Role of the Transcription Factor Nrf2 in Parkinson’s Disease: New Insights
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Abstract
Parkinson’s disease (PD) is a slow progressive neurodegenerative disorder associated with motor and non-motor symptoms, with no neuroprotective therapies. This chronic disease is characterized by loss of dopaminergic neurons from the substantia nigra pars compacta and the presence of cytoplasmic α-synuclein-positive inclusions called Lewy bodies in the surviving neurons. Although PD has unknown etiology, familiar forms of PD have bring new insights in the causes of the pathology. At the molecular level, PD is characterized by proteinopathy (aggregation of α-synuclein, proteasome dysfunction and autophagy alterations), oxidative stress (increased production of reactive oxidative species, iron accumulation and dopamine oxidation) and neuroinflammation (microgliosis, reactive astrogliosis and increased levels of pro-inflammatory cytokines). A link has been revealed between the transcription factor NRF2 and PD at genetic level, showing that a functional haplotype in the human NFE2L2 gene promoter of NRF2 with slightly increased transcriptional activity, is associated with decreased risk and with delayed age at onset of PD. Moreover, since NRF2 is able to modulate the three main hallmarks of PD, several pharmacological approaches have been used to determine the role of NRF2 targeting in the development of PD. In this review we are going to evaluate the possible role of NRF2 as a pharmacological target to modify the development of PD and how some compounds that have been promising in PD mice models could be transferred to the study in clinical trials.

Keywords: Parkinson’s disease; NRF2; Inflammation; Oxidative stress; Neurodegeneration; Proteinopathy

Abbreviations: ALP: Autophagy-Lysosomal Pathway; DMF: Dimethyl Fumarate; KEAP1: Kelch-like ECH-Associated Protein 1; LPS: Lipopolysaccharide; METC: Mitochondrial Electron Transporter; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; PD: Parkinson’s Disease; ROS: Reactive Oxygen Species; SFN: Sulforaphane; SNpc: Substantia Nigra pars compacta

Introduction
Parkinson’s disease (PD) is a chronic and progressive disorder of the central nervous system that mainly affects the motor system. PD is the second most common neurodegenerative disease after Alzheimer’s disease. The incidence rate is around 1-4% of the population above the age of 60 and 80 years, although there is a lower incidence in younger people. The major clinical hallmarks are manifested by resting tremor, rigidity, postural instability and akinesia, symptoms that are often accompanied by cognitive impairment. At the molecular level, the main characteristics of PD are the loss of dopaminergic neurons in the substantia nigra pars compacta, the formation of Lewy bodies, oxidative stress and chronic low-grade inflammation. Nowadays, the main standard clinical treatment for PD patients is based on dopamine replacement with levodopa, which manages to ameliorate only motor symptoms and does not delay the neurodegenerative process. Therefore, it is essential to find out new therapies that allow us to improve not only motor symptoms, but non-motor symptoms like cognitive impairment and the dysfunction of the autonomic nervous system, and modulate disease progression. During the last decade, the transcription factor NRF2 has emerged as a suitable target to modulate PD related molecular hallmarks. NRF2 was first described as a master regulator of oxidative stress, but new evidences showed that NRF2 is also implicated in the modulation of inflammatory processes through its crosstalk with the transcription factor NF-κB, the principal regulator of inflammation. Additionally, it has been described that NRF2 is essential in proteostasis, modulating the proteasome and autophagy processes. Thus, pharmacological targeting of NRF2 could be an effective treatment for PD patients.

Parkinson’s Disease Molecular Hallmarks
Parkinson’s disease (PD) is one of the most common neurologic disorders, with evolving layers of complexity, characterised by a large number of motor and non-motor features that can impact on function to a variable degree [1,2]. Nowadays the only pharmacologic treatment of PD is based on symptomatic therapy mainly focused on levodopa treatment, which is not a disease modifying/neuroprotective therapy. Therefore, it is very important to find key targets to focus the treatment for neuroprotection or disease-modifying therapies.

Two of the major neuropathological hallmarks are the loss of dopaminergic neurons from the Substantia Nigra pars compacta (SNpc) and the presence of α-synuclein-containing Lewy bodies (LB) in the surviving neurons [3] (Figures 1 and 2). Most PD cases are sporadic and of unknown etiology, although during the last years the identification of gene mutations responsible for familial forms of PD and the mapping of risk variants for the disease [4] have improved our understanding of the disease. One of the first mutated gene that was found to be associated with familial PD was α-synuclein [5,6] and additional missense mutations and duplications have been found to be rare causes of hereditary PD or PD-like syndromes [7-10]. Moreover, genome-wide association studies have demonstrated an association between non-coding variants in and around the α-synuclein gene and sporadic disease [11]. The relevance of α-synuclein has raised...
due to its implication in Gaucher disease, a lysosomal storage disease. Decreased turnover of α-synuclein correlates with increased PD susceptibility in people that carry even a single mutation in the glucocerebrosidase gene, responsible for Gaucher disease [12,13]. Furthermore, α-synuclein has been implicated in other important steps of PD like the enteric nervous system dysfunction [14,15] and the cell-to-cell transmission [16].

Related to α-synuclein toxicity, in the SNpc of patients with the sporadic disorder it has been suggested that impaired protein clearance is a crucial factor in the pathogenesis of cell death in PD [17]. Disruption of the ubiquitin–proteasome system (UPS), which normally identifies and degrades intracellular proteins, is thought to promote the toxic accumulation of proteins detrimental to neuronal survival, thereby contributing to their demise [18]. These findings were supported by the discovery that mutations in the genes encoding α-synuclein and two enzymes of the ubiquitin-proteasome system, parkin and ubiquitin C-terminal hydrolase L1, are associated with neurodegeneration in some familial forms of PD [19]. Additionally, 20S proteasomal enzymatic activities were impaired in the SNpc in sporadic PD [19]. Importantly, α-synuclein is not degraded only by the proteasome but also by autophagy. A role for autophagy was further supported by the presence of α-synuclein in organelles with the ultrastructural features of autophagic vesicles [20,21] and that α-synuclein overexpression impairs macroautophagy in mammalian cells and in transgenic mice via Rab1a inhibition [24]. In α-synuclein transgenic mice alterations of the UPS have been reported, indicating a role of the UPS in α-synuclein degradation and with increased α-synuclein burden the autophagy-lysosomal pathway (ALP) is recruited. These results provided evidence that the UPS and ALP might be functionally connected such that impairment of one can upregulate the other [25] (Figure 2). These data indicate that the components of the cellular quality control system represent an important focus for the development of targeted and potent therapies for managing PD.

At the molecular level, in both idiopathic and genetic cases of PD,
the disease is associated with excess production of reactive oxygen species (ROS), alterations in catecholamine metabolism, modifications in mitochondrial electron transporter chain (METC) function or increase of iron deposition in the SNpc [26] (Figure 2), which leads to oxidative stress implicated in cellular dysfunction and demise. The failure of normal cellular processes that occur in relation to the aging process are also believed to contribute to the increased vulnerability of dopaminergic neurons [27]. There are many evidences indicating that oxidative stress is a key player in PD [28,29]. For example, the SNpc of PD patients exhibit increased levels of oxidized lipids [30], proteins and DNA [31] and decreased levels of reduced glutathione (GSH) [32]. Related to the vulnerability of the dopaminergic neurons from the SNpc to oxidative stress, one of the causes could be the presence of ROS-generating enzymes such as tyrosine hydroxylase and monoamine oxidase in these neurons. Besides, the nigral dopaminergic neurons contain iron, which catalyzes the Fenton reaction, in which superoxide radicals and hydrogen peroxide can contribute to further oxidative stress [28,33]. Therefore, the major sources of oxidative stress generated for the nigral dopaminergic neurons are produced during dopamine metabolism, mitochondrial dysfunction, and neuroinflammation (Figure 2).

Neuroinflammation is another feature of PD pathology. The presence of an active inflammatory response in the brain mediated primarily by resident astrocytes and microglia has been long recognized. A link between inflammation and PD was first described in a postmortem study by McGee et al. in 1988, where activated microglia was found in the SN of PD patients [34]. Furthermore, several clinical studies have confirmed this association by reporting increased microglial activation and elevated pro-inflammatory cytokines in post-mortem brains and CSF [35-37] (Figure 2). These data have been also reproduced by experimental studies in animal models of the disease [23,38,39], where neuroinflammation has been shown to be an important contributor to PD progression. Moreover, preclinical PD models suggest that inflammation is a driving force in DA neuron loss [37]. This idea is supported by experiments where chronic intraperitoneal injection of bacterial lipopolysaccharide (LPS) elicits a systemic immune response and leads to DA neuron loss and PD pathology in mice [40,41]. This inflammatory model of PD suggest that inflammatory stress can manifest in DA neuron loss likely through infiltration of peripheral leukocytes. Related to the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) PD model, it has been described a NRF2-dependent induction of proteasome required for proteostasis and key in the modulation of proteostasis as well inflammation. In response to endogenous and exogenous stresses caused by ROS and electrophiles, NRF2 translocates from the cytoplasm into the nucleus and binds together with small Maf proteins to the Antioxidant Response Element in the regulatory regions of target genes and transactives expression of genes with antioxidant activity [50]. Small Maf (MafG, MafK and MafF) proteins are b-Zip proteins that lack a transcriptional activation domain. It is known that they form homodimers and heterodimers with other b-Zip proteins including NRF2 [51]. Under basal condition, Maf proteins bind to BACH1 [52], but after induction, BACH1 is replaced by NRF2, resulting in activation and suggesting competition between BACH1 and NRF2 for the same DNA binding site [53].

All together, these different mechanisms of NRF2 regulation indicate that this transcription factor could be a suitable pharmacological target to modulate NRF2-dependent functions.

NRF2 Modulation of Proteostasis, Oxidative Stress and Inflammation

Although NRF2 was first described as the master regulator of redox homeostasis, this transcription factor has been revealed as an essential key in the modulation of proteostasis as well inflammation. Related to the proteasome, cells that constitutively express NRF2 exhibit elevated levels of proteasome activities [54] while NRF2-deficient cells have impaired proteasome activity and also less expression of proteasome proteins [39] (Figure 1). Related to oxidative stress, it has been observed a NRF2-dependent induction of proteasome required for adaptation to the stress [55]. These data were corroborated by the fact that an NRF2 inducer, sulforaphane (SFN), increases the expression of NRF2-regulated genes as well as the expression of the catalytic subunits of the proteasome and proteasomal peptidease activities [56,57]. The ubiquitin-proteasome system and autophagy are crucial for maintaining the proteostasis and are interdependent pathways. In mice with reduced proteasome activity in their livers, proteasome dysfunction activated autophagy and KEAP1/NRF2 pathway [58]. Recently, NRF2 has been identified as a regulator of autophagy gene expression [59] indicating its potential in regulating cellular proteostasis (Figure 1).

NRF2 controls the basal and induced expression of an array of antioxidant response element-dependent genes to regulate the
physiological and pathophysiological outcomes of oxidant exposure [60] (Figure 1). These function can be differentiated in several pathways, depending on the function [61]. First, enzymes regulating iron sequestration, such as heme oxygenase (HMOX1), ferritin heavy chain (FTH) and ferritin light chain (FTL). The second is NADPH production, which is controlled for example, by glucose-6-phosphate dehydrogenase (G6PD), phosphoglycerate dehydrogenase (PHGDH), among others. The third is glutathione (GSH) production and regeneration, which is regulated mainly by glutamate–cysteine ligase complex modifier subunit (GCLM), the GCL catalytic subunit (GCLC). The fourth type are antioxidants that are implicated in quinone detoxification like NAD(P)H quinone oxidoreductase 1 (NQO1). And finally, is thioredoxin (TXN) production, regeneration and utilization, which is regulated by Txn1, thioredoxin reductase 1 (TXNRD1) and peroxiredoxin 1 (PRDX1) [61,62]. These four groups of antioxidant genes have both complementary and overlapping functions. These interactions give the global idea of the huge complexity of the antioxidant system regulated by NRF2 and its implication of the regulation of oxidative stress-related diseases like PD.

The role of NRF2 in inflammation is supported by the fact that NRF2-deficient mice exhibited exacerbated inflammatory process under different stimuli [39,63-67]. In the absence of NRF2, NF-κB lacks a controller to switch-off the inflammatory signal [68] (Figure 1). Consistently, in animals treated with SFN, an NRF2 inducer, the production of inflammatory markers in response to LPS was attenuated [63]. These results are sustained by the presence of a NF-κB binding site in the NRF2 coding gene [69] and by the fact that IkB-β (IκBα kinase) contains an ETGE motif that enables it to bind to KEAP1 [70], the repressor protein of NRF2. In addition, NRF2-Deficiency results in increased ROS levels, which induce IκBα phosphorylation and subsequent degradation, increasing p65-NF-κB levels and NF-κB proinflammatory processes. Moreover, NRF2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. NRF2 binds to the proximity of IL-6 and IL-1 β and inhibits RNA Pol II recruitment, although this inhibition is independent of the NRF2-binding motif [71]. On the other hand, NRF2 activation increased the expression levels of anti-inflammatory markers like IL-4 or sphingosine kinase 2 (Sphk2) in a microglial cell line [23]. Overall, NRF2 is highly involved in the regulation of inflammation and therefore would be very promising to use NRF2 as a target for pharmacological treatment of neuroinflammation associated with PD.

Parkinson’s Disease and its Connection with NRF2

Although there is not a direct link between PD and NRF2, there is circumstantial evidence that connects loss of NRF2 with the disease. So, NRF2 activity declines with ageing, which is the main risk factor for PD. In the dopaminergic neurons from the SNpc, NRF2 is located in the cytosol, whereas in age-matched PD patients, it is found in the nucleus [72] and the NRF2 signature, represented by expression of NQO1 [73] and HO-1 [39,74-76] is up-regulated, suggesting an attempt of brain protection through this pathway [77]. In postmortem samples of PD patients, the cytoprotective proteins associated with NRF2 expression, NQO1 and p62, were partly sequestered in Lewy bodies, suggesting impaired neuroprotective capacity of the NRF2 signature [23]. However, the most compelling evidence comes from the genetic associations showing that a functional haplotype in the human NFE2L2 gene promoter (here termed Nr2f for the mouse gene), which confers slightly increased transcriptional activity, is associated with decreased risk and with delayed age at onset of the disease [78,79] in an European case-control groups. Further studies have been performed investigating whether genetic variations in and around NFE2L2 modify susceptibility to PD using a large case-control sample recruited via the Queensland Parkinson’s Project. They have identified a number of SNPs associated with a significantly later age at onset as well as common NFE2L2 variants that may reduce PD susceptibility in certain conditions, such as regular exposure to pesticides [80].

Related to familiar PD mutations, leucine-rich repeat kinase 2 (LRRK2) gene mutations are the most common genetic cause of PD, and therefore could be used as a useful tool to find biomarkers. It has been observed a strong positive correlation between NRF2 concentrations with Unified Parkinson’s Disease Rating Scale (UPDRS) in cerebrospinal fluid (CSF) from LRRK2-PD-patients. Partial correlation coefficient calculations indicated that disease duration contributed to the associations of NRF2 levels with UPDRS scores in this group [81]. Another studies with induced pluriotent stem cells (iPSCs) from PARK2 (parkin gene) patients showed increased oxidative stress and enhanced activity of NRF2 pathway, which correlated with abnormal mitochondrial morphology and impaired mitochondrial homeostasis [82].

Other evidence that connect PD with NRF2 is with the disease associated protein DJ-1. Missense, truncation and splice site mutations in DJ-1 lead to an autosomal recessive, early-onset familial form of PD [83]. Interestingly, it has been shown that DJ-1 is involved in the NRF2-dependent oxidative stress response that leads to the upregulation of the 20S proteasome and its regulator, NQO1 [84]. Furthermore, DJ-1 induces thioredoxin 1 expression through NRF2 pathway [85] and that DJ-1 stabilizes NRF2 by preventing association with KEAP1, and NRF2’s subsequent ubiquitination and degradation [86]. DJ-1/- mice did not exhibit widespread neuronal loss in a PD disease model [87,88], but these neurons were more susceptible to death after toxic insults [87], indicating a similar behaviour between DJ-1/- and Nr2f/- mice [89] that could be explained by the loss of antioxidant gene transcription.

In connection with α-synuclein, it has been demonstrated that expression of human α-SYN in Nr2f/- mice, exhibited exacerbated degeneration of nigral dopaminergic neurons and increased dystrophic dendrites, reminiscent of Lewy neurites, which correlated with impaired proteasome gene expression and activity [39]. Also, dopaminergic neuron loss was associated with an increase in neuroinflammation and gliosis that were intensified in Nr2f/- mice, indicating the relevance of NRF2 expression in the regulation of neurodegenerative and neuroinflammatory processes. α-synuclein was able to induce antioxidant enzyme genes in BV2 microglial cells and these effects was NRF2-dependent [39]. These results were supported by the findings that misfolded α-synuclein directly activates microglia and increased antioxidant enzyme expression [90] and that these enzymes are upregulated in another mouse model of α-synuclein overexpression. In mice that selectively overexpress NRF2 in astrocytes and human mutant α-synuclein (A53T) in neurons, showed delayed onset and extended life span which correlated with increased motor neuron survival, reduced oxidative stress and attenuated gliosis in the spinal cord in comparison to mutant α-synuclein (A53T) mice [91]. In vitro studies in SK-N-SH cells showed that ferrous iron induces α-synuclein aggregation and neurotoxicity by inhibiting NRF2/HO-1. Inhibition of NRF2/HO-1 leads to more α-synuclein aggregation and greater toxicity induced by iron, creating a vicious cycle of iron accumulation, α-synuclein aggregation and HO-1 disruption in PD [92]. All together, these evidence indicate the significant role of NRF2 in PD.
Pharmacologic Targeting of NRF2 as a Disease Modifying Therapy for Parkinson's Disease

Due to the fact that NRF2 is controlling the expression of genes related to proteostasis, oxidative stress and inflammation, NRF2 is a promising candidate for pharmacological targeting for the treatment of PD. There is a huge amount of compounds that target NRF2 in different ways, but looking from the clinical perspective, only few of them could be used for treatment of PD patients.

Sulforaphane (SFN), one of the main activators of NRF2, is a compound within the isothiocyanate group of organosulfur compounds. It is obtained from cruciferous vegetables such as broccoli, Brussels sprouts and cabbages. Intrapertitoneal administration of the SFN increased NRF2 protein levels in the basal ganglia and led to upregulation of phase II antioxidant enzymes HO-1 and NQO1 [38]. Related to PD, patient-derived cellular model generated from biopsies of the olfactory mucosa (termed olfactory neurosphere-derived (hONS) cells) had a 20% reduction in reduced glutathione levels and MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt] metabolism compared to cultures from healthy control donors. But more importantly, activation of the NRF2 pathway with SFN in PD hONS cultures restored glutathione and MTS metabolism to control levels [93]. In wild-type mice, but not in Nrf2-knockout mice, SFN protected against MPTP-induced death of nigral dopaminergic neurons. The neuroprotective effects were accompanied by a decrease in astrogliosis, microgliosis, and release of pro-inflammatory cytokines [38]. Similar effects have been demonstrated in other animal models of PD [94-96].

Oleanolic acid is a naturally occurring triterpenoid, which has been found to be potent inducers of the transcriptional activity of NRF2, resulting in marked induction of NQO1, HO-1, glutathione transferases, and other cytoprotective enzymes, as well as suppressing induction of iNOS and COX2 [97-100]. CDDO-methyl amide (2-cyano-N-methyl-3,12-dioxooleana-1,9(11)-dien-28 amide; CDDO-MA) treatment of neuroblastoma SH-SY5Y cells resulted in NRF2 upregulation and translocation from cytosol to nucleus and subsequent activation of ARE pathway genes. Oral administration of CDDO-MA resulted in significant protection against MPTP-induced nigrostriatal dopaminergic neurodegeneration, pathological α-synuclein accumulation and oxidative damage in mice [101]. Two other structural analogues of CDDO (TP-319 and TP-500) had been modified to improve blood-brain-barrier permeability, and reduced MPTP-induced oxidative stress and inflammation, and ameliorated dopaminergic neurotoxicity in mice. The neuroprotective effect of these TP against MPTP neurotoxicity was dependent on NRF2, since treatment with TP in NRF2 knockout mice

Figure 3: Effects of DMF on a Parkinson's disease mouse model. Diagram of the molecular events triggered by α-synuclein and the protective way of action of DMF through NRF2 activation. DMF through NRF2 is able to modulate protein aggregation (modifying proteasome and autophagy), oxidative stress (increasing the expression of antioxidant enzymes) and neuroinflammation (increasing anti-inflammatory markers and reducing pro-inflammatory cytokines)
failed to block against MPTP neurotoxicity and induce NRF2-dependent cytoprotective genes [102].

The third class of compound that activates NRF2 and could be used for clinical purposes is dimethyl fumarate (DMF), the methyl ester of fumaric acid and its metabolite, monomethyl fumarate. DMF was initially recognized as a very effective hypoxic cell radiosensitizer. Phase III clinical trials found that DMF (BG-12) successfully reduced relapse rate and increased time to progression of disability in multiple sclerosis (trade name Tecfidera) [103]. The first evidence of the benefits of DMF in PD is as quinone reductase inducer that abolish tetrahydrobiopterin BH4 (an obligatory cofactor for dopamine synthesis, also contributes to the vulnerability of dopamine-producing cells by generating oxidative stress)-induced cell death, suggesting that quinone production plays an important role [104]. More importantly, it has been shown that daily oral gavage of DMF protected nigral dopaminergic neurons against α-synuclein toxicity and decreased astrocytosis and microgliosis after 1, 3 and 8 weeks from stereotactic delivery to the ventral midbrain of recombinant adeno-associated viral vector expressing human α-synuclein [23]. This protective effect was not observed in Nrf2-knockout mice. In vitro studies indicated that this neuroprotective effect was correlated with altered regulation of autophagy markers SQSTM1/p62 and LC3 in M9N9D, BV2 and JMA 2.1 and with a shift in microglial dynamics toward a less pro-inflammatory and a more wound-healing phenotype (Figure 3). These data demonstrate that NRF2 targeting by DMF could modulate the main hallmarks of PD: proteinopathy, oxidative stress and neuroninflammation. These observations were reinforced by the fact that DMF significantly reduced neuronal cell degeneration of the dopaminergic tract and behavioural impairments induced by injections of the dopaminergic neurotoxin MPTP [105,106]. Interestingly, the pharmacodynamics of DMF are tissue specific and involve NRF2-dependent and -independent mechanisms [107].

One of the main actions of DMF is modulating inflammation, inhibiting the transcription factor NF-kB, that could be also independent of NRF2 [108-110]. But, NRF2 involvement cannot be ruled out due to Osgin-1, a transcriptional target of NRF2, contributes to monomethyl fumarate-mediated cytoprotection in human astrocytes [111] and is highly regulated in the ventral midbrain after DMF exposure [23] in a NRF2-dependent way.

Conclusion

Parkinson’s disease is the second most common multisystemic neurodegenerative disorder associated with ageing. At the pathologic level, PD is characterized by the selective loss of dopaminergic neurons in the SNpc and accumulation of α-synuclein in Lewy bodies and Lewy neurites [112]. It is a progressive movement disorder, and the main therapeutic treatment is focused on dopamine replacement therapy with levodopa, accompanied with complications related to long-term symptomatic treatment. Moreover, these treatments did not delay or stop disease progression. Although the first description of the disease was made two centuries ago, the treatments have not evolved in a great manner.

Transcription factor NRF2 has emerged as a suitable candidate for pharmacological targeting for the treatment of PD. There are consistent bases relating PD and NRF2 and several basic research based on parkinsonian animal models which reinforce the idea of modulation of the expression of the NRF2 pathway is beneficial for delaying the disease progression. Several compounds that have been promising in PD mouse models could be transferred to the study in clinical trials, for example DMF, that already is used to treat multiple sclerosis patients.

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