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Nrf2 and Parkinson's Disease

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Abstract

Parkinson's disease (PD) results from a complex interaction of environmental and genetic influences on a background of aging. Regardless of etiology, significant clinical advances rely on identifying the common biological pathways that underpin neuronal degeneration. Oxidative stress is consistently reported as a hallmark feature of PD. Recently, it has been demonstrated that Nrf2 modulation can protect neurons from parkinsonian agents and, in some instances, reverse motor symptoms of animal models. Furthermore, baseline aberrations of Nrf2 and its associated pathway have been reported in PD patients, and genetic variability—within and around the Nrf2 gene—may modify PD susceptibility and onset. Overall, Nrf2 dysregulation has been tentatively implicated in the pathogenesis of PD and may prove to be an effective therapeutic target.

Keywords: Parkinson's disease, Nrf2, oxidative stress, inflammation, dopamine

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a range of motor and nonmotor features. Clinically, PD diagnosis is based on the presence of distinctive cardinal motor features, including bradykinesia, resting tremor, postural instability, and rigidity [1]. Disease progression can be staged in accordance with developing neuropathological hallmarks that advance through presymptomatic and symptomatic phases [2]. The presymptomatic stages may last years to decades before the manifestation of classical PD-related motor symptoms [3–5]. Motor dysfunction is commonly associated with the loss of dopamine-producing neurons in the *substantia nigra pars compacta*, projecting throughout the nigrostriatal pathway. Further progressive and selective neuron loss will continue, ultimately culminating in a debilitating multisystem disorder [6].

Currently, the most efficacious medical treatments are limited to dopamine replacement therapies (levodopa), however, such medications wane in efficacy and can produce debilitating motor and nonmotor symptoms, prompting alternative approaches [7, 8]. Generally, PD medications agonize dopaminergic receptors, antagonize cholinergic receptors, and/or prolong dopamine activity (monoamine oxidase type-B inhibitors) [8]. While these approaches address symptoms, they provide no curative or disease-modifying effect, provoking researchers to isolate the pathogenic mechanism/s that underpin dopaminergic degeneration.

While the majority of PD cases are idiopathic (90–95%), etiological risk has been attributed to herbicide/pesticide exposure, heavy metals, rural living, aging, and genetic variability [9–11]. The role of these contributing factors in the pathogenesis of PD can be summarized as a complex interaction of environmental and genetic influences on a background of aging. Regardless of etiology, significant clinical advances rely on identifying the common biological pathways that underpin neuronal degeneration. Increasing evidence in this field suggests that oxidative stress is a major contributor in this process.

Free radicals, including reactive oxygen species (ROS) and reactive nitrogen species, are endogenous molecules, produced in cells as a by-product of metabolic systems (such as mitochondrial oxidative phosphorylation) and/or in response to an altered chemical environment. ROS are molecular species that contain an unpaired electron and are unstable and reactive. They are often implicated in disease (including numerous neurodegenerative diseases) and consist of hydroxyl, hydrogen peroxide, oxygen singlet, and superoxide radicals. Within a "steady-state" environment, the levels of ROS are often balanced by endogenous antioxidant defense mechanisms. However, if this balance is disrupted in the favor of ROS accumulation, a condition referred to as oxidative stress arises. Mitochondrial dysfunction, inflammation, and exercise are common endogenous generators of ROS. Environmental generators of ROS include cigarette smoke, pesticide exposure, and radiation. Overexposure to one or more of these factors may result in oxidative stress. Additionally, oxidative stress may occur if normal production of these reactive species cannot be appropriately managed. Thus, an inefficient antioxidant response mechanism may also result in increased risk for oxidative stress. An inability to balance redox systems and dispose of damaged cellular components may exacerbate ROS production and dramatically affect the survival of the cell through ROS-mediated lipid, protein, and DNA oxidation [12].

In general, neuronal cells are vulnerable to oxidative changes because of their high oxygen consumption and enrichment in fatty acids [13]. Furthermore, dopaminergic neurons are especially prone to oxidative-induced injury due to their capacity to produce ROS as a metabolic by-product. This can occur in two ways: (1) when dopamine is metabolized enzymatically (via monoamine oxidase) or (2) through auto-oxidation of dopamine (ultimately forming neuromelanin) [14]. Both means of processing dopamine produce ROS; enzymatic oxidation (1) forms hydrogen peroxide (H_2O_2), and nonenzymatic oxidation (2) produces superoxide (O^{2-}) and reactive quinones [15]. The production of ROS may be exacerbated by inflammation, neuronal damage, impaired mitochondrial management, and dysfunctional antioxidant response mechanisms [16]. However, the vast majority of ROS has been attributed to the mitochondria.

The major source of cellular energy (ATP) is produced by the mitochondria. This system is dependent on the simultaneous generation of a proton-motive force (termed the electron transport chain; ETC) across the mitochondrial inner membrane, driving the formation of ATP. The mitochondrial ETC came to the forefront of PD research after studies reported that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a mitochondrial ETC complex I inhibitor, induced Parkinsonian symptoms as a result of a toxic insult on nigrostriatal neurons [17]. Following these initial studies, complex I deficits have been identified not only in pharmacologically induced cases but also in idiopathic PD cases [18].

Endogenous antioxidants are required to maintain redox balance throughout the system. Many are transcriptionally regulated by the antioxidant "master regulator" Nrf2, which, upon direct stimulation from electrophilic compounds and ROS, will translocate to the nucleus and activate gene transcription of a gamut of antioxidant enzymes. Nrf2 supports and regulates, among others, the most abundant antioxidant family in the cell, glutathione. Interestingly, deficiency of reduced glutathione (GSH)—in the *substantia nigra* of PD brains—has consistently been reported [19, 20]. Recently, the Nrf2-mediated antioxidant response pathway has been directly and indirectly implicated in PD. This chapter will explore the role of Nrf2 and its pathway, in the development and management of PD, as stated within the contemporary literature.

2. The role of oxidative stress in Parkinson's disease

For years, markers of oxidative stress have been observed in postmortem brain tissue and disease models of PD. Currently it is unclear whether these factors are primary causes of PD or the result of established neurodegeneration. Regardless, studies have demonstrated that chronic ROS exposure can lead to the exacerbation of dopaminergic neuron death; implicating these processes in the pathophysiology of PD.

2.1. Mitochondria and oxidative stress

The brain is a major producer of ROS due to its extensive oxygen consumption; the nervous tissue is responsible for ~20% of total body oxygen consumption. The tightly regulated signaling systems of these neurons have a high energy demand provided primarily by the oxygen-dependent ATP production of the mitochondria. The ability of the mitochondria to fuse, divide, and migrate throughout the extended processes of neurons provide a dynamic adaptability in order to meet metabolic demands [21, 22]. Under normal resting conditions, mitochondria produce the ROS precursor molecule, superoxide ($O_2^{\bullet-}$), as a by-product of the electron transport chain. $O_2^{\bullet-}$ can produce hydrogen peroxide (H_2O_2) and hydroxyl ($^\bullet OH$); endogenous free radicals that can initiate lipid peroxidation. The brain is especially sensitive to lipid peroxidation due to the high concentration of polyunsaturated fatty acids. Because of this, neurons cells are extremely sensitive to the oxidative environment caused by mitochondrial defects; a number of these mitochondrial deficiencies have been implicated in neurodegenerative diseases, such as PD.

In the late 1970s, drug addicts presenting with Parkinsonian-like symptoms led to the discovery of MPTP, a contaminant of illicit meperidine synthesis (a synthetic analogue of heroin). Soon after its discovery, MPTP was used to produce a clinical phenotype, indistinguishable from PD, in primate species [23]. MPTP was shown to oxidize intraneuronally, the effect of which (underscored amongst other clinical hallmarks) was the selective destruction of dopaminergic neurons in the nigrostriatal system. More recently, a number of pesticides/herbicides have also demonstrated their efficacy as neurotoxins. Rotenone, a common herbicide, is often used in a manner similar to MPTP, to induce dopaminergic neurodegeneration in animal models. Both MPTP and rotenone, mechanistically, act upon the same pathway and inhibit complex I of the mitochondrial oxidative phosphorylation pathway [17]. Following these initial studies, complex I deficits have been identified not only in pharmacologically induced cases but also in idiopathic PD cases [18]. Furthermore, this reduction of complex I activity is not localized to the *substantia nigra*, but has been found in skeletal muscle, platelets, and fibroblasts of PD patients [24–27]. This evidence further implicates mitochondrial maintenance and subsequent free radical production in the pathogenesis of PD.

While the majority of PD is sporadic, rare genetic forms of the disease have been identified. So far, 23 chromosomal loci, termed the *PARK* loci, have been linked to both autosomal-dominant and autosomal-recessive inheritance patterns of PD. Interestingly, mutations within many of these loci have been associated with mitochondrial dysfunction and oxidative stress.

Dominantly inherited mutations in the alpha-synuclein (*SNCA*) gene were the first identified genetic forms of familial PD. Alpha-synuclein is the major proteinaceous constituent of the Lewy body, the key pathological hallmark of PD and other so-called synucleinopathies. This protein provided the first solid link between sporadic and familial forms of Parkinson's disease. Currently, studies suggest that, normally, alpha-synuclein plays a "protective role" as a chaperone, sequestering dysfunction proteins into aggregates [28–30]. However, these aggregates may lead to synaptic degeneration and ultimately cell death [31]. More recently, studies have suggested that alpha-synuclein aggregation can be induced by increased levels of ROS as a consequence of mitochondrial dysfunction, *in vitro* [32, 33]. Moreover, alpha-synuclein aggregation may further damage mitochondria, compounding the effects of oxidative stress [34].

Mutations within three *PARK* loci—*PARK2* (gene: *PARK2*; protein: Parkin), *PARK6* (gene: *PINK1*; protein: PINK1), and *PARK7* (gene: *PARK7*; protein: DJ-1)—are inherited in an autosomal recessive manner and have been linked to early-onset PD (i.e., symptoms present <45 years of age). Interestingly, animal genetic models have identified common and converging pathways for these gene products; these pathways focus on mitochondrial maintenance/dynamics, oxidative stress, and disrupted antioxidant pathways [35]. Individual disease models that knockout these genes result in increased susceptibility to H_2O_2 and excess ROS production [36–40]. Overall, converging evidence implicates certain *PARK* gene products in mitochondrial maintenance and ROS management. Subsequent dysfunction of these pathways therefore suggests that oxidative stress plays a central role in PD pathogenesis.

2.2. Dopamine metabolism and oxidative stress

As previously discussed, mitochondrial defects are associated with increased free radical production, and this has been theorized to play an important role in the pathogenesis of PD. However, these effects may be compounded by the ROS-enriched environment of highly metabolic dopamine-producing neurons. Dopamine can be metabolized enzymatically (via monoamine oxidase) or through auto-oxidation (ultimately forming neuromelanin) [14]. Both means of dopamine-processing produce ROS; enzymatic oxidation forms H_2O_2, and nonenzymatic oxidation produces O^{2-} and reactive quinones [15]. Production of ROS may be exacerbated by inflammation, neuronal damage, impaired mitochondrial management, and dysfunctional antioxidant response mechanisms [16].

Current evidence supports the hypothesis that PD is a consequence of genetic variation and environmental exposures, converging—ultimately—on oxidative stress. Therefore, it is important to characterize the role of antioxidant-response mechanisms, specifically Nrf2—commonly touted as the "master regulator" of oxidative stress—in the pathophysiology of PD.

3. Nrf2 in Parkinson's disease progression and pathology

Maintaining redox balance within an aging brain is reliant upon an efficient and an effective Nrf2-mediated pathway. However, aging appears to correlate with a decline in Nrf2 expression and transcriptional response, potentiating an individual's susceptibility to ROS accumulation [41, 42].

Nrf2 protein concentration, when isolated from the cerebral spinal fluid of PD patients with *LRRK2* mutations (G2019S), was positively, and significantly, associated with disease duration, motor scores, and the Unified Parkinson's Disease Rating Scale (UPDRS; well-established rating scale of Parkinson's disease symptom severity) [43]. This indicates that Nrf2 concentration (at least in the CSF) may increase with disease progression. Moreover, Nrf2 location may change in response to the oxidative profile of the cellular environment. This is also highlighted in a study that demonstrated that Nrf2 was found in the nucleus of nigral dopaminergic neurons in early Braak staging (1–2) PD patients, while a cytosolic localization was predominantly found for healthy, age-matched controls [44]. This translocation of Nrf2 to the nucleus in PD patients indicates an attempt to upregulate antioxidant responsive genes. Of these, the potent and diverse antioxidants, NQO1 and HO-1, are two that are strongly enhanced by Nrf2 activation. NQO1 is a successful metabolizer of dopamine-derived quinones [45] and has been reported at higher levels within the *subtantia nigra pars compacta* of PD patients compared to healthy controls [46]. NQO1 overexpression appears to protect cells against dopamine-mediated mitochondrial damage *in vitro* [47] and *in vivo* reduces MPTP toxicity [48]. Another Nrf2-transcribed antioxidant, HO-1, is also observed at higher concentrations in PD patients' blood serum compared to healthy controls [49]; the higher HO-1 concentrations were not observed in the blood serum of Alzheimer's disease patients, suggesting a disease-dependent Nrf2 recruitment. Unlike NQO1, no disease-specific differences for HO-1 expression have been observed in the *subtantia nigra pars compacta* of PD patients. However, PD patients exhibiting

Lewy body pathology had a distinct HO-1 staining pattern within the periphery of these proteinaceous Lewy body inclusions [50]. This curious finding demonstrates the oxidative nature of Lewy bodies and the relationship between the Nrf2 pathway and PD pathology.

It is well established that the Nrf2 pathway is an integral player in the cellular response to the oxidative stress commonly associated with PD. It follows that a dysfunctional Nrf2 response may interfere with the normal healthy antioxidant management, and there is evidence that this contributes to risk for disease [51]. A number of studies have reported reduced antioxidant enzyme activity in the *substantia nigra pars compacta* of PD patient brains [52, 53]. Also, contemporary evidence suggests that genetic variability, in and around the Nrf2 encoding gene, is associated with disease susceptibility and modulates disease age-at-onset [11, 54, 55].

4. Nrf2 genetics and Parkinson's disease

Oxidative stress appears to lie at the nexus of genetic, pharmacologically induced, and idiopathic cases of Parkinsonism. Considering this, studies have begun to investigate the degree of influence that transcriptional "master regulators" of antioxidant response may impose on disease pathogenesis. A recent study has comprehensively screened *NFE2L2*, the gene that encodes Nrf2, for genetic sequence variants and correlated genetic variability with disease susceptibility [11]. Prior to this report, few candidate gene studies had investigated this relationship. A Taiwanese case–control study (PD = 480; controls = 526), which genotyped three Nrf2 promoter single nucleotide polymorphisms (SNPs), did not observe any significant individual polymorphism associations with PD [56]. Interestingly, a Polish case–control group reported that a specific haplotype (comprising these three promoter SNPs) was associated with disease protection and a delayed age-at-onset of PD. A further publication suggested that haplotypes of eight other SNPs found within and around *NFE2L2* altered disease risk and disease age-at-onset within two independent case–control groups (Polish and Swedish) [55]. This study was subsequently replicated in a European meta-analysis and in a larger Australian case–control study. The European case–control study (PD = 1038; controls = 1600) re-established the previously identified protective and disease-delaying Nrf2 promoter SNP haplotype and a number of individual polymorphisms associated with both earlier and delayed PD age-at-onset [54]. A large Australian study (PD = 1338; controls = 1379) further replicated the disease-delaying Nrf2 promoter haplotype and identified a SNP associated with an reduced disease risk [11]. Recently, two novel Nrf2-coding SNPs were identified and associated with PD within a Chinese population [57]. This study further demonstrated that overexpressing these alternate alleles reduced the expression of downstream Nrf2 products—glutathione s-transferase and HO-1. These studies provide compelling evidence that genetic variability within and around Nrf2 modulates PD risk and susceptibility. Due to the important role of Nrf2 as a functional respondent to oxidative threat, it is important to understand its influence on PD in the context of environmental exposures.

5. Nrf2 and environmental exposures in Parkinson's disease

A number of exogenous agents have shown to influence the development of PD; heavy metals (iron, copper, cadmium, manganese), insecticides/herbicides, and organic solvents are often reported in human epidemiological and animal studies [9, 10, 58]. Nrf2 stabilization from its constitutive repressor, KEAP1, and subsequent translocation to the nucleus are dependent upon exposure to electrophilic compounds and oxidative stress [59]. Some of the previously mentioned exogenous agents, implicated in PD, upregulate the Nrf2 signaling pathway as a response to mitigate potential damage [60]. The heavy metals, copper and iron, have been linked to oxidative stress and alpha-synuclein aggregation in PD. Experimental data have shown that accumulated ferrous iron downregulates Nrf2 and HO-1 expression, *in vitro*, promoting alpha-synuclein aggregation [61]. Furthermore, overexpression of HO-1 mitigates ferrous iron-induced cellular damage. Also, the ROS-mediated neurotoxic effects of excess copper exposure have shown to induce the Nrf2 pathway in zebrafish [62]. Acute cadmium exposure, tentatively associated with Parkinsonism [63], and manganese, known to produce Parkinson's-like motor dysfunction [64], both induce Nrf2 transcriptional activity *in vivo* [65].

Pesticide/herbicide exposures, classified as risk factors for PD, induce oxidative stress as a mechanism of neuronal cell death [66, 67]. The pesticide, deltamethrin, activates Nrf2 and downstream gene expression in rat brains [68]. Furthermore, Nrf2 activation protects neuronal cell lines from paraquat—a herbicide used to produce Parkinsonism in animal models. This data tentatively support the hypothesis that the Nrf2 pathway is modulated in response to PD-associated environmental exposures. Further studies have investigated whether genetic variability underlying Nrf2 and its various downstream products affect their cytoprotective activity in response to environmental insult.

One study observed that human olfactory neurosphere-derived cell lines carrying the minor allele of an Nrf2 SNP were significantly resilient to rotenone-induced cell death over a 5-day exposure [11]. In addition to Nrf2, PD risk from pesticide exposure has been associated, within certain populations, with genetic variability of Nrf2-transcribed genes. Individuals carrying *NQO1* SNPs are more susceptible to PD when exposed to pesticide compared to exposed individuals not carrying the variant [69]; while GST genotype has also shown to influence PD susceptibility upon exposure to paraquat [70, 71].

6. Nrf2 modulation as a neuroprotective strategy

As demonstrated in the literature, oxidative stress is highlighted as a major contributing factor in the pathogenesis of PD. Genetic, environmental, and idiopathic cases of PD have reported ROS imbalance, thereby tentatively implicating the "master regulator" of oxidative management, Nrf2, in the pathophysiological process. Numerous studies have decided to evaluate whether modulating Nrf2—either genetically or pharmacologically—influences disease susceptibility *in vitro* or *in vivo*. **Table 1** summarizes a number of these studies.

Target	Intervention	Model	Neuroprotective against:	References
Nrf2	Dimethyl fumarate (DMF)	Alpha-synuclein mouse model	Dopamine neuron loss in substantia nigra	[78]
	Overexpression	Mouse	H_2O_2 –and glutamate-treated cortical neurons	[79]
	Overexpression	Mixed primary neuron culture	Rotenone/ionomycin-induced cell death	[84]
	DMF[1,2]	Mouse[1] SH-SY5Y cells[2]	MPTP-induced neurotoxicity[1], 6-OHDA-treated cells[2]	[85][1], [86][2]
NQO1	Overexpression	SK-N-MC neuroblastoma	Dopamine-induced toxicity	[47]
Nrf[3,4], NQO1[9]	Triterpenoids[3] KMS04014[4,9]	C57B16 mouse[3,4,9]	MPTP-induced dopaminergic neuron toxicity[3,4,9]	[48][4], [87][3], [88][9]
Nrf2[5,6,10], NQO1[5,6], HO-1[5,6]	Bromocriptine[5], torularhodin[6], Selegiline[7]	PC12 cells[5,6,7]	H_2O_2-induced oxidative damage[5,6], MPP^+-induced oxidative damage[7]	[89][5], [90][6], [83][7]
Nrf2, NQO1, HO-1	α-Iso-cubebene	HT22 cells	Glutamate-induced oxidative damage	[91]
NQO1[8,9], HO-1[9]	KMS04014[8], isothiocyanate-3[9]	CATH.a cells[8,9], BV-2 cells[9]	H_2O_2/MPP^+–treated cells[8], lipopolysaccharide-treated cells[9]	[48][8], [88][9]

Superscript 1–9 denotes information obtained from a single source.

Table 1. Nrf2 and neuroprotection.

The ability of Nrf2 to attenuate disease relevant perturbations has been evaluated in neuronal cell line derivatives and various animal models. Many of these studies utilize a post-treatment strategy, perturbing the cells after Nrf2 is upregulated. Nrf2 activation can be influenced either pharmacologically (e.g., dimethyl fumarate (DMF), sulforaphane (SFN), or with tert-butyl hydroquinone (tBHQ)) or genetically. Perturbations are often performed with known Parkinsonian agents such as paraquat, rotenone, MPTP, 6-hydroxy dopamine (6-OHDA), or hydrogen peroxide (H_2O_2). This approach has consistently demonstrated that Nrf2 activation provides a successful neuroprotective strategy [72–77]. However, it must be noted that modulating Nrf2, prior to toxic treatment, does not reflect the insidious nature of PD and does not take into consideration the decades of accumulated cellular damage that has existed prior to clinical intervention. Notwithstanding this caveat, animal models of PD are providing compelling evidence that Nrf2 modulation offers significant protection against neuronal cell loss.

Current PD mouse models can recapitulate the histological hallmark of alpha-synuclein-containing aggregates and selective nigral dopaminergic neuron loss. The pharmacological targeting of Nrf2 in these models, via oral administration of DMF, can attenuate dopaminergic

neuron loss in the *substantia nigra* [78]. Interestingly, this effect was not observed in Nrf2 knockout mice. Furthermore, Nrf2 knockout mice are more susceptible to cortical neuron cell damage caused by H_2O_2 and glutamate, while, on the other hand, they are significantly protected when Nrf2 is overexpressed [79]. Some studies have also shown that, in addition to Nrf2 overexpression, Keap1 repression may offer a successful strategy to restore neuron degeneration and motor dysfunction in an alpha-synuclein *Drosophila* model of PD [80].

To date, no studies have directly evaluated the efficacy of pharmacologically targeting Nrf2 as a treatment strategy for PD. Since the 1990s, the drug deprenyl (selegiline)—a type-B monoamine oxidase inhibitor (MAOI-B)—has been used as a pharmacological means to treat PD. The mechanism of action of MAOI-B is to inhibit the breakdown of monoamine neurotransmitters (such as dopamine). While this strategy temporally maintains synaptic dopamine concentrations, it also reduces the oxidative stress associated with dopamine metabolism [81]. While it has been known, since early in its use, that selegiline induced the expression of antioxidant enzymes [82], it has only recently been discovered that this is mediated by the activation of Nrf2 [83] and that activation of this pathway was sufficient to protect a neuronal-based cell line from oxidative damage.

7. Conclusion

Oxidative stress has been identified as a major contributor in the pathogenesis of PD. Mechanisms of ROS production—contributing to the oxidative profile of neuronal cells—include mitochondrial respiration, dopamine metabolism, and environmental exposures. Normally, redox balance is managed by the transcription factor and antioxidant "master regulator," Nrf2. Studies have demonstrated that Nrf2 and its associated pathway products can be upregulated in PD patient brains; potentially, this highlights the body's attempt to mitigate oxidative stress. Furthermore, studies have also shown that reduced or dysfunctional Nrf2 can be found in PD tissue. Genetic variability within and around the Nrf2 gene has been associated with PD risk and age-at-onset, while genetic aberrations in Nrf2-mediated genes may influence an individual's risk of PD after exposure from environmental agents. Due to the functional role of Nrf2 in mitigating oxidative stress, many studies have investigated Nrf2 as a modulator of Parkinson's disease. Activation of Nrf2 attenuates neuronal damage caused by Parkinsonian agents, *in vitro* and *in vivo*. Overall, Nrf2 has been tentatively implicated in the pathophysiology of PD and may prove to be an effective therapeutic target.

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References

[1] Jankovic, J., *Parkinson's disease: clinical features and diagnosis*. J Neurol Neurosurg Psychiatry, 2008. 79(4): p. 368–76.

[2] Braak, H., et al., *Staging of brain pathology related to sporadic Parkinson's disease*. Neurobiol Aging, 2003. 24(2): p. 197–211.

[3] Hawkes, C.H., K. Del Tredici, and H. Braak, *Parkinson's disease: the dual hit theory revisited*. Ann N Y Acad Sci, 2009. 1170: p. 615–622.

[4] Goldman, S.M., *A diagnostic algorithm for Parkinson's disease: what next?* Lancet Neurol, 2015. 14(10): p. 971–973.

[5] Haas, B.R., T.H. Stewart, and J. Zhang, *Premotor biomarkers for Parkinson's disease—a promising direction of research*. Transl Neurodegener, 2012. 1(1): p. 11.

[6] Braak, H., et al., *Pathology associated with sporadic Parkinson's disease—where does it end?* J Neural Transm Suppl, 2006. (70): p. 89–97.

[7] Siddiqi, S.H., et al., *The human experience with intravenous Levodopa*. Front Pharmacol, 2015. 6: p. 307.

[8] Connolly, B.S. and A.E. Lang, *Pharmacological treatment of Parkinson disease: a review*. JAMA, 2014. 311(16): p. 1670–1683.

[9] Montgomery, E.B., Jr., *Heavy metals and the etiology of Parkinson's disease and other movement disorders*. Toxicology, 1995. 97(1–3): p. 3–9.

[10] Tanner, C.M. and J.W. Langston, *Do environmental toxins cause Parkinson's disease? A critical review*. Neurology, 1990. 40(10 Suppl 3): p. suppl 17–30; discussion 30–1.

[11] Todorovic, M., et al., *Comprehensive assessment of genetic sequence variants in the antioxidant 'master regulator' nrf2 in idiopathic Parkinson's disease*. PLoS One, 2015. 10(5): p. e0128030.

[12] Young, I.S. and J.V. Woodside, *Antioxidants in health and disease*. J Clin Pathol, 2001. 54(3): p. 176–86.

[13] de Vries, H.E., et al., *Nrf2-induced antioxidant protection: a promising target to counteract ROS-mediated damage in neurodegenerative disease?* Free Radic Biol Med, 2008. 45(10): p. 1375–83.

[14] Sulzer, D., et al., *Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles*. Proc Natl Acad Sci U S A, 2000. 97(22): p. 11869–11874.

[15] Miyazaki, I. and M. Asanuma, *Dopaminergic neuron-specific oxidative stress caused by dopamine itself*. Acta Med Okayama, 2008. 62(3): p. 141–50.

[16] Lev, N., et al., *DJ-1 protects against dopamine toxicity*. J Neural Transm, 2009. 116(2): p. 151–160.

[17] Langston, J.W. and P. Ballard, *Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): implications for treatment and the pathogenesis of Parkinson's disease*. Can J Neurol Sci, 1984. 11(1 Suppl): p. 160–165.

[18] Schapira, A.H., et al., *Mitochondrial complex I deficiency in Parkinson's disease*. J Neurochem, 1990. 54(3): p. 823–827.

[19] Sian, J., et al., *Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia*. Ann Neurol, 1994. 36(3): p. 348–355.

[20] Pearce, R.K., et al., *Alterations in the distribution of glutathione in the substantia nigra in Parkinson's disease*. J Neural Transm, 1997. 104(6–7): p. 661–677.

[21] Bender, A., et al., *High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease*. Nat Genet, 2006. 38(5): p. 515–517.

[22] Court, F.A. and M.P. Coleman, *Mitochondria as a central sensor for axonal degenerative stimuli*. Trends Neurosci, 2012. 35(6): p. 364–372.

[23] Markey, S.P., et al., *Intraneuronal generation of a pyridinium metabolite may cause drug-induced parkinsonism*. Nature, 1984. 311(5985): p. 464–467.

[24] Parker, W.D., Jr., S.J. Boyson, and J.K. Parks, *Abnormalities of the electron transport chain in idiopathic Parkinson's disease*. Ann Neurol, 1989. 26(6): p. 719–723.

[25] Bindoff, L.A., et al., *Respiratory chain abnormalities in skeletal muscle from patients with Parkinson's disease*. J Neurol Sci., 1991. 104(2): p. 203–208.

[26] Krige, D., et al., *Platelet mitochondrial function in Parkinson's disease. The Royal Kings and Queens Parkinson Disease Research Group*. Ann Neurol, 1992. 32(6): p. 782–788.

[27] Wiedemann, F.R., et al., *Detection of respiratory chain defects in cultivated skin fibroblasts and skeletal muscle of patients with Parkinson's disease*. Ann N Y Acad Sci, 1999. 893: p. 426–429.

[28] Chandra, S., et al., *Double-knockout mice for alpha- and beta-synucleins: effect on synaptic functions*. Proc Natl Acad Sci U S A, 2004. 101(41): p. 14966–14971.

[29] Chandra, S., et al., *Alpha-synuclein cooperates with CSPalpha in preventing neurodegeneration*. Cell, 2005. 123(3): p. 383–396.

[30] Abeliovich, A., et al., *Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system*. Neuron, 2000. 25(1): p. 239–252.

[31] Masliah, E., et al., *Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders*. Science, 2000. 287(5456): p. 1265–1269.

[32] Esteves, A.R., et al., *Oxidative stress involvement in alpha-synuclein oligomerization in Parkinson's disease cybrids*. Antioxid Redox Signal, 2009. 11(3): p. 439–448.

[33] Pukass, K., O. Goldbaum, and C. Richter-Landsberg, *Mitochondrial impairment and oxidative stress compromise autophagosomal degradation of alpha-synuclein in oligodendroglial cells*. J Neurochem, 2015. 135(1): p. 194–205.

[34] Hsu, L.J., et al., *alpha-synuclein promotes mitochondrial deficit and oxidative stress*. Am J Pathol, 2000. 157(2): p. 401–410.

[35] Dodson, M.W. and M. Guo, *Pink1, Parkin, DJ-1 and mitochondrial dysfunction in Parkinson's disease*. Curr Opin Neurobiol, 2007. 17(3): p. 331–337.

[36] Gautier, C.A., T. Kitada, and J. Shen, *Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress*. Proc Natl Acad Sci U S A, 2008. 105(32): p. 11364–11369.

[37] Clark, I.E., et al., *Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin*. Nature, 2006. 441(7097): p. 1162–1166.

[38] Clements, C.M., et al., *DJ-1, a cancer- and Parkinson's disease-associated protein, stabilizes the antioxidant transcriptional master regulator Nrf2*. Proc Natl Acad Sci U S A, 2006. 103(41): p. 15091–15096.

[39] Krebiehl, G., et al., *Reduced basal autophagy and impaired mitochondrial dynamics due to loss of Parkinson's disease-associated protein DJ-1*. PLoS One, 2010. 5(2): p. e9367.

[40] Zhou, W., et al., *The oxidation state of DJ-1 regulates its chaperone activity toward alpha-synuclein*. J Mol Biol, 2006. 356(4): p. 1036–1048.

[41] Suh, J.H., et al., *Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid*. Proc Natl Acad Sci U S A, 2004. 101(10): p. 3381–3386.

[42] Shih, P.H. and G.C. Yen, *Differential expressions of antioxidant status in aging rats: the role of transcriptional factor Nrf2 and MAPK signaling pathway*. Biogerontology, 2007. 8(2): p. 71–80.

[43] Loeffler, D.A., et al., *CSF Nrf2 and HSPA8 in Parkinson's disease patients with and without LRRK2 gene mutations*. J Neural Transm (Vienna), 2016. 123(3): p. 179–187.

[44] Ramsey, C.P., et al., *Expression of Nrf2 in neurodegenerative diseases*. J Neuropathol Exp Neurol, 2007. 66(1): p. 75–85.

[45] Jia, Z., et al., *Dopamine as a potent inducer of cellular glutathione and NAD(P)H:quinone oxidoreductase 1 in PC12 neuronal cells: a potential adaptive mechanism for dopaminergic neuroprotection*. Neurochem Res, 2008. 33(11): p. 2197–2205.

[46] van Muiswinkel, F.L., et al., *Expression of NAD(P)H:quinone oxidoreductase in the normal and Parkinsonian substantia nigra*. Neurobiol Aging, 2004. 25(9): p. 1253–1262.

[47] Zafar, K.S., et al., *Overexpression of NQO1 protects human SK-N-MC neuroblastoma cells against dopamine-induced cell death*. Toxicol Lett, 2006. 166(3): p. 261–267.

[48] Son, H.J., et al., *Induction of NQO1 and neuroprotection by a novel compound KMS04014 in Parkinson's disease models*. J Mol Neurosci, 2015. 56(2): p. 263–272.

[49] Mateo, I., et al., *Serum heme oxygenase-1 levels are increased in Parkinson's disease but not in Alzheimer's disease*. Acta Neurol Scand, 2010. 121(2): p. 136–138.

[50] Schipper, H.M., A. Liberman, and E.G. Stopa, *Neural heme oxygenase-1 expression in idiopathic Parkinson's disease*. Exp Neurol, 1998. 150(1): p. 60–68.

[51] Cook, A.L., et al., *NRF2 activation restores disease related metabolic deficiencies in olfactory neurosphere-derived cells from patients with sporadic Parkinson's disease*. PLoS One, 2011. 6(7): p. e21907.

[52] Sofic, E., et al., *Antioxidant capacity in postmortem brain tissues of Parkinson's and Alzheimer's diseases*. J Neural Transm Suppl, 2006(71): p. 39–43.

[53] Perry, T.L. and V.W. Yong, *Idiopathic Parkinson's disease, progressive supranuclear palsy and glutathione metabolism in the substantia nigra of patients*. Neurosci Lett, 1986. 67(3): p. 269–74.

[54] von Otter, M., et al., *Genetic associations of Nrf2-encoding NFE2L2 variants with Parkinson's disease—a multicenter study*. BMC Med Genet, 2014. 15: p. 131.

[55] von Otter, M., et al., *Association of Nrf2-encoding NFE2L2 haplotypes with Parkinson's disease*. BMC Med Genet, 2010. 11: p. 36.

[56] Chen, Y.C., et al., *Genetic analysis of NFE2L2 promoter variation in Taiwanese Parkinson's disease*. Parkinsonism Relat Disord, 2013. 19(2): p. 247–250.

[57] Gui, Y., et al., *NFE2L2 variations reduce antioxidant response in patients with Parkinson disease*. Oncotarget, 2016. 7(10): p. 10756–10764.

[58] Menegon, A., et al., *Parkinson's disease, pesticides, and glutathione transferase polymorphisms*. Lancet, 1998. 352(9137): p. 1344–1346.

[59] Kobayashi, A., et al., *Oxidative and electrophilic stresses activate Nrf2 through inhibition of ubiquitination activity of Keap1*. Mol Cell Biol, 2006. 26(1): p. 221–229.

[60] Osburn, W.O. and T.W. Kensler, *Nrf2 signaling: an adaptive response pathway for protection against environmental toxic insults*. Mutat Res, 2008. 659(1–2): p. 31–39.

[61] He, Q., et al., *Role of alpha-synuclein aggregation and the nuclear factor E2-related factor 2/heme oxygenase-1 pathway in iron-induced neurotoxicity*. Int J Biochem Cell Biol, 2013. 45(6): p. 1019–1030.

[62] Jiang, W.D., et al., *Copper exposure induces oxidative injury, disturbs the antioxidant system and changes the Nrf2/ARE (CuZnSOD) signaling in the fish brain: protective effects of myo-inositol*. Aquat Toxicol, 2014. 155: p. 301–313.

[63] Okuda, B., et al., *Parkinsonism after acute cadmium poisoning*. Clin Neurol Neurosurg, 1997. 99(4): p. 263–265.

[64] Aschner, M., *Manganese: brain transport and emerging research needs*. Environ Health Perspect, 2000. 108 Suppl 3: p. 429–432.

[65] Casalino, E., et al., *The Nrf2 transcription factor contributes to the induction of alpha-class GST isoenzymes in liver of acute cadmium or manganese intoxicated rats: comparison with the toxic effect on NAD(P)H:quinone reductase*. Toxicology, 2007. 237(1–3): p. 24–34.

[66] Dick, S., et al., *Occupational titles as risk factors for Parkinson's disease*. Occup Med (Lond), 2007. 57(1): p. 50–56.

[67] Baltazar, M.T., et al., *Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases—a mechanistic approach*. Toxicol Lett, 2014. 230(2): p. 85–103.

[68] Li, H.Y., S.Y. Wu, and N. Shi, *Transcription factor Nrf2 activation by deltamethrin in PC12 cells: involvement of ROS*. Toxicol Lett, 2007. 171(1–2): p. 87–98.

[69] Fong, C.S., et al., *Pesticide exposure on southwestern Taiwanese with MnSOD and NQO1 polymorphisms is associated with increased risk of Parkinson's disease*. Clin Chim Acta, 2007. 378(1–2): p. 136–141.

[70] Dick, F.D., et al., *Gene-environment interactions in parkinsonism and Parkinson's disease: the Geoparkinson study*. Occup Environ Med, 2007. 64(10): p. 673–680.

[71] Goldman, S.M., et al., *Genetic modification of the association of paraquat and Parkinson's disease*. Mov Disord, 2012. 27(13): p. 1652–1658.

[72] Siebert, A., et al., *Nrf2 activators provide neuroprotection against 6-hydroxydopamine toxicity in rat organotypic nigrostriatal cocultures*. J Neurosci Res, 2009. 87(7): p. 1659–1669.

[73] Duffy, S., A. So, and T.H. Murphy, *Activation of endogenous antioxidant defenses in neuronal cells prevents free radical-mediated damage*. J Neurochem, 1998. 71(1): p. 69–77.

[74] Li, J., J.M. Lee, and J.A. Johnson, *Microarray analysis reveals an antioxidant responsive element-driven gene set involved in conferring protection from an oxidative stress-induced apoptosis in IMR-32 cells*. J Biol Chem, 2002. 277(1): p. 388–394.

[75] Li, J., et al., *Stabilization of Nrf2 by tBHQ confers protection against oxidative stress-induced cell death in human neural stem cells*. Toxicol Sci, 2005. 83(2): p. 313–328.

[76] Jazwa, A., et al., *Pharmacological targeting of the transcription factor Nrf2 at the basal ganglia provides disease modifying therapy for experimental parkinsonism*. Antioxid Redox Signal, 2011. 14(12): p. 2347–2360.

[77] Jakel, R.J., et al., *Nrf2-mediated protection against 6-hydroxydopamine*. Brain Res, 2007. 1144: p. 192–201.

[78] Lastres-Becker, I., et al., *Repurposing the NRF2 activator dimethyl fumarate as therapy against synucleinopathy in Parkinson's disease*. Antioxid Redox Signal, 2016. 25(2): p. 61–77.

[79] Kraft, A.D., D.A. Johnson, and J.A. Johnson, *Nuclear factor E2-related factor 2-dependent antioxidant response element activation by tert-butylhydroquinone and sulforaphane occurring preferentially in astrocytes conditions neurons against oxidative insult.* J Neurosci, 2004. 24(5): p. 1101–1112.

[80] Barone, M.C., G.P. Sykiotis, and D. Bohmann, *Genetic activation of Nrf2 signaling is sufficient to ameliorate neurodegenerative phenotypes in a Drosophila model of Parkinson's disease.* Dis Model Mech, 2011. 4(5): p. 701–707.

[81] Birkmayer, W., et al., *Implications of combined treatment with 'Madopar' and L-deprenil in Parkinson's disease. A long-term study.* Lancet, 1977. 1(8009): p. 439–443.

[82] Carrillo, M.C., et al., *The optimal dosage of (-)deprenyl for increasing superoxide dismutase activities in several brain regions decreases with age in male Fischer 344 rats.* Life Sci, 1993. 52(24): p. 1925–1934.

[83] Xiao, H., et al., *Deprenyl prevents MPP(+)-induced oxidative damage in PC12 cells by the upregulation of Nrf2-mediated NQO1 expression through the activation of PI3K/Akt and Erk.* Toxicology, 2011. 290(2–3): p. 286–94.

[84] Lee, J.M., et al., *NF-E2-related factor-2 mediates neuroprotection against mitochondrial complex I inhibitors and increased concentrations of intracellular calcium in primary cortical neurons.* J Biol Chem, 2003. 278(39): p. 37948–37956.

[85] Ahuja, M., et al., *Distinct Nrf2 signaling mechanisms of fumaric acid esters and their role in neuroprotection against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced experimental Parkinson's-like disease.* J Neurosci, 2016. 36(23): p. 6332–6351.

[86] Jing, X., et al., *Dimethyl fumarate attenuates 6-OHDA-induced neurotoxicity in SH-SY5Y cells and in animal model of Parkinson's disease by enhancing Nrf2 activity.* Neuroscience, 2015. 286: p. 131–140.

[87] Kaidery, N.A., et al., *Targeting Nrf2-mediated gene transcription by extremely potent synthetic triterpenoids attenuate dopaminergic neurotoxicity in the MPTP mouse model of Parkinson's disease.* Antioxid Redox Signal, 2013. 18(2): p. 139–157.

[88] Lee, J.A., et al., *A novel compound ITC-3 activates the Nrf2 signaling and provides neuroprotection in Parkinson's disease models.* Neurotox Res, 2015. 28(4): p. 332–345.

[89] Lim, J.H., et al., *Bromocriptine activates NQO1 via Nrf2-PI3K/Akt signaling: Novel cytoprotective mechanism against oxidative damage.* Pharmacol Res, 2008. 57(5): p. 325–331.

[90] Wu, J.L., et al., *Neuroprotective effects of torularhodin against H_2O_2-induced oxidative injury and apoptosis in PC12 cells.* Pharmazie, 2015. 70(1): p. 17–23.

[91] Park, S.Y., et al., *Neuroprotective effects of alpha-iso-cubebene against glutamate-induced damage in the HT22 hippocampal neuronal cell line.* Int J Mol Med, 2015. 35(2): p. 525–532.