledge regarding the real impact of these treatments in Nrf2 pathway. On the other hand, inhibition of p38 MAPK and NF- κ B pathways, which result in augmented Nrf2 activation, also appear as promising targets for AD treatment.

3.2. Parkinson's disease and oxidative stress

PD is the most prevalent neurodegenerative disease affecting movement. PD prevalence is 160 per 100.000 in Western world (Alves et al., 2008; Dawson and Dawson, 2003) and is characterized by motor symptoms such as rest tremor, rigidity, bradykinesia, loss of postural reflexes, and non-motor problems including autonomic failure, sleep abnormalities, cognitive/neurobehavioral disorders and dementia (Jankovic, 2008). An important hallmark of PD is the loss of dopaminergic neurons in *substantia nigra pars compacta* (SNpc), which results in decreased dopamine (DA) nerve terminals projecting to the striatum (Blesa et al., 2017; Lang and Lozano, 1998). The main feature of PD is

Table 1

Nrf2-related pathways inhibitors or activators shown to be beneficial in Alzheimer's disease.

Alzheimer's Disease				
Nrf2-related pathways	Compounds	Chemical structure 2D	Models	References
PKC	Mini-GAGR	—	Mouse cortical neurons / 3xTg-AD mice	Murphy et al., 2018
	Benzolactam		APP transgenic mice	Etcheberrigaray et al., 2004
	Bryostatin-1		APP/PS1 transgenic mice/ Tg2576 mice	Etcheberrigaray et al., 2004; Hongpaisan et al., 2011
PI3K/Akt	Gypenoside XVII (GP-17)		$\text{A}\beta_{25-35}$ -treated PC12 cells	Meng et al., 2014
	Sulfuretin		$\text{A}\beta_{25-35}$ -treated hippocampal neurons	Kwon et al., 2015
	Puerarin		APP/PS1 mice	Zhou et al., 2014
	Hesperidin		APP/PS1 mice	Hong and An, 2015
	Vanillic acid		$\text{A}\beta_{1-42}$ injection in mouse brain	Amin et al., 2017b
p38 MAPK	Eriodictyol		$\text{A}\beta_{25-35}$ -treated cortical neurons	Jing et al., 2015
	An-NPs Semapimod or CNI-1493		$\text{A}\beta_{1-42}$ -treated SH-SY5Y cells TgCRND8 mice	Amin et al., 2017a Bacher et al., 2008
	Indole-5-carboxamide (SD-282)		APP751 mice	Koistinaho et al., 2002
GSK-3??	MW01-2-069A-SRM Lithium	—	$\text{A}\beta_{1-42}$ injection in mouse brain N2A neuroblasts / APP transgenic mice	Munoz et al., 2007 Phiel et al., 2003; Rojo et al., 2008a, 2008b
	Pyrrolidine dithiocarbamate (PDTC)		APP/PS1 mice	Malm et al., 2007
	Dimethyl fumarate (DMF)		mouse model of tauopathy	Cuadrado et al., 2018
p65 NF-κB	Hesperidin (HP)		APP/PS1 mice	Hong and An, 2015
	Sulforaphane		N2a/APPswe cells	Zhao et al., 2018
	L-Theanine		$\text{A}\beta_{1-42}$ injection in mouse brain	Kim et al., 2009

the presence of intracellular inclusion bodies, formed by α -synuclein (α -Syn), also known as Lewy bodies, in different regions of the brain such as SNpc, olfactory bulb and neocortex (Lee Mosley et al., 2006). The majority of PD cases are sporadic with unknown etiology (Samii et al., 2004), however 15% of PD patients have family history. HUGO Gene Nomenclature Committee identified and related the familial PD form with at least 23 loci and 19 disease-causing genes, which include 10 autosomal dominant genes and 9 autosomal recessive genes, as recently described in detail by Deng and colleagues (Deng et al., 2018). The etiology of PD is not completely elucidated, however oxidative stress, mitochondrial dysfunction, and neuroinflammation are considered the major mechanisms involved in cell death in PD (Jenner and Olarow, 2006; Yacoubian and Standaert, 2009).

Several studies in PD tissues have shown an oxidant status (Zuo and Motherwell, 2013), which is largely linked to both mitochondrial complex I dysfunction and dopamine auto-oxidation. Indeed, the *substantia nigra* of postmortem PD brains shows reduced GSH concentrations, indicating a failure in antioxidant activity (Sofic et al., 1992) and further increased levels of iron, a neurotoxic trace element (Dexter et al., 1989b), which invokes toxic effects and ROS production in this brain area (Kaur et al., 2003). Concordantly, analysis of postmortem PD brains also showed lipid peroxidation (Dexter et al., 1989a) and increased damage due to protein oxidation (Alam et al., 2002; Yoritaka et al., 1996). In addition, significant increments in oxidized coenzyme Q10 and the nuclear DNA oxidation biomarker 8-OHdG were observed in cerebrospinal fluid samples of PD patients (Isobe et al., 2010), illustrating the existence of DNA oxidative damage and mitochondria in those patients (Isobe et al., 2010). Furthermore, evidences of mitochondrial dysfunction were also observed in PD brains, namely reduced mitochondrial complex I catalytic activity (Keeney et al., 2006), down-regulated mitochondrial biogenesis in the frontal cortex (Thomas et al., 2012) and reduced mitochondrial DNA levels in the prefrontal cortex (Gatt et al., 2016), leading to ROS production and oxidative stress. Additionally, we previously evidenced increased ROS production and impaired mitochondrial complex I activity in human neuroblastoma SH-SY5Y cells overexpressing wild-type α -Syn (Perfeito et al., 2016). Increased levels of 8-OHdG were further found in urine, serum, and *substantia nigra* of rats lesioned with 6-hydroxydopamine (6-OHDA) in the medial forebrain bundle, when compared with sham controls (Yasuhara et al., 2007), which was consistent with human findings.

3.2.1. Nrf2-ARE pathway in Parkinson's disease

Several studies linked the Nrf2 pathway with different PD models. Surprisingly, data in human samples report increased Nrf2 nuclear translocation. Ramsey and colleagues evidenced increased Nrf2 levels in the nucleus of human PD nigral neurons (Ramsey et al., 2007), reflecting higher nuclear translocation than in age-matched control individuals. Furthermore, in the *substantia nigra* of human PD brains, GSH levels were decreased (Perry and Yong, 1986), while HO-1 levels were increased (Schipper et al., 1998). Moreover, astrocytes, endothelial cells and dopaminergic neurons from PD postmortem brains showed increased NQO1 levels (Van Muiswinkel et al., 2004). Thus, these postmortem studies suggest a higher Nrf2 nuclear translocation in PD brains, concomitantly with an increase in some Nrf2-regulated genes. To understand the role of Nrf2 in PD, α -Syn was stereotaxic delivery, using adeno-associated viral (AAV) vectors, in the ventral midbrain of Nrf2^{-/-} mice (Lastres-Becker et al., 2012). Nrf2^{-/-}/ α -Syn mice showed augmented nigral dopaminergic neuronal loss, dystrophic dendrites, protein aggregates and increased neuroinflammation (Lastres-Becker et al., 2012). Similar results were obtained in Nrf2^{-/-} mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Chen et al., 2009; Innamorato et al., 2010) or 6-OHDA (Jakel et al., 2005), which increases ROS formation and are commonly used to mimic PD in rodents. Moreover, transplantation of astrocytes overexpressing Nrf2 into striatum of wild-type mice decreased the susceptibility to 6-OHDA (Jakel et al., 2007) and MPTP (Chen et al., 2009).

similar results were obtained in primary cortical neurons from Nrf2^{+/+} mice, after 6-OHDA exposure (Jakel et al., 2007). Interestingly, crossing mice selectively overexpressing Nrf2 in astrocytes with mice selectively expressing human mutant SYN (hSYN^{A53T}) in neurons, showed slowed motor pathology, decreased α -Syn aggregation, reduced oxidative stress and reduced gliosis in the spinal cord (Gan et al., 2012).

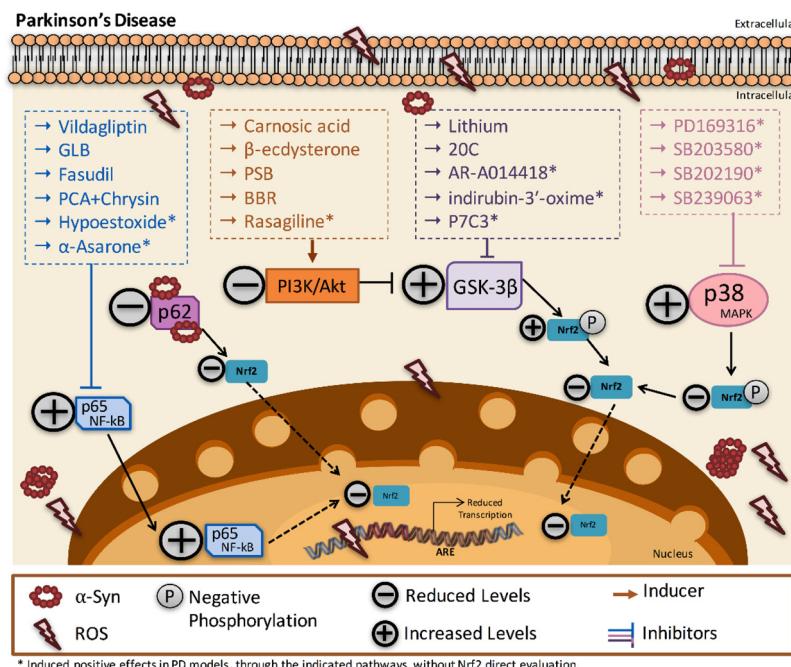
Mutations in the PTEN-induced putative kinase 1 (*PINK1*) gene are known to cause familial PD (Valente et al., 2004). *PINK1* is an important protein for mitochondrial quality control, contributing to mitophagy through *PINK1* accumulation on the outer membrane of depolarized mitochondria (Matsuda et al., 2010). Interestingly, Nrf2 is an important transcriptional up-regulator of the *PINK1* gene in response to different stimulus, being protective for mitochondria and enhancing cell survival (Murata et al., 2015). Tecfidera, an oral formulation of DMF and a putative Nrf2 activator, was shown to be neuroprotective in MPTP-induced experimental PD model, with antioxidant and anti-inflammatory properties and upregulating mitochondrial biogenesis, in an Nrf2-dependent manner (Ahuja et al., 2016). On the other hand, moderate physical exercise was shown to be protective in mice treated with 6-OHDA through Nrf2 neuroprotective activity, favoring mitochondrial biogenesis activation and preventing the development of parkinsonism (Aguilar et al., 2016). Thus, altered mitochondrial mitophagy, function and biogenesis are important pathological features in PD, and Nrf2 is an important transcription factor that regulates mitochondrial quality control and homeostasis (Dinkova-Kostova and Abramov, 2015). Therefore, there are several evidences of the involvement of Nrf2 activity in PD etiopathology, suggesting the interest of targeting the Nrf2-ARE pathway as an efficient PD therapeutics.

3.2.2. Targeting Nrf2-regulator pathways as potential therapeutic targets in Parkinson's disease

As in AD, several Nrf2 regulatory pathways are altered in PD. Thus, next we describe promising results obtained by the regulation of Nrf2-regulator proteins.

The p62 protein was shown to participate in proteasomal and/or autophagic degradation of misfolded or aggregated proteins and to indirectly regulate the Nrf2 pathway. Several studies highlighted the importance of p62 in PD pathogenesis. Importantly, p62 appears physically associated to abnormal α -Syn inclusions in the *substantia nigra* of PD brains at early stages (Kuusisto et al., 2003). Concordantly, the p62 gene promoter showed oxidative damage in PD brain frontal cortex, which may result in decreased p62 expression (Du et al., 2009b). Huang and co-workers reported that β -asarone and L-dopa co-administration, two compounds shown to be protective in PD, act synergistically and are protective after 6-OHDA damage in parkinsonian rat mesencephalon, due to enhanced p62 expression (Huang et al., 2015). Moreover, p62 KO in transgenic mice overexpressing α -Syn evidenced increased α -Syn accumulation when compared with mice overexpressing α -Syn alone (Tanji et al., 2015). On the other hand, parkin, which interacts with p62 in normal conditions, is able to stabilize p62 possibly through its E3 ligase activity (Song et al., 2016). However, in PD cases associated with mutations in *parkin* gene (Lesage and Brice, 2009), changes in parkin function lead to p62 proteasomal degradation (Song et al., 2016), which may be involved in the selective vulnerability verified in PD-affected neurons. Thus, augmented p62 expression or activity, which theoretically might result in enhanced Nrf2 target genes expression, may be a potential target for PD treatment (Fig. 5). Nevertheless, up to now, there are no studies regarding the use of p62 modulators and their effect on Nrf2 signaling in PD.

GSK-3 β kinase can negatively modulate Nrf2, resulting in decreased Nrf2 activity through enhanced degradation (Fig. 5). Moreover, there are evidences of altered GSK-3 β activation in PD. In fact, both in the midbrain and upper pons (Nagao and Hayashi, 2009), as well as in striata and inferior frontal gyri (Wills et al., 2010) from PD human brains, cytosolic GSK-3 β levels were increased and co-localized with α -Syn in Lewy bodies. Concordantly, transgenic mice overexpressing α -



* Induced positive effects in PD models, through the indicated pathways, without Nrf2 direct evaluation.

Syn presented enhanced GSK-3 β activation, which suggest a role of α-Syn accumulation in GSK-3 β upregulation (Duka et al., 2009). Furthermore, in the 6-OHDA rat model, a single striatal injection of 6-OHDA led to increased GSK-3 β activation in the *substantia nigra* (Hernandez-Baltazar et al., 2013). GSK-3 β inhibitors, such as indirubin-3'-oxime or AR-A014418 (N-(4-methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-YL)urea) in dopaminergic neurons (Wang et al., 2007) and P7C3 in MES23.5 cells (Gu et al., 2017) protected against MPTP-induced cell death. Paraquat is a foliar-applied and non-selective bipyridinium herbicides that has been used to produce experimental models of PD, through ROS production via mitochondria (Castello et al., 2007). Importantly, in SH-SY5Y cells exposed to paraquat, the GSK-3 β inhibitor, lithium, reduced cell death and apoptosis, leading to increased Nrf2 levels and enhanced mRNA of related genes, such as *HO-1*, *GSH*, *NQO1* (Alural et al., 2015). Furthermore, 20C (2-[4-hydroxy-3-(4-hydroxyphenyl)benzyl]-4-(4-hydroxyphenyl) phenol), a bibenzyl compound with antioxidant properties, protected PC12 and SH-SY5Y cells against rotenone (mitochondrial complex I inhibitor)-induced oxidative stress, through the enhancement of Nrf2 activity, through GSK-3 β inhibition, and increased PI3K/Akt activation (Zhang et al., 2017b). In fact, the PI3K/Akt pathway, which down-regulates GSK-3 β , is decreased in dopaminergic neurons of PD human brains (Malagelada et al., 2008) and can be considered as a potential target for PD therapeutics (Fig. 5). Thus, administration of rasagiline in MPTP-treated mice, normally used as monotherapy to treat early PD symptoms, prevents the death of dopaminergic neurons in *substantia nigra* through PI3K/Akt activation (Weinreb et al., 2006). Moreover, in SH-SY5Y cells exposed to paraquat, treatment with carnosic acid, a phenolic diterpene isolated from *Rosmarinus officinalis* with antioxidant proprieties, increased PI3K/Akt activation, resulting in improved Nrf2 activity (de Oliveira et al., 2016). Similarly, the use of β-ecdysterone, a phytoestrogen (Zou et al., 2015), and pinostrobin (PSB), a dietary bioflavonoid (Li et al., 2018), respectively in PC12 cells and SH-SY5Y cells, decreased the oxidative stress induced by the toxic metabolite of MPTP, MPP $^{+}$, and reduced apoptosis, through PI3K/Akt activation, GSK-3 β inhibition and consequent enhanced Nrf2 target genes expression. Furthermore, berberine (BBR), an isoquinoline alkaloid with PI3K-activating activity, diminished the 6-OHDA-induced dopaminergic neuron loss and behavior movement alterations in zebrafish, through augmented PI3K/Akt activation and consequent increased Nrf2 activity (Zhang et al., 2017a). Altogether,

Fig. 5. Altered mechanisms of Nrf2 regulation in PD and some drugs shown to be protective in PD. Nrf2 activity and related genes expression are decreased in PD. PI3K/Akt was shown to be diminished in PD models, and the inducer agents referred were tested in different PD models, producing positive effects, most of them through augmented Nrf2 activity. Conversely, p38 MAPK, GSK-3 β and NF-κB p65 are increased in several PD models. The use of respectively inhibitors were tested in different PD models, which were shown to be protective, some of them via augmented Nrf2 function.

data suggest that both GSK-3 β and PI3K/Akt pathways are considerable targets for PD treatment and act, at least in part, through the re-establishment of functional Nrf2 pathway.

Due to its role in cell death and neuroinflammation, besides its role on Nrf2 negative modulation (Wilms et al., 2003; Yasuda et al., 2011), p38 MAPK is considered as a relevant target for PD therapeutic development (Fig. 5). In fact, p38 MAPK activation is induced in dopaminergic neurons from PD mouse model treated with MPTP (Karunakaran and Ravindranath, 2009) or human dopaminergic SH-SY5Y cells treated with rotenone (Newhouse et al., 2004). Concordantly, neurons from PD patient's brains *substantia nigra pars compacta* showed increased phosphorylated p38 MAPK levels, suggesting the involvement of this kinase in dopaminergic neuronal loss (Karunakaran et al., 2008). Interestingly, α-Syn can be released from damaged Lewy bodies containing neurons and interact with microglia, leading to p38 MAPK activation (Klegeris et al., 2008). Furthermore, mutant parkin might also participate in p38 MAPK activation, suggesting that p38 MAPK dysregulation may be a common feature in both familial and sporadic forms of PD (Hasegawa et al., 2008). Zawada and co-workers (2001) demonstrated that the p38 MAPK inhibitors, PD169316 (4-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole), SB203580 (4-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-5-(4-pyridyl)-1H-imidazole) and SB202190 (4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1H-imidazole), enhanced rat dopaminergic neuronal survival, after rat ventral mesencephalic dopamine neurons transplantation into hemiparkinsonian rats, administered with 6-OHDA in the medial forebrain bundle (Zawada et al., 2001). SB239063, another p38 MAPK inhibitor, was also shown to be protective in MPTP-mediated cell death in primary dopaminergic neurons derived from human progenitor cells (Karunakaran et al., 2008). In this way, p38 inhibitors may potentiate neuronal surviving in PD, delaying disease progression; however, no data reported the effects of p38 inhibitors in Nrf2 activation.

PD patients brains studies, evidenced accumulation and increased translocation of NF-κB, a negative regulator of Nrf2 (Liu et al., 2008), into the nucleus (Mogi et al., 2007; Soós et al., 2004; Hunot et al., 1997). Additionally, different studies reported NF-κB-dependent apoptosis in PD cybrid model (Onyango et al., 2005) and NF-κB-induced neuroinflammation in *substantia nigra* of MPTP-treated mice (Mitra et al., 2016). Importantly, NF-κB inhibition, decreased nigral microglial activation and improved motor function in MPTP-treated mice (Ghosh

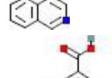
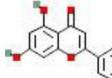
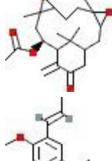
Table 2

Nrf2-related pathways inhibitors or activators shown to be beneficial in Parkinson's disease.

Parkinson's Disease				
Nrf2-related Pathways	Compounds	Chemical structure 2D	Models	References
PI3K/Akt	Carnosic acid		Paraquat-treated SH-SY5Y cells	de Oliveira et al., 2016
	β -Ecdysterone		MPTP-treated PC12 cells	Zou et al., 2015
	Pino strobin (PSB)		MPTP-treated SH-SY5Y cells	Li et al., 2018
	Berberine (BBR)		6-OHDA-treated Zebrafish	Zhang et al., 2017a
	Rasagiline		MPTP-treated mice	Weinreb et al., 2006
p38 MAPK	4-(4-Fluorophenyl)-2-(4-nitrophenyl)-5-(4-pyridyl)-1H-imidazole (PD169316) and 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole (SB203580) and 4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-1H-imidazole (SB202190)		6-OHDA-treated hemiparkinsonian rat	Zawada et al., 2001
	SB239063		MPTP-treated dopaminergic neurons	Karunakaran et al., 2008
GSK-3??	Lithium 2-[4-hydroxy-3-(4-hydroxyphenyl)benzyl]-4-(4-hydroxyphenyl)phenol (20C)		Paraquat-treated SH-SY5Y cells Rotenone-treated PC12 and SH-SY5Y cells	Alural et al., 2015 Zhang et al., 2017b
	N-(4-Methoxybenzyl)-N'-(5-nitro-1,3-thiazol-2-YL)urea (AR-A014418) and Indirubin-3'-oxime		MPTP-treated dopaminergic neurons	Wang et al., 2007
	P7C3		MPTP-treated MES23.5 cells	Gu et al., 2017

(continued on next page)

Table 2 (continued)

Parkinson's Disease		Chemical structure 2D	Models	References
Nrf2-related Pathways	Compounds			
p65 NF- κ B	Vildagliptin		Rotenone-induced PD rat model	Abdelsalam and Safar, 2015
	Glauccalyxin B (GLB)		Lipopolysaccharide-induced PD rat model	Xu et al., 2017
	Fasudil		MPTP-treated mice	Zhao et al., 2015
	Protocatechuic acid (PCA) and Chrysin		6-OHDA-treated PC12 cells	Zhang et al., 2015
		and		
	Hypoestoxide		mThy1- α -syn transgenic mice	Kim et al., 2015b
	α -Asarone		mThy1- α -syn transgenic mice	Kim et al., 2015a

et al., 2007). Concordantly, other authors showed that treatment with 6-OHDA in PC12 cells (Blum et al., 2001) or dopamine in SH-SY5Y neuroblastoma cells (Lee et al., 2001; Panet et al., 2001) induced translocation of NF- κ B to the nucleus. In this way, different studies reported NF- κ B modulators as possible PD strategies (Fig. 5). Thus, hypoestoxide, a NF- κ B modulator, declined microgliosis, astrogliosis, and pro-inflammatory cytokine gene expression (Kim et al., 2015b); decreased dopaminergic neurons loss and nuclear levels of phosphorylated NF- κ B (in the frontal cortex) and prevented motor behavioral deficits in the mThy1- α -syn transgenic mice overexpressing human wild-type α -syn under the mThy1 promoter (Kim et al., 2015b). In addition, treatment of mThy1- α -syn transgenic mice with α -asarone, an active compound found in Araceae and Annonaceae plant species, decreased NF- κ B p65 subunit in the nucleus, reduced microglial activation and improved PD-related motor behavioral deficits (Kim et al., 2015a). Although, no effect on Nrf2 has been assessed in these previous studies and can only be hypothesized, increased Nrf2 activity under NF- κ B inhibition was evaluated in recent studies in the context of PD. Thus, vildagliptin, a dipeptidyl peptidase inhibitor, reduced cerebral inflammation and apoptosis in a rotenone-induced PD rat model through decreased NF- κ B signaling and enhanced Nrf2 activity (Abdelsalam and Safar, 2015). Similarly, glaucocalyxin B (GLB), an ent-kauranoid diterpenoid isolated from *Rabdosia japonica*, reduced inflammation and oxidative stress via NF- κ B downregulation and enhanced Nrf2 activation, in a lipopolysaccharide-induced PD rat model (Xu et al., 2017). The Rho-associated kinase inhibitor, fasudil, also decreased NF- κ B expression and improved Nrf2 target genes expression in the MPTP mouse model (Zhao et al., 2015). In addition, protocatechuic acid or PCA, combined with chrysin, pre-characterized to have antioxidant properties (Yao et al., 2014), increased cell viability as well as Nrf2 expression

and transcriptional activity through NF- κ B inhibition in 6-OHDA-treated PC12 cells (Zhang et al., 2015).

Overall, modulation of the PI3K/Akt/GSK-3 β pathway and inhibition of the p38 MAPK appear as the most promising target pathways in several PD models, leading to the activation of Nrf2 and consequent stress response (Table 2). Moreover, considering studies in PD post-mortem tissues compounds that are able to inhibit NF- κ B activity and thus reduce neuroinflammation and boost Nrf2/ARE pathway should be seriously considered in PD treatment.

4. Conclusion

Oxidative stress, misfolded proteins, inflammation and consequent neuronal death are common features of AD and PD. The Nrf2 pathway, an intrinsic defense mechanism to combat oxidative stress and neuroinflammation, may be activated under mild oxidant conditions and leads to the expression of innumerable cytoprotective and detoxifying genes. Thus, changes in Nrf2 pathway are expected to have a major impact in early stages of NDD.

Nrf2 activation is compromised in neurodegeneration and the reason for this deregulation is still unclear, however several evidences suggest that endogenous Nrf2 signaling is impaired, possibly due to altered Nrf2-regulator pathways. In this review, we summarize some important modulators of Nrf2 pathways, described to be altered in NDD, focusing on AD and PD. Results herewith reported show a positive regulation of Nrf2 activity involving the PI3K/Akt/GSK-3 β pathway, which appears to be the most well studied for AD and PD treatments. Additionally, inhibition of NF- κ B pathway should be further considered as a potential target for the treatment of AD and PD. Data strongly suggest that compounds capable of activating Nrf2, some shown to

enhance the expression of Nrf2-related genes, are protective in experimental models of AD and PD.

Some clinical trials have been developed for AD with Nrf2 inducing agents. Studies in phase 2, with resveratrol (Turner et al., 2015) and curcumin (Baum et al., 2008; Ringman et al., 2012), showed limited results, possibly due to reduced brain penetrance and bioavailability of the compounds. However, the recent published clinical trial using resveratrol showed positive results, although Nrf2 levels or activity were not analyzed. Indeed, resveratrol reduced metalloproteinases, modulated neuroinflammation and induced adaptive immunity, when compared with the placebo-treated group (Moussa et al., 2017). Other ongoing clinical trials for AD are being developed using compounds known to activate Nrf2, such as DL-3-n-butylphthalide (NCT02711683), lithium (1R01AG055389-01) and methylene blue (NCT03446001). Methylene blue was shown to be protective by increasing the expression of several genes relevant to mitochondria biogenesis, bioenergetics, and antioxidant defense and more interestingly by activating the Nrf2/ARE pathway in aged mice (Gureev et al., 2016). Additionally, methylene blue was also protective in P301S mouse model of tauopathy, improving behavioral abnormalities and reducing tau pathology, inflammation and oxidative damage due to Nrf2/ARE pathway activation (Stack et al., 2014). Currently, there is one ongoing clinical trial in phase 3 for PD (NCT02642393) using oral inosine, which is converted to uric acid. Urate was previously shown to be protective in dopaminergic SH-SY5Y and MES23.5 cells after 6-OHDA exposure due to increased Nrf2 activation, nuclear accumulation and augmented Nrf2-targeted antioxidant genes transcription (Zhang et al., 2014). Another ongoing phase 1 clinical trial related with Nrf2 was found using Cu^{II} (ATSM) (NCT03204929). Cu^{II} (ATSM) was shown to induce Nrf2 activation in mice smooth muscle cells and cardiac myocytes (Srivastava et al., 2016). Thus, several clinical trials testing Nrf2 activators in NDDs are being developed, reinforcing their clear utility and beneficial effects.

Considering that augmented oxidative stress, inflammation and Nrf2 deregulation are common degenerative pathways in NDD, resulting in impaired neuronal function and death, strategies to combat these NDD features may likely encompass modulating Nrf2-regulatory pathways, namely PI3K/Akt/GSK-3 β or NF- κ B pathways. In this perspective, targeting of Nrf2, or its modulators, may represent “universal” early therapeutics for age-dependent NDD, AD and PD.

Declaration of Competing Interest

The authors declare no competing financial interests or any conflict of interest.

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