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REVIEW ARTICLE

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Nurr1-Based Therapies for Parkinson's Disease

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SUMMARY

Previous studies have documented that orphan nuclear receptor Nurr1 (also known as NR4A2) plays important roles in the midbrain dopamine (DA) neuron development, differentiation, and survival. Furthermore, it has been reported that the defects in Nurr1 are associated with Parkinson's disease (PD). Thus, Nurr1 might be a potential therapeutic target for PD. Emerging evidence from *in vitro* and *in vivo* studies has recently demonstrated that Nurr1-activating compounds and Nurr1 gene therapy are able not only to enhance DA neurotransmission but also to protect DA neurons from cell injury induced by environmental toxin or microglia-mediated neuroinflammation. Moreover, modulators that interact with Nurr1 or regulate its function, such as retinoid X receptor, cyclic AMP-responsive element-binding protein, glial cell line-derived neurotrophic factor, and Wnt/β-catenin pathway, have the potential to enhance the effects of Nurr1-based therapies in PD. This review highlights the recent progress in preclinical studies of Nurr1-based therapies and discusses the outlook of this emerging therapy as a promising new generation of PD medication.

Introduction

Parkinson's disease (PD), affecting 1.5% of the global population aged over 65 years [1], is a common neurodegenerative disease characterized by the progressive loss of dopamine (DA) neurons in the substantia nigra (SN) pars compacta and the striatal DA deficiency. The main clinical manifestations of PD, including bradykinesia, rigidity, resting tremor, postural instability, and nonmotor symptoms, seriously impair patients' quality of life. Although the pathogenesis of PD is still far from being clearly understood, it has been accepted that the occurrence of PD might attribute to the interplay of genetic and environmental factors [2]. Until now, at least 15 causal genes have been identified to be related to PD, such as α-synuclein, parkin, LARRK2, PINK, and DJ1 [3]. In addition, exposure to certain environmental toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat, has been found to increase the risk of developing PD. Pathologically, PD has also been characterized by the presence of Lewy bodies containing aggregated and misfolded α-synuclein. Moreover, neuroinflammation, reactive oxygen species, mitochondrial dysfunction, and autophagy or proteasome system impairment are considered as major pathogenic contributors to PD [4–6].

Current available PD therapies are mainly aimed at ameliorating motor symptoms associated with DA deficiency, including levodopa, DA agonists, catechol-O-methyltransferase inhibitors, and monoamine oxidase-B inhibitors [7]. Unfortunately, the current pharmaceutical treatments cannot prevent the degeneration of DA neurons and usually lose their efficacy over time, while often accompany severe side effects such as dyskinesia, on–off fluctuation, and peripheral reactions. Other medications such as deep brain stimulation, cell transplantation, and gene therapy have limitations too, concerning the surgery risk and potential safety hazard. In addition, the symptomatic alleviating effects from alternative therapies lack robust improvement, so that they usually just serve as adjunctive medications in clinic. In general, none of these treatments can either slow the disease progression or maintain the viability and functions of DA neurons [8]. Therefore, mechanism-based and/or disease-modifying therapies are in urgent need for better management of PD progression. For example, several preclinical tests of molecular targeted therapies have been conducted and the results seem promising [8]. It is highly speculated that these therapies may not only have symptomatic effects, but also provide neuroprotective and neurorepairable benefits in the treatment of PD [8]. Among those, Nurr1-based therapies for PD have attracted great attention. Thus, in this review, we will highlight the progress of several potential Nurr1-based strategies, including Nurr1-activating compounds and Nurr1 gene therapy, hoping that they may become future medication against PD.

Identifying Nurr1 as a Therapeutic Target of PD

Functions of Nurr1 in DA Neurons

Nurr1 (also known as NR4A2) is a member of NR4A subgroup of nuclear receptor superfamily. The other two members in NR4A subgroup are Nur77 (NR4A1) and Nor1 (NR4A3), which may possess quite different functions as compared with Nurr1 [9]. There are many studies demonstrating that Nurr1 plays an essential role in the development, differentiation, maintenance, and survival of midbrain DA neurons that are mostly affected in the brain of PD [10]. Nurr1, as a transcriptional factor, seems to express earlier than numerous phenotypic markers of DA neurons, such as tyrosine hydroxylase (TH), DA transporter (DAT), aromatic amino acid carboxylase (AADC), and vesicular monoamine transporter (VMAT) [10,11]. There is an age-dependent reduction in Nurr1 expression in the midbrain DA neurons, which arouses much interest because it may possibly explain the high morbidity of PD in the elderly people [12,13]. In addition, it has been reported that Nurr1's immunoreactivity is significantly decreased in the SN of patients with PD [14–16] and numerous polymorphisms and mutations in Nurr1 have been identified to be associated with both familial and sporadic PD [17]. In consistence with those clinical observations, preclinical studies have also demonstrated the essential role of Nurr1 in the midbrain DA neuron development and functional maintenance [11,18–21]. Genetic deletion of Nurr1 in mice can cause the absence of DA neurons in the SN and ventral tegmental area, which may result in the death of the newborn mice [11]. Several DA neuronal phenotypes such as TH and AADC that are important in the neurotransmission of nigrostriatal pathway are missing in Nurr1-deficient mice [10]. Meanwhile, the heterozygous Nurr1-deficient mice show a higher susceptibility of DA neurons to neurotoxins and exert the similar age-dependent DA dysfunction even before the DA neuron loss [18–20]. Moreover, recent Nurr1 conditional ablation mice simulate the early features of PD, showing a series of pathological changes, including DA neuronal loss, striatal DA reduction, and motor deficiency, which could serve as suitable model to study PD [21].

It is clear that Nurr1 works as a transcriptional factor to regulate several genes involved in the DA neuronal phenotypes, ranging from the DA metabolism, neurotransmission, axonal growth, mitochondrial function, and cell survival [17,21–23]. More and more target genes have been found that are transcriptionally controlled by Nurr1 in DA neurons, including Dlk1, Ptpru, Klhl1, GTP, and VIP [24–26]. Emerging evidence has suggested that there is a complicated network between Nurr1 and other essential transcriptional factors during the DA neuron development. Pix3 and Wnt/β-catenin pathways are the two major signaling molecules contributing to the midbrain DA neurogenesis via cooperating with the Nurr1 transcription complex [27–29]. In addition, the overexpression and accumulation of α-synuclein may interrupt the function of Nurr1 through the direct or indirect interference with the signaling of glial cell line-derived neurotrophic factor (GDNF), whose receptor proto-oncogene tyrosine-protein kinase receptor Ret is regulated by Nurr1 [30,31], and the interaction with α-synuclein makes GDNF fail to exert neuroprotective effect in PD [32]. In addition, mitochondrial dysfunction and the correlative oxidative phosphorylation impairment have been indicated as major risk factors of PD [5]. In Nurr1-ablated DA neurons, more than 90% of genes encoding respiratory chains are downregulated [21]. More importantly, Saijo et al. [33] have recently identified a new pathogenic mechanism linking Nurr1 and PD, that is, the suppressive effect of Nurr1 in the production of inflammatory factors induced neuronal injury. Corepressor for repressor element 1 silencing transcription factor (CoREST) repressor complex is identified as an essential modulator in Nurr1-mediated transrepression that inflammatory signals promote the recruitment of CoREST and Nurr1 to the p65 subunit of NF-κB, resulting in the reduction in gene transcription of inflammatory factors [33]. Interestingly, microglia and astrocytes seem to be the primary targets for the neuroprotective effects of Nurr1, rather than DA neurons themselves [33]. These findings provide us an insight understanding of the effect of Nurr1 in PD pathogenesis and open a door for future research for the therapeutic strategies based on Nurr1.

Structure and Potential Activating Sites of Nurr1

Basically, Nurr1 is an immediate early gene and its transcription can be rapidly induced by various stimuli such as cAMP, inflammatory signals, hormones, calcium, and growth factors. These modulators can influence the Nurr1 expression by directly acting on the promoters or transcription regulatory element (cAMP-response element, CArG-like element, SP-1 element) [34,35]. Nurr1, as a member of NR4A subfamily, shares similar structural features with Nur77 and Nor1, including (1) a modulator domain, referred to as activation function (AF)-1 in the N-terminus; (2) a conversed DNA-binding domain (DBD); (3) ligand-binding domain (LBD); and its transactivation-dependent AF-2 in the C-terminus [9]. The high conserved DBD has two zinc fingers, which is able to bind to nerve growth factor-inducible β-binding response element as monomer or homodimers, or Nur response element as homodimers, which are involved in the transcription process to activate TH and DAT genes [36,37]. In addition, Nurr1 and Nur77 can bind as monomers, homodimers, and heterodimers with retinoid X receptor (RXR). These RXR heterodimers bind a motif called DR5 and can be efficiently activated by RXR ligands [38]. Unlike other nuclear receptors, NR4A subfamily does not have LBD cavity due to the occupation of several bulky hydrophobic residues [39]. Instead, its transcriptional activity appears to be dependent on the AF-1 domain [40]. This feature of Nurr1 makes it difficult to discover compounds that can directly activate Nurr1 through LBD. However, several coregulator interaction surfaces in Nurr1 LBD have been identified, such as residues 592, 593, and 577, especially the groove between helices 11 and 12, which provides the possibility in developing Nurr1-activating compounds based on their binding to LBD [41,42]. Furthermore, several compounds have already been identified to activate Nurr1 or Nur77 via their LBDs [43–45]. In general, based on the activated functions of these regions of Nurr1 and numerous studies of Nurr1-activating compounds, it is possible to identify small molecules activating a Nurr1 through its different domains.

Nurr1-Activating Compounds

Great efforts have been taken to explore novel Nurr1-activating compounds in recent years (as summarized in Table 1). These compounds can activate Nurr1 functions and further exert neuroprotective, neurogenic, or antiinflammatory effects.

Mercaptopurine (6-mercaptopurine or 6-MP), an antileukemia drug, is the first identified Nurr1/Nor1 agonist from high-throughput screening, which stimulates Nurr1/Nor1 through directly binding to the N-terminal AF-1 domain [46,47]. In addition to 6-MP, a series of benzimidazole-based compounds with Nurr1-activating properties (EC_{50}: 8–70 nM) have been identified and synthesized [48]. Given that no Nurr1 ligands have been found, a group of compounds with benzimidazole scaffold have been screened through a reporter gene (luciferase) assay, whose expression is regulated by Nurr1-specific DNA-binding elements. However, only the Nurr1 biological functions, not the antiparkinsonian effects of these compounds have been tested.

Previous reports have demonstrated that 1,1-bis (3′-indolyl)-1-(aromatic) methane (C-DIM) analogs can influence the expression of NR4A subfamily in several cancer cells [49–52]. Recently, the antiparkinsonian effects of C-DIM analogs have been identified. Interestingly, it shows similar activating capacities with different p-substituted phenyl (OCH_3, CI, CF_3, Br, t-Bu, CN, I, and OCF_3), suggesting a structure-activating relation (SAR) existing in these compounds that contain a bis (3′-indolyl) moiety. In addition, Li et al. have demonstrated that both N- and C-terminal domains are involved in the activation of Nurr1, but without evidence to confirm the direct binding between C-DIM analogs and Nurr1 [52]. Among these C-DIM analogs, C-DIM5 and C-DIM8 have a higher affinity for Nur77 but with opposite effect [49,51]. After a comparative analysis, C-DIM12 (higher affinity for Nurr1) has the most potent neuroprotective activity and anti-inflammatory effect in MPTP-lesioned rat model of PD [53]. It could enhance the expressions of Nurr1 and Nurr1-regulated proteins such as TH and DAT, and Nurr1-mediated recruitment of CoREST and the NF-κB-mediated inflammatory gene expression are suppressed in SN [53–55].

Another Nurr1 activator, isoxazolo-pyridinone 7e (IP7e), has been reported to attenuate the inflammation and neurodegeneration via inhibiting NF-κB-dependent process [56]. IP7e seems to be a promising candidate due to its high oral bioavailability of 95% plus rapid and extensive brain absorption and distribution [57]. However, the Nurr1-activating effect of IP7e has only been tested in multiple sclerosis models, not in PD models. As for PD, the analog of isoxazolo-pyridinone derivative, SH1, has been demonstrated to be effective to improve behavioral performance in lactacystin-lesioned PD mouse model, of which inhibition of microglia-mediated neuroinflammation and increasing the DA-specific phenotypes may be the main mechanisms to explain its effect [58]. In addition, SA00025, another novel Nurr1 agonist (EC_{50}: 2.5 nM), shows a partial neuroprotective effect in PD models induced by inflammatory stimulant poly (I:C) and 6-hydroxydopamine (6-OHDA). It can modulate several DA target genes and display antiinflammatory activity by reducing the activation of microglia and astrocytes [59].

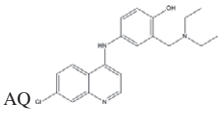
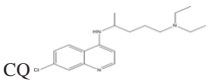
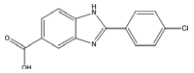
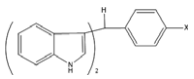
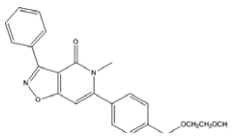
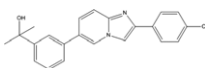
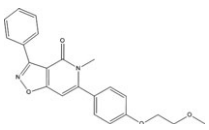
While all the above compounds have been identified as Nurr1-activating compounds, none of them are shown to activate Nurr1 by direct physical interaction with LBD. Strikingly, Kim et al. have recently identified antimalarial drugs amodiaquine (AQ) and chloroquine (CQ) together with a pain-relieving drug glafenine as a novel group of Nurr1 activators and finally demonstrated that AQ/CQ (EC50: 20–50 μM) can interact with Nurr1-LBD via direct physical binding [43]. They used a series of analyses, including Biacore S51 SPR sensor, fluorescence quenching analysis, a radioligand-binding assay by [^{3}H]-CQ, and nuclear magnetic resonance to estimate this phenomenon. This finding advances our current understanding of the LBD binding properties and opens the door for further research and development of Nurr1 agonists. Interestingly, these compounds contain an identical 4-amino-7-chloroquinoline scaffold, which may predict a possible SAR. As for the underlying mechanisms, the inhibition of microglia-mediated neuroinflammation and increase in DA-specific gene expression are involved in the antiparkinsonian effect of AQ/CQ. Moreover, the autophagy-regulating effects of AQ/CQ may also predict potential interactions between Nurr1 and autophagy for their antiparkinsonian effects [60].

These Nurr1-activating compounds provide much promising possibilities for PD treatment and most of them exert the antiparkinsonian effect through both the activating and suppressing functions of Nurr1. Although these compounds have the ability to activate Nurr1, it is still not clear the exact regions of Nurr1 targeted by these compounds. Among them, only 6-MP and AQ have been confirmed to directly bind to the AF-1 or LBD of Nurr1, so further studies are in urgent need to discover the specific binding regions on Nurr1. Furthermore, the pharmacodynamic and pharmacokinetic properties and the side effects of those compounds are also required to evaluate. As the other two members of NR4A subfamily, Nur77 and Nor1, share high similar structure with Nurr1, and they are both involved in the regulation of neurological functions and inflammation, it is of importance to test the specificity of the existing Nurr1-activating compounds [61,62]. Wei et al. have recently indicated that Nurr1 and Nur77 might present a contradirectionally coupling interaction in memantine-mediated neuroprotection [63]. This complicated network makes it very difficult to predict the therapeutic outcome if both Nurr1 and its homologs are activated through the conserved regions. Moreover, SAR has been a research hotpot recently, especially after the presentation of the Nurr1-activating effects of C-DIM analogs and AQ/CQ. Meanwhile, we should notice the fact that subtle alternations of the functional structure might result in a great or even opposite effects [49,51]. Only after those concerns are well addressed, we might be able to determine whether Nurr1-activating compounds can provide an alternative therapy for PD.

Nurr1 Modulators

In addition to activate Nurr1 by recognition on the specific target region of Nurr1, some other compounds, such as DA agonists, memantine, retinoic acid-loaded polymeric nanoparticles (RA-NPs), and herbal extracts (as summarized in Table 2), have also been demonstrated to upregulate Nurr1 expression in

Table 1 The characteristics of Nurr1-activating compounds

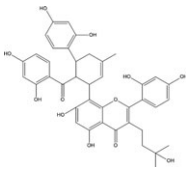
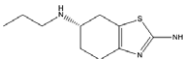
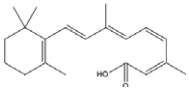
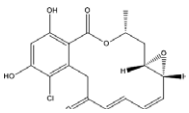
Compounds	Structural formula	Targeted regions	Animal/cell models	Outcomes	References
6-MP		AF-1 domain in the N-terminus of Nurr1	CV-1 cells	Activate both Nurr1 and Nor-1	[46,47]
AQ/CQ	 AQ	Putative LBD resides in the C-terminus of Nurr1	6-OHDA lesioned rats	Improve behavioral deficits without any dyskinesia	[43]
	 CQ		Primary DA neurons, PC12 cells	Increase the expression of DA specific genes; inhibit microglia-mediated neuroinflammation; protect DA neurons against 6-OHDA-induced neurotoxicity	
Benzimidazole-based compounds		Putative LBD resides in the C-terminus of Nurr1	None	Activate Nurr1 by increasing the activity of luciferase (a reporter for Nurr1 monomer binding)	[48]
C-DIM compounds		Both N- and C-terminal regions of Nurr1	MPTP lesioned rats	Increase the expression of DA specific genes; inhibit microglia-mediated neuroinflammation; attenuate DA neurons loss; supress expression of NF-κB in SN	[53]
			BV-2 microglia cells	Suppress NF-κB–induced gene expression in microglia	[54]
			N2A, N27	Protect DA neurons against 6-OHDA-induced neurotoxicity	[55]
IP7e		Putative LBD resides in the C-terminus of Nurr1	Multiple sclerosis models	Inhibit expression of NF-κB	[56,57]
SA00025		Unknown	6-OHDA lesioned rats	Increase the expression of DA specific genes; inhibit microglia-mediated neuroinflammation; preserve TH positive fibers in the striatum from 6-OHDA	[59]
SH1		Unknown	Lactacystin leisioned mice	Improve rotarod performance; increase the expression of DA specific genes; inhibit microglia-mediated neuroinflammation; protect DA neurons against lactacystin	[58]

preclinical tests of PD treatment although there have not any report to confirm that they can activate Nurr1 by direct binding [63–69].

The neuroprotective effect of DA agonists has been a controversial topic for decades [70]. One recent clinical trial supports that DA agonists can exert neuroprotection by inducing Nurr1 expression in peripheral blood mononuclear cells [71]. Additionally, in DA neuron cell lines, D2/D3 agonist pramipexole has a profound effect to increase Nurr1 expression, which precedes the upregulation of DAT and VMAT2 expressions [64], suggesting that Nurr1 may serve as a key target for DA agonist-mediated neuroprotection.

Memantine, an N-methyl-D-aspartate receptor antagonist, has been demonstrated to restore PC12 cell survival from 6-OHDA-induced neurotoxicity through upregulating Nurr1 and downregulating Nur77 and partially inhibit migration of Nur77 from nucleus to mitochondria [63]. Different from Nurr1, Nur77 usually triggers apoptotic process when migrates to mitochondria

Table 2 The characteristics of Nurr1 modulators

Compounds	Structural formula	Targeted regions	Animal/cell models	Outcomes	References
BHD	None	Unknown	6-OHDA lesioned rats	Improve behavioral deficits; increase Nurr1 mRNA expression and TH positive cell; repairing the injured neuron in SN	[68]
EGb 761	None	Unknown	MPTP lesioned mice	Increase the expression of Nurr1 and other DA specific genes	[66]
Memantine		NMDA receptor	PC12	Upregulate Nurr1 and downregulate Nur77; inhibit translocation of Nur77 to cytosol	[63]
Moracenin D		Unknown	SH-SY5Y	Protect SH-SY5Y cells against dopamine-induced cell loss; increase Nurr1 mRNA; decrease α-synuclein mRNA	[65]
Pramipexole		DA receptors	SH-SY5Y	Increase the expression of Nurr1 and other DA specific genes	[64]
RA-NPs		RAR-RXR heterodimers	MPTP lesioned mice	Protect DA neurons against MPTP; preserve TH positive fibers in the striatum from MPTP; increase Nurr1 and Pitx3 expression	[69]
Radicicol		Unknown	SH-SY5Y	Increase the Nurr1 expression	[67]

NMDA, N-methyl-D-aspartate.

and induces inflammation via NF-κB pathway [72,73]. Interestingly, administration of DA activators could decrease Nur77 expression [74], suggesting that Nurr1 together with the contradirectional coupling of Nurr1/Nur77 might be involved in PD pathogenesis.

Besides those chemically synthesized compounds, several Nurr1-modulators from natural source, such as moracenin D, EGb 761, radicicol, and Bushen Huoxue decoction (BHD), are also effective in PD therapy [65–68]. Moracenin D, an extract from Mori Cortex radices, significantly upregulates Nurr1 expression and downregulates α-synuclein expression [65]. EGb 761, extracted from Ginkgo biloba leaves, has been applied in clinical trials of treating several neuropsychiatric diseases [75,76]. It also exerts neuroprotective effect in MPTP-lesioned mice via increasing the expression of a series of DA-related genes, of which Nurr1 is increased by 148% in SN [66]. Our previous study has shown that radicicol could induce HSP70 expression in SH-SY5Y cells against rotenone-induced apoptosis through the inhibition of P53 and induction of Nurr1 [67]. It has been reported that the medical decoction BHD could also increase Nurr1 expression. The antiparkinsonian effect of BHD has been tested in clinical trials [68,77].

Biomaterials as therapeutic tools have been developed to help Nurr1-based PD therapy recently. Retinoic acid (RA) can enhance the survival and maturation of neuronal cells and RA receptors are highly expressed in DA neurons [78]. In contrast to conventional RA formulations, the recently developed novel nanoparticles coupled with RA could rapidly transport into cells to release RA, and exert neuroprotection against DA neuronal damage in MPTP mouse model of PD. More importantly, RA-NP administration increases the expression levels of Pitx3 and Nurr1, showing its supportive effect on the development and functional maintenance of DA neurons in PD [69].

Although the specific mechanisms for the Nurr1 upregulating effects of the above-mentioned compounds, natural products, and biomaterials still remain poorly understood, those candidates have a common feature to promote Nurr1 expression or functions, and part of those candidates have been shown to exert potent

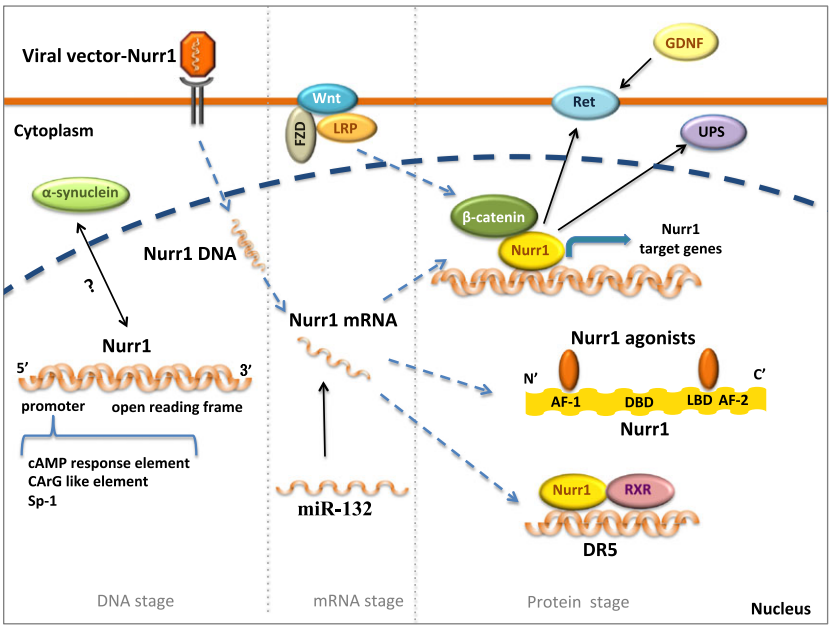


Figure 1 Nurr1 pathway and Nurr1-based therapies for Parkinson's disease. This figure summarizes the present potential Nurr1-based therapies, including Nurr1 agonists, gene therapy, and potential regulatory targets of Nurr1 expression. Abbreviations: AF, activation function; cAMP, cyclic adenosine monophosphate; DBD, DNA-binding domain; FZD, frizzled; GDNF, glial cell line-derived neurotrophic factor; LBD, ligand-binding domain; LRP, lipoprotein receptor; microRNA-132, miR-132; Ret, proto-oncogene tyrosine-protein kinase receptor; RXR, retinoid X receptor; UPS, ubiquitin proteasome system.

antiparkinsonian properties in clinic [64,68]. Further exploration of those modulators should focus on identifying their direct binding regions to Nurr1 and the Nurr1 upstream molecules. All of these efforts may lead to a better understanding of their Nurr1 upregulating mechanisms and discovery of more potent Nurr1-modulators for the treatment of PD.

Nurr1 Gene Therapy

Recent animal trials of Nurr1 gene therapy have shown a gratifying progress. Two months after midbrain AAV-Nurr1/Foxa2 injection, the DA neuron density and neurotrophic factor expression are significantly increased in MPTP-lesioned mice model of PD together with a suppression of proinflammatory cytokine secretion [79]. Remarkably, this Nurr1/Foxa2-mediated cytoprotective effect is observed even 1 year after injection, suggesting that transfection of these genes is an intriguing approach in PD therapy [79]. Although the outcome of this trial seems exciting, the safety and feasibility of Nurr1 gene therapy still needs further verification. Firstly, the long-term effect of constitutive overexpression is not clear. Secondly, this therapeutic strategy has only been tested in toxin-induced animal models (such as MPTP), but not in transgenic PD models that may mimic a broader pathology of PD. Thirdly, to achieve a better therapeutic outcome, the time window of treatment and a controllable regulation of Nurr1 expression are yet to be further explored.

Interestingly, it has been reported that GDNF which fails to restore DA neuron loss is due to the toxicity of α-synuclein [32]. Considering that the overexpression of Nurr1 may protect DA neurons against α-synuclein [32], a combinatory delivery of AAV-Nurr1 with GDNF or neurturin into the midbrain might improve the outcome of the existing preclinical or clinical trials, and predict a very attractive alternative therapy for PD [80].

Prospect of Nurr1-Based Therapy for PD

Nurr1 serves as a promising target for PD therapy by promoting the survival or genesis of DA neurons [17]. As Nurr1 is encoded by an immediate early gene, many modulators are implicated in the Nurr1 pathway. A wide range of physiological signals, such as prostaglandins, fatty acids, calcium, stress, growth factors, inflammatory cytokines, and even physical stimuli, such as membrane depolarization, have been shown to induce Nurr1 expression [81–86]. Besides, aging is a negative factor causing the decline of Nurr1 expression [17], which in turn may reduce the compensatory protective capability of Nurr1 and increase the susceptibility to develop PD. Restoring the impaired Nurr1 functions by Nurr1-based therapies could provide tentative therapeutic strategies for PD.

RXR, neurotropic factors, cAMP-responsive element-binding protein (CREB), and Wnt/β-catenin pathway seem to play positive roles in regulating Nurr1 expression [87–89]. Thus, we propose that it may be an alternative way to facilitate Nurr1 functions through activating or increasing those modulators. Inspiringly, RXR ligands, such as docosahexaenoic acid, bexarotene, LG100268, and XCT0139508, have been demonstrated to protect DA neurons through interaction with Nurr1/RXR heterodimers [87,90,91]. Although the biological functions of bexarotene still remain to be defined, one recent study has revealed that bexarotene might have the capacity to rescue the disrupted GDNF signaling and regulate oxidative phosphorylation and Nurr1-related genes [92]. In addition, animal tests have indicated that transplantation of GDNF-pretreated NSCs could dramatically enhance the expression of Nurr1 and TH [88]. Given that GDNF has a poor blood–brain barrier penetrating feature, GDNF inducers, such as telmisartan, calcitriol, rhus verniciflua stokes, and cabergoline, can stimulate GDNF expression [93–98]. Moreover, CREB as an upstream regulator of Nurr1 may play an

important role in the process of most modulator-mediated Nurr1 upregulation, such as prostaglandin E2, thromboxane A2, vascular endothelial growth factor, and N-methyl-d-aspartate [81,84,99,100]. Thus, CREB activators or other cAMP increasing agents may also have the capacity to restore Nurr1 functions. However, considering that CREB activates many signal pathways, they in general may not be suitable to treat PD. Furthermore, several studies have indicated that activation of Wnt/β-catenin signaling pathway could induce the transcription of Nurr1 [101–103]. Given that Wnt/β-catenin pathway is involved in the PD pathogenesis and exogenous Wnt1 could attenuate DA neuron loss in animal models of PD [104,105], we propose that activating Wnt/β-catenin pathway, such as GSK-3β antagonists, may be effective in treating PD through the enhancement of Nurr1 expression [103]. Furthermore, Nurr1 activity can be affected by several PD-related molecules, such as α-synuclein and microRNA-132 (miR-132) [106,107]. Therefore, these molecules may be potential therapeutic targets against PD. Indeed, it has been reported that oligomer selective α-synuclein antibodies and prolyl oligopeptidase inhibitors are effective in PD models through decelerating the accumulation of α-synuclein [108–110]. It is plausible that Nurr1 may be involved in the antiparkinsonian effects of those compounds. Moreover, several studies have described a potential role of microRNAs in PD pathogenesis [111,112], and miR-132 can directly inhibit Nurr1 expression [107]; thus, miR-132 antagonist may be a potential modulator for PD treatment [107].

Nurr1-based cell transplantation is another therapy currently under investigation. Several animal experiments have shown the therapeutic potential of Nurr1-based cell transplantation, not only in ameliorating the behavioral abnormality, but also restoring the DA neuron deficits [113–118]. However, they have not been tested in patients with PD concerning the biosafety and long-term efficacy of cell transplantation in general [119].

It has been noticed that Nurr1 modulators may have other functions in addition to regulating Nurr1, and most of those compounds have not been evaluated in PD models yet, nor their side effects have been systematically determined. Furthermore, Nurr1 also expresses in nonnervous system [120]. Therefore, the non-neurological effects of Nurr1 should not be neglected.

Conclusion

In summary, Nurr1-activating compounds, Nurr1 modulators, and Nurr1-based gene therapy have shown their therapeutic potential for PD treatment (as summarized in Figure 1). The pharmacological effects of Nurr1-based therapies against PD are proposed as follows: (1) increase the expression of DA-related genes; (2) protect or repair DA neurons against neurotoxins; (3) inhibit the microglia activation and suppress neuroinflammation. These versatile functions make Nurr1 an attracting target for treating PD. Further studies should focus on identifying small molecules, which can effectively activate Nurr1 functions through either direct binding to the specific regions of Nurr1 or modulating the Nurr1-related signaling. Furthermore, the study of Nurr1 conditional knockout mouse models would be beneficial to better understand the critical roles of Nurr1 in PD pathogenesis, and help screen more specific Nurr1-activating or Nurr1-modulating compounds. Although it is still a long way to go for the clinical use in patients with PD, the Nurr1-based therapies provide a very promising outlook as the next-generation PD treatment.

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Conflict of Interests

The authors confirm that this article content has no conflict of interest.

References

1. Meissner WG, Frasier M, Gasser T, et al. Priorities in Parkinson's disease research. *Nat Rev Drug Discov* 2011;**10**:377–393.
2. Le WD, Chen S, Jankovic J. Etiopathogenesis of Parkinson disease: a new beginning? *Neuroscientist* 2009;**15**:28–35.
3. Verstraeten A, Theuns J, Van Broeckhoven C. Progress in unraveling the genetic etiology of Parkinson disease in a genomic era. *Trends Genet* 2015;**31**:140–149.
4. Nolan YM, Sullivan AM, Toulouse A. Parkinson's disease in the nuclear age of neuroinflammation. *Trends Mol Med* 2013;**19**:187–196.
5. Zuo L, Motherwell MS. The impact of reactive oxygen species and genetic mitochondrial mutations in Parkinson's disease. *Gene* 2013;**532**:18–23.
6. Hirsch EC, Jenner P, Przedborski S. Pathogenesis of Parkinson's disease. *Mov Disord* 2013;**28**:24–30.
7. Goetz CG, Pal G. Initial management of Parkinson's disease. *BMJ* 2014;**349**:g6258.
8. Dong J, Cui Y, Li S, Le W. Current pharmaceutical treatments and alternative therapies of Parkinson's diseases. *Curr Neuropharmacol* 2015. [Epub ahead of print].
9. Giguere V. Orphan nuclear receptors: from gene to function. *Endocr Rev* 1999;**20**:689–725.
10. Jankovic J, Chen S, Le WD. The role of Nurr1 in the development of dopaminergic neurons and Parkinson's disease. *Prog Neurobiol* 2005;**77**:128–138.
11. Zetterström RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T. Dopamine neuron agenesis in Nurr1-deficient mice. *Science* 1997;**276**:248–250.
12. Chu Y, Kompoliti K, Cochran EJ, Mufson EJ, Kordower JH. Age-related decreases in Nurr1 immunoreactivity in the human substantia nigra. *J Comp Neurol* 2002;**450**:203–214.
13. Chu Y, Kordower JH. Age-associated increases of α-synuclein in monkeys and humans are associated with nigrostriatal dopamine depletion: is this the target for Parkinson's disease? *Neurobiol Dis* 2007;**25**:134–149.
14. Chu Y, Le W, Kompoliti K, Jankovic J, Mufson EJ, Kordower JH. Nurr1 in Parkinson's disease and related disorders. *J Comp Neurol* 2006;**494**:495–514.
15. Moran LB, Croisier E, Duke DC, et al. Analysis of alpha-synuclein, dopamine and parkin pathways in neuropathologically confirmed parkinsonian nigra. *Acta Neuropathol* 2007;**113**:253–263.
16. Le W, Pan T, Huang M, et al. Decreased NURR1 gene expression in patients with Parkinson's disease. *J Neurol Sci* 2008;**273**:29–33.
17. Decressac M, Volakakis N, Björklund A, Perlmann T. NURR1 in Parkinson disease—from pathogenesis to therapeutic potential. *Nat Rev Neurol* 2013;**9**:629–636.
18. Le W, Conneely OM, He Y, Jankovic J, Appel SH. Reduced Nurr1 expression increases the vulnerability of mesencephalic dopamine neurons to MPTP-induced injury. *J Neurochem* 1999;**73**:2218–2221.
19. Le W, Conneely OM, Zou L, et al. Selective agenesis of mesencephalic dopaminergic neurons in Nurr1-deficient mice. *Exp Neurol* 1999;**159**:451–458.
20. Jiang C, Wan X, He Y, Pan T, Jankovic J, Le W. Age-dependent dopaminergic dysfunction in Nurr1 knockout mice. *Exp Neurol* 2005;**191**:154–162.
21. Kadkhodaei B, Alvarsson A, Schintu N, et al. Transcription factor Nurr1 maintains fiber integrity and nuclear-encoded mitochondrial gene expression in dopamine neurons. *Proc Natl Acad Sci USA* 2013;**110**:2360–2365.

22. Heng X, Jin G, Zhang X, et al. Nurr1 regulates Top IIβ and functions in axon genesis of mesencephalic dopaminergic neurons. *Mol Neurodegener* 2012;**7**:4.
23. Eells JB, Misler JA, Nikodem VM. Reduced tyrosine hydroxylase and GTP cyclohydrolase mRNA expression, tyrosine hydroxylase activity, and associated neurochemical alterations in Nurr1-null heterozygous mice. *Brain Res Bull* 2006;**70**:186–195.
24. Jacobs FMJ, van der Linden AJ, Wang Y, et al. Identification of Dlk1, Ptpru and Klhl1 as novel Nurr1 target genes in meso-diencephalic dopamine neurons. *Development* 2009;**136**:2363–2373.
25. Gil M, McKinney C, Lee MK, Eells JB, Phyillaier M, Nikodem VM. Regulation of GTP cyclohydrolase I expression by orphan receptor Nurr1 in cell culture and in vivo. *J Neurochem* 2007;**101**:142–150.
26. Luo Y, Henricksen LA, Giuliano RE, Prifti L, Callahan LM, Federoff HJ. VIP is a transcriptional target of Nurr1 in dopaminergic cells. *Exp Neurol* 2007;**203**:221–232.
27. Castelo-Branco G, Wagner J, Rodriguez FJ, et al. Differential regulation of midbrain dopaminergic neuron development by Wnt-1, Wnt-3a, and Wnt-5a. *Proc Natl Acad Sci USA* 2003;**100**:12747–12752.
28. Joksimovic M, Yun BA, Kittappa R, et al. Wnt antagonism of Shh facilitates midbrain floor plate neurogenesis. *Nat Neurosci* 2009;**12**:125–131.
29. Saucedo-Cardenas O, Quintana-Hau JD, Le WD, et al. Nurr1 is essential for the induction of the dopaminergic phenotype and the survival of ventral mesencephalic late dopaminergic precursor neurons. *Proc Natl Acad Sci USA* 1998;**95**:4013–4018.
30. Lin X, Parisiadou L, Sgobio C, et al. Conditional expression of Parkinson's disease-related mutant α-synuclein in the midbrain dopaminergic neurons causes progressive neurodegeneration and degradation of transcription factor nuclear receptor related 1. *J Neurosci* 2012;**32**:9248–9264.
31. Wallén Aa, Castro DS, Zetterström RH, et al. Orphan nuclear receptor Nurr1 is essential for Ret expression in midbrain dopamine neurons and in the brain stem. *Mol Cell Neurosci* 2001;**18**:649–663.
32. Decressac M, Kadkhodaei B, Mattsson B, Laguna A, Perlmann T, Bjorklund A. α-Synuclein-induced down-regulation of Nurr1 disrupts GDNF signaling in nigral dopamine neurons. *Sci Transl Med* 2012;**4**:163ra156.
33. Saijo K, Winner B, Carson CT, et al. A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. *Cell* 2009;**137**:47–59.
34. Maxwell Ma, Muscat GEO. The NR4A subgroup: immediate early response genes with pleiotropic physiological roles. *Nucl Recept Signal* 2006;**4**:002.
35. Ichinose H, Ohye T, Suzuki T, et al. Molecular cloning of the human Nurr1 gene: characterization of the human gene and cDNAs. *Gene* 1999;**230**:233–239.
36. Paulsen RF, Granas K, Johnsen H, Rolseth V, Sterri S. Three related brain nuclear receptors, NGFI-B, Nurr1, and NOR-1, as transcriptional activators. *J Mol Neurosci* 1995;**6**:249–255.
37. Maira M, Martens C, Philips A, Drouin J. Heterodimerization between members of the Nur subfamily of orphan nuclear receptors as a novel mechanism for gene activation. *Mol Cell Biol* 1999;**19**:7549–7557.
38. Perlmann T, Jansson L. A novel pathway for vitamin A signaling mediated by RXR heterodimerization with NGFI-B and NURR1. *Genes Dev* 1995;**9**:769–782.
39. Wang Z, Benoit G, Liu J, et al. Structure and function of Nurr1 identifies a class of ligand-independent nuclear receptors. *Nature* 2003;**423**:555–560.
40. Maira M, Martens C, Batsché E, Gauthier Y, Drouin J. Dimer-specific potentiation of NGFI-B (Nur77) transcriptional activity by the protein kinase A pathway and AF-1-dependent coactivator recruitment. *Mol Cell Biol* 2003;**23**:763–776.
41. Codina A, Benoit G, Gooch JT, Neuhaus D, Perlmann T, Schwabe JWR. Identification of a novel Co-regulator interaction surface on the ligand binding domain of Nurr1 using NMR footprinting. *J Biol Chem* 2004;**279**:53338–53345.
42. Volakakis N, Malewicz M, Kadkhodai B, Perlmann T, Benoit G. Characterization of the Nurr1 ligand-binding domain co-activator interaction surface. *J Mol Endocrinol* 2006;**37**:317–326.
43. Kim CH, Han BS, Moon J, et al. Nuclear receptor Nurr1 agonists enhance its dual functions and improve behavioral deficits in an animal model of Parkinson's disease. *Proc Natl Acad Sci* 2015;**112**:8756–8761.
44. Zhan Y, Du X, Chen H, et al. Cytosporone B is an agonist for nuclear orphan receptor Nur77. *Nat Chem Biol* 2008;**4**:548–556.
45. Chintharlapalli S, Burghardt R, Papineni S, Ramaiah S, Yoon K, Safe S. Activation of Nur77 by selected 1,1-Bis (3′-indolyl)-1-(p-substituted phenyl)methanes induces apoptosis through nuclear pathways. *J Biol Chem* 2005;**280**:24903–24914.
46. Ordentlich P, Yan Y, Zhou S, Heyman RA. Identification of the antineoplastic agent 6-mercaptopurine as an activator of the orphan nuclear hormone receptor Nurr1. *J Biol Chem* 2003;**278**: 24791–24799.
47. Wansa KDSA, Harris JM, Yan G, Ordentlich P, Muscat GEO. The AF-1 domain of the orphan nuclear receptor NOR-1 mediates trans-activation, coactivator recruitment, and activation by the purine anti-metabolite 6-mercaptopurine. *J Biol Chem* 2003;**278**:24776–24790.
48. Dubois C, Hengerer B, Mattes H. Identification of a potent agonist of the orphan nuclear receptor Nurr1. *ChemMedChem* 2006;**1**:955–958.
49. Hedrick E, Lee SO, Kim G, et al. Nuclear receptor 4A1 (NR4A1) as a drug target for renal cell adenocarcinoma. *PLoS ONE* 2015;**10**:e0128308.
50. Inamoto T, Papineni S, Chintharlapalli S, Cho SD, Safe S, Kamat AM. 1,1-Bis(3′-indolyl)-1-(p-chlorophenyl) methane activates the orphan nuclear receptor Nurr1 and inhibits bladder cancer growth. *Mol Cancer Ther* 2008;**7**:3825–3833.
51. Yoon K, Lee SO, Cho SD, Kim K, Khan S, Safe S. Activation of nuclear TR3 (NR4A1) by a diindolylmethane analog induces apoptosis and proapoptotic genes in pancreatic cancer cells and tumors. *Carcinogenesis* 2011;**32**:836–842.
52. Li X, Lee SO, Safe S. Structure-dependent activation of NR4A2 (Nurr1) by 1,1-bis(3′-indolyl)-1-(aromatic) methane analogs in pancreatic cancer cells. *Biochem Pharmacol* 2012;**83**:1445–1455.
53. De Miranda BR, Popichak KA, Hammond SL, Miller JA, Safe S, Tjalkens RB. Novel para-phenyl substituted diindolylmethanes protect against MPTP neurotoxicity and suppress glial activation in a mouse model of Parkinson's disease. *Toxicol Sci* 2015;**143**:360–373.
54. De Miranda BR, Popichak KA, Hammond SL, et al. The Nurr1 activator 1,1-Bis(3′-Indolyl)-1-(p-Chlorophenyl) methane blocks inflammatory gene expression in BV-2 microglial cells by inhibiting nuclear factor κB. *Mol Pharmacol* 2015;**87**:1021–1034.
55. Hammond SL, Safe S, Tjalkens RB. A novel synthetic activator of Nurr1 induces dopaminergic gene expression and protects against 6-hydroxydopamine neurotoxicity in vitro. *Neurosci Lett* 2015;**607**:83–89.
56. Montarolo F, Raffaele C, Perga S, et al. Effects of isoxazolo-pyridinone 7e, a potent activator of the Nurr1 signaling pathway, on experimental autoimmune encephalomyelitis in mice. *PLoS ONE* 2014;**9**:e108791.
57. Hintermann S, Chiesi M, von Krosigk U, Mathé D, Felber R, Hengerer B. Identification of a series of highly potent activators of the Nurr1 signaling pathway. *Bioorg Med Chem Lett* 2007;**17**:193–196.
58. Zhang Z, Li X, Xie W, et al. Anti-parkinsonian effects of Nurr1 activator in ubiquitin-proteasome system impairment induced animal model of Parkinson's disease. *CNS Neurol Disord Drug Targets* 2012;**11**:768–773.
59. Smith GA, Rocha EM, Rooney T, et al. A Nurr1 agonist causes neuroprotection in a Parkinson's disease lesion model primed with the toll-like receptor 3 dsRNA inflammatory stimulant poly(I:C). *PLoS ONE* 2015;**10**: e0121072.
60. Qiao S, Tao S, Rojo de la Vega M, et al. The antimalarial amodiaquine causes autophagic-lysosomal and proliferative blockade sensitizing human melanoma cells to starvation- and chemotherapy-induced cell death. *Autophagy* 2013;**9**:2087–2102.
61. Eells JB, Wilcots J, Sisk S, Guo-Ross SX. NR4A gene expression is dynamically regulated in the ventral tegmental area dopamine neurons and is related to expression of dopamine neurotransmission genes. *J Mol Neurosci* 2012;**46**:545–553.
62. McMorrow JP, Murphy EP. Inflammation: a role for NR4A orphan nuclear receptors? *Biochem Soc Trans* 2011;**39**:688–693.
63. Wei X, Gao H, Zou J, et al. Contra-directional coupling of Nur77 and Nurr1 in Neurodegeneration: a novel mechanism for memantine-induced anti-inflammation and anti-mitochondrial impairment. *Mol Neurobiol* 2015. [Epub ahead of print].
64. Pan T, Xie W, Jankovic J, Le W. Biological effects of pramipexole on dopaminergic neuron-associated genes: relevance to neuroprotection. *Neurosci Lett* 2005;**377**:106–109.
65. Ham A, Lee HJ, Hong SS, Lee D, Mar W. Moracenin D from Mori Cortex radicis protects SH-SY5Y cells against dopamine-induced cell death by regulating nurr1 and α-synuclein expression. *Phytother Res* 2012;**26**:620–624.
66. Rojas P, Ruiz-Sánchez E, Rojas C, Ogren SO. Ginkgo biloba extract (EGb 761) modulates the expression of dopamine-related genes in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in mice. *Neuroscience* 2012;**223**:246–257.
67. Pan T, Xie W, Jankovic J, Le WD. Radicicol induces heat shock protein expression and neuroprotection against rotenone-mediated apoptosis in SH-SY5Y cells. *Mov Disord* 2005;**20**:S86–S86.
68. Li M, Yang MH, Liu Y, Luo XD, Chen JZ, Shi HJ. Analysis of clinical evaluation of response to treatment of Parkinson's disease with integrated Chinese and Western medicine therapy. *Chin J Integr Med* 2015;**21**:17–21.
69. Esteves M, Cristóvão AC, Saraiva T, et al. Retinoic acid-loaded polymeric nanoparticles induce neuroprotection in a mouse model for Parkinson's disease. *Front Aging Neurosci* 2015;**7**:20.
70. Blandini F, Armentero MT. Dopamine receptor agonists for Parkinson's disease. *Expert Opin Investig Drugs* 2014;**23**:387–410.
71. Zhang LM, Sun CC, Mo MS, et al. Dopamine agonists exert Nurr1-inducing effect in peripheral blood mononuclear cells of patients with Parkinson's disease. *Chin Med J. (Engl)* 2015;**128**:1755–1760.
72. Kiss B, Tóth K, Sarang Z, Garabuczi É, Szondy Z. Retinoids induce Nur77-dependent apoptosis in mouse thymocytes. *Biochim Biophys Acta* 2015;**1853**:660–670.
73. Li L, Liu Y, Chen H, et al. Impeding the interaction between Nur77 and p38 reduces LPS-induced inflammation. *Nat Chem Biol* 2015;**11**:339–346.
74. Gervais J, Soghomonian JJ, Richard D, Rouillard C. Dopamine and serotonin interactions in the modulation of the expression of the immediate-early transcription factor, nerve growth factor-inducible B, in the striatum. *Neuroscience* 1999;**91**:1045–1054.

75. Von Gunten A, Schlaefke S, Überla K. Efficacy of Ginkgo biloba extract EGb 761(®) in dementia with behavioural and psychological symptoms: a systematic review. *World J Biol Psychiatry* 2015;1–12.
76. Chen X, Hong Y, Zheng P. Efficacy and safety of extract of ginkgo biloba as an adjunct therapy in chronic schizophrenia: a systematic review of randomized, double-blind, placebo-controlled Studies with meta-analysis. *Psychiatry Res* 2015;**228**:121–127.
77. Yang MH, Wang HM, Liu Y. Effect of Bushen Huoxue Decoction on the orphan receptor and tyrosine hydroxylase in the brain of rats with Parkinson's disease. *Chin J Integr Med* 2011;**17**:43–47.
78. Katsuki H, Kurimoto E, Takemori S, et al. Retinoic acid receptor stimulation protects midbrain dopaminergic neurons from inflammatory degeneration via BDNF-mediated signaling. *J Neurochem* 2009;**110**:707–718.
79. Oh S, Chang M, Song J, et al. Combined Nurr1 and Foxa2 roles in the therapy of Parkinson's disease. *EMBO Mol Med* 2015;**7**:510–525.
80. Bartus RT, Baumann TL, Siffert J, et al. Safety/feasibility of targeting the substantia nigra with AAV2-neurturin in Parkinson patients. *Neurology* 2013;**80**:1698–1701.
81. Ji R, Sanchez CM, Chou CL, Chen XB, Woodward DF, Regan JW. Prostanoid EP_1 receptors mediate up-regulation of the orphan nuclear receptor Nurr1 by cAMP-independent activation of protein kinase A, CREB and NF-κB. *Br J Pharmacol* 2012;**166**:1033–1046.
82. Bousquet M, Gue K, Emond V, et al. Transgenic conversion of omega-6 into omega-3 fatty acids in a mouse model of Parkinson's disease. *J Lipid Res* 2011;**52**:263–271.
83. Kovalovsky D, Refojo D, Liberman AC, et al. Activation and induction of NUR77/NURR1 in corticotrophs by CRH/cAMP: involvement of calcium, protein kinase A, and MAPK pathways. *Mol Endocrinol* 2002;**16**:1638–1651.
84. Zhao D, Desai S, Zeng H. VEGF stimulates PKD-mediated CREB-dependent orphan nuclear receptor Nurr1 expression: role in VEGF-induced angiogenesis. *Int J Cancer* 2011;**128**:2602–2612.
85. Bandoh S, Tsukada T, Maruyama K, Ohkura N, Yamaguchi K. Mechanical agitation induces gene expression of {NOR}-1 and its closely related orphan nuclear receptors in leukemic cell lines. *Leukemia* 1997;**11**:1453–1458.
86. Tokuoka H, Hatanaka T, Metzger D, Ichinose H. Nurr1 expression is regulated by voltage-dependent calcium channels and calcineurin in cultured hippocampal neurons. *Neurosci Lett* 2014;**559**:50–55.
87. Friling S, Bergsland M, Kjellander S. Activation of Retinoid X Receptor increases dopamine cell survival in models for Parkinson's disease. *BMC Neurosci* 2009;**10**:146.
88. Lei Z, Jiang Y, Li T, Zhu J, Zeng S. Signaling of glial cell line-derived neurotrophic factor and its receptor GFRα1 induce Nurr1 and Pitx3 to promote survival of grafted midbrain-derived neural stem cells in a rat model of Parkinson disease. *J Neuropathol Exp Neurol* 2011;**70**:736–747.
89. Lonze BE, Ginty DD. Function and regulation of CREB family transcription factors in the nervous system. *Neuron* 2002;**35**:605–623.
90. Chang YL, Chen SJ, Kao CL, et al. Docosahexaenoic acid promotes dopaminergic differentiation in induced pluripotent stem cells and inhibits teratoma formation in rats with Parkinson-like pathology. *Cell Transplant* 2012;**21**:313–332.
91. McFarland K, Spalding TA, Hubbard D, Ma J-N, Olsson R, Burstein ES. Low dose bexarotene treatment rescues dopamine neurons and restores behavioral function in models of Parkinson's disease. *ACS Chem Neurosci* 2013;**4**:1430–1438.
92. Volakakis N, Tiklova K, Decressac M, et al. Nurr1 and retinoid X receptor ligands stimulate ret signaling in dopamine neurons and can alleviate-synuclein disrupted gene expression. *J Neurosci* 2015;**35**:14370–14385.
93. Kordower JH, Palfi S, Chen EY, et al. Clinicopathological findings following intraventricular glial-derived neurotrophic factor treatment in a patient with Parkinson's disease. *Ann Neurol* 1999;**46**:419–424.
94. Lang AE, Gill S, Patel NK, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol* 2006;**59**:459–466.
95. Sathiya S, Ranju V, Kalaivani P, et al. Telmisartan attenuates MPTP induced dopaminergic degeneration and motor dysfunction through regulation of α-synuclein and neurotrophic factors (BDNF and GDNF) expression in C57BL/6J mice. *Neuropharmacology* 2013;**73**:98–110.
96. Naveilhan P, Neveu I, Wion D, Brachet P. 1,25-Dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor. *NeuroReport* 1996;**7**:2171–2175.
97. Sapkota K, Kim S, Kim MK, Kim SJ. A detoxified extract of Rhus verniciflua Stokes upregulated the expression of BDNF and GDNF in the rat brain and the human dopaminergic cell line SH-SY5Y. *Biosci Biotechnol Biochem* 2010;**74**:1997–2004.
98. Ohta K, Fujinami A, Kuno S, et al. Cabergoline stimulates synthesis and secretion of nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor by mouse astrocytes in primary culture. *Pharmacology* 2004;**71**:162–168.
99. Li X, Tai H-H. Activation of thromboxane A2 receptors induces orphan nuclear receptor Nurr1 expression and stimulates cell proliferation in human lung cancer cells. *Carcinogenesis* 2009;**30**:1606–1613.
100. Barneda-Zahonero B, Servitja JM, Badiola N, et al. Nurr1 protein is required for N-methyl-D-aspartic acid (NMDA) receptor-mediated neuronal survival. *J Biol Chem* 2012;**287**:11351–11362.
101. L'Episcopo F, Tirolo C, Testa N, et al. Wnt/β-catenin signaling is required to rescue midbrain dopaminergic progenitors and promote neurorepair in ageing mouse model of Parkinson's disease. *Stem Cells* 2014;**32**:2147–2163.
102. Rajalin A-M, Aarnisalo P. Cross-talk between NR4A orphan nuclear receptors and β-catenin signaling pathway in osteoblasts. *Arch Biochem Biophys* 2011;**509**:44–51.
103. Berthon A, Drelon C, Ragazzon B, et al. WNT/β-catenin signalling is activated in aldosterone-producing adenomas and controls aldosterone production. *Hum Mol Genet* 2014;**23**:889–905.
104. L'Episcopo F, Tirolo C, Testa N, et al. Reactive astrocytes and Wnt/β-catenin signaling link nigrostriatal injury to repair in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *Neurobiol Dis* 2011;**41**:508–527.
105. Wei L, Sun C, Lei M, et al. Activation of Wnt/β-catenin Pathway by Exogenous Wnt1 Protects SH-SY5Y Cells Against 6-Hydroxydopamine Toxicity. *J Mol Neurosci* 2013;**49**:105–115.
106. Devine MJ. Proteasomal inhibition as a treatment strategy for Parkinson's disease: the impact of α-synuclein on Nurr1. *J Neurosci* 2012;**32**:16071–16073.
107. Yang D, Li T, Wang Y, et al. miR-132 regulates the differentiation of dopamine neurons by directly targeting Nurr1 expression. *J Cell Sci* 2012;**125**:1673–1682.
108. Myöhänen TT, Hannula MJ, Van Elzen R, et al. A prolyl oligopeptidase inhibitor, KYP-2047, reduces α-synuclein protein levels and aggregates in cellular and animal models of Parkinson's disease. *Br J Pharmacol* 2012;**166**:1097–1113.
109. Fagerqvist T, Lindström V, Nordström E, et al. Monoclonal antibodies selective for α-synuclein oligomers/protofibrils recognize brain pathology in Lewy body disorders and α-synuclein transgenic mice with the disease-causing A30P mutation. *J Neurochem* 2013;**126**:131–144.
110. Kalia LV, Kalia SK, McLean PJ, Lozano AM, Lang AE. α-Synuclein oligomers and clinical implications for Parkinson disease. *Ann Neurol* 2013;**73**:155–169.
111. Gascon E, Gao FB. Cause or Effect: misregulation of microRNA Pathways in Neurodegeneration. *Front Neurosci* 2012;**6**:48.
112. Harraz MM, Dawson TM, Dawson VL. MicroRNAs in Parkinson's disease. *J Chem Neuroanat* 2011;**42**:127–130.
113. Li QJ, Tang YM, Liu J, et al. Treatment of Parkinson disease with C17.2 neural stem cells overexpressing NURR1 with a recombined republic-deficit adenovirus containing the NURR1 gene. *Synapse* 2007;**61**:971–977.
114. Shim JW, Park CH, Bae YC, et al. Generation of functional dopamine neurons from neural precursor cells isolated from the subventricular zone and white matter of the adult rat brain using Nurr1 overexpression. *Stem Cells* 2007;**25**:1252–1262.
115. Park CH, Kang JS, Shin YH, et al. Acquisition of in vitro and in vivo functionality of Nurr1-induced dopamine neurons. *FASEB J* 2006;**20**:2553–2555.
116. Tan X, Zhang L, Qin J, et al. Transplantation of neural stem cells co-transfected with Nurr1 and Brn4 for treatment of Parkinsonian rats. *Int J Dev Neurosci* 2013;**31**:82–87.
117. Lee HS, Bae EJ, Yi SH, et al. Foxa2 and Nurr1 synergistically yield A9 nigral dopamine neurons exhibiting improved differentiation, function, and cell survival. *Stem Cells* 2010;**28**:501–512.
118. Ko TL, Fu YY, Shih YH, et al. A high efficiency induction of dopaminergic cells from human umbilical mesenchymal stem cells for the treatment of hemiparkinsonian rats. *Cell Transplant* 2014;**24**:2251–2262.
119. Gross RE, Watts RL, Hauser R, et al. Intrastriatal transplantation of microcarrier-bound human retinal pigment epithelial cells versus sham surgery in patients with advanced Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* 2011;**10**:509–519.
120. Zhao Y, Bruemmer D. NR4A orphan nuclear receptors: transcriptional regulators of gene expression in metabolism and vascular biology. *Arterioscler Thromb Vasc Biol* 2010;**30**:1535–1541.