

Neural stem cells in Parkinson's disease: a role for neurogenesis defects in onset and progression

Jaclyn Nicole Le Grand · Laura Gonzalez-Cano ·
Maria Angeliki Pavlou · Jens C. Schwamborn

Received: 4 July 2014/Revised: 9 October 2014/Accepted: 3 November 2014/Published online: 18 November 2014
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Abstract Parkinson's disease (PD) is the second most common neurodegenerative disorder, leading to a variety of motor and non-motor symptoms. Interestingly, non-motor symptoms often appear a decade or more before the first signs of motor symptoms. Some of these non-motor symptoms are remarkably similar to those observed in cases of impaired neurogenesis and several PD-related genes have been shown to play a role in embryonic or adult neurogenesis. Indeed, animal models deficient in *Nurr1*, *Pitx3*, *SNCA* and *PINK1* display deregulated embryonic neurogenesis and *LRRK2* and *VPS35* have been implicated in neuronal development-related processes such as Wnt/ β -catenin signaling and neurite outgrowth. Moreover, adult neurogenesis is affected in both PD patients and PD animal models and is regulated by dopamine and dopaminergic (DA) receptors, by chronic neuroinflammation, such as that observed in PD, and by differential expression of wild-type or mutant forms of PD-related genes. Indeed, an increasing number of in vivo studies demonstrate a role for *SNCA* and *LRRK2* in adult neurogenesis and in the generation and maintenance of DA neurons. Finally, the roles of PD-related genes, *SNCA*, *LRRK2*, *VPS35*, *Parkin*, *PINK1* and *DJ-1* have been studied in NSCs, progenitor cells and induced pluripotent stem cells, demonstrating a role for some of these genes in stem/progenitor cell proliferation and maintenance. Together, these studies strongly suggest a link between deregulated neurogenesis and the onset and progression of PD and present strong evidence that, in

addition to a neurodegenerative disorder, PD can also be regarded as a developmental disorder.

Keywords Parkinson's disease · Neural stem cells · Neurogenesis · Development · *LRRK2* · *SNCA*

Abbreviations

6-OHDA	6-Hydroxydopamine
aPKC	Atypical protein kinase C
DA	Dopaminergic
DG	Dentate gyrus
DKO	Double knockout
dNB	Drosophila neuroblasts
ESC	Embryonic stem cell
iPSC	Induced pluripotent stem cell
KD	Knockdown
KO	Knockout
LRRK2	Leucine-rich repeat kinase 2
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NB	Neuroblast
NF- κ B	Nuclear factor-kappaB
NPC	Neural progenitor cell
NSC	Neural stem cell
OB	Olfactory bulb
PCNA	Proliferating cell nuclear antigen
PD	Parkinson's disease
PINK1	PTEN-induced putative kinase 1
RMS	Rostral migratory stream
SN	Substantia nigra
SNpc	Substantia nigra pars compacta
SNCA	α -Synuclein
SGZ	Subgranular zone
SVZ	Subventricular zone
TH	Tyrosine hydroxylase

J. N. Le Grand · L. Gonzalez-Cano · M. A. Pavlou ·
J. C. Schwamborn (✉)
Luxembourg Centre for Systems Biomedicine (LCSB),
University of Luxembourg, 4362 Esch-sur-Alzette, Luxembourg
e-mail: jens.schwamborn@uni.lu

VPS35 Vacuolar protein sorting 35
 WT Wild type

Introduction

Parkinson's disease (PD), first described in 1817 by James Parkinson [1], is the second most common neurodegenerative disease after Alzheimer's disease and the first most common motor neurodegenerative disease, affecting approximately 2 % of the population aged 60 years and older [2, 3]. The disease is characterized by its locomotor phenotypes, which include resting tremors, difficulty initiating movement, postural instability, bradykinesia and rigidity as well as the formation of intracytoplasmic inclusions or protein aggregates called Lewy bodies, containing insoluble α -synuclein (SNCA) protein. Several non-motor symptoms of PD have also been described, including anhedonia [4–8], depression [9], anxiety [10], olfactory deficits [11–13], sleep disturbances [14, 15] and cognitive dysfunction [16–18]. These non-motor symptoms often precede the prototypical motor symptoms of PD by years or even decades [19, 20]. The PD-associated motor symptoms primarily result from the degeneration of DA neurons in the *substantia nigra pars compacta* (SNpc), although degeneration has also been observed in the striatum, hippocampus, and neocortex [21]. Interestingly, changes in DA innervation and DA concentration in the striatum can occur 20–30 years prior to the onset of any motor symptoms [22, 23].

Over 90 % of all PD cases appear to occur sporadically and most of them are idiopathic cases. Most plausibly, these cases arise from multiple factors acting simultaneously, including genetic susceptibility, environmental factors and, most importantly, age. Familial variants of PD result from genetic mutations leading to either autosomal dominant forms of PD, such as those caused by mutations in the *SNCA*, *LRRK2*, *VPS35* or *GBA* gene, or autosomal recessive forms of PD, such as those caused by mutations in the *PINK1*, *Parkin* or *DJ-1* gene. Several other genes have been described to confer an increased susceptibility to PD, including *EIF4G1*, *ATP13A2*, *PLA2G6*, *FBXO7*, *DNAJC6*, *DNAJC13*, *SYNJ1*, *MAPT*, *Pitx3*, *Nurr1* and *UCHL1*. Although familial variants of PD account for up to only 10 % of all cases [24, 25], an induced pluripotent stem cells (iPSC)-based study has recently suggested that even in idiopathic cases of PD, the increased susceptibility of DA neurons is probably encoded in the genome [26]. Moreover, sporadic and genetic forms of PD have comparable motor phenotypes, implying that they share common neurodegenerative mechanisms [27].

No matter what the etiology, in PD, more than 50 % of SN neurons degenerate before the onset of motor symptoms and many of the non-motor symptoms of PD precede the occurrence of motor symptoms by years or even decades [19, 28–30]. Some of the prominent non-motor symptoms described during the premotor phase of PD such as hyposmia, depression and anxiety are also phenotypes observed in models of deregulated neurogenesis [31–34] and medications and treatments for depression and anxiety have been shown to increase adult neurogenesis (reviewed in [35]). Although a causative role for neurogenesis in depression and anxiety has yet to be demonstrated, it is likely that hyposmia is caused, at least in part, by deregulated neural stem cell (NSC) activity already occurring during development and/or in adult NSCs.

NSCs are self-renewing, multipotent progenitors that give rise to multiple types of neurons and glial cells during embryonic brain development as well as during adult neurogenesis (more detailed information in [36–51]). NSCs represent a potential endogenous source for neuronal replacement therapy in neurodegenerative disorders such as PD. Moreover, studies focusing on adult NSCs and neurogenesis in PD models offer the potential for earlier diagnosis, stratification and possibly therapeutic treatments for this debilitating disease.

Evidence for a developmental component of PD: deregulated embryonic neurogenesis

A number of PD-associated genes have been implicated in DA neuronal development during embryogenesis. Here, we discuss studies using mice deficient for *Nurr1*, *Pitx3*, and *SNCA* that have demonstrated deregulated embryonic neurogenesis of DA neurons in the midbrain as well as studies describing the role of *PINK1*, *LRRK2* and *VPS35* in neuronal development and the altered expression of the developmentally related brain-derived neurotrophic factor in PD.

The orphan nuclear receptor, *Nurr1*, is expressed principally in the limbic and ventral midbrain and plays an important role in the development and maintenance of DA neurons [52–55]. As previously mentioned, mutations in the *Nurr1* transcription factor have been associated with a susceptibility to PD [56–60]. Moreover, *Nurr1* gene and *Nurr1* protein expression is reduced in DA neurons of the SN in PD patients [57, 61].

Given its role in the induction of differentiation of progenitor cells to tyrosine hydroxylase (TH)-positive DA neurons, it is likely that *Nurr1* mutations contribute to PD pathology early in development, during the formation of the ventral midbrain DA neuron pool. Indeed, reduced *Nurr1* expression in heterozygous mutant mice leads to

decreased DA transporter expression [62], decreased TH-positive neurons in SNpc and less DA concentration in the dorsal striatum [63]. Moreover, these mice display morphological, biochemical and behavioral phenotypes similar to those observed in PD, reflecting the reduced number of DA neurons in the SNpc [62, 64, 65]. *Nurr1* also inhibits expression of pro-inflammatory molecules involved in the neurotoxic response in microglia and astrocytes [66] and acts to transcriptionally downregulate *SNCA* [67]. Reduced expression of *Nurr1* would also therefore lead to an increased inflammatory response, an unregulated increase in *SNCA* expression and possibly DA neuron cell death, further reducing the number of DA neurons in the developing brain, all factors that increase the risk to develop PD.

Another PD-susceptibility gene involved in neuronal development is the *Pitx3* gene. The Pitx3 protein is a transcription factor necessary for terminal differentiation of TH-expressing neurons in the SN through the potentiation of *Nurr1* transcription [68]. In mice lacking *Pitx3*, SN neuronal precursor numbers are dramatically decreased and these cells fail to produce TH, demonstrating that the Pitx3 protein is important for SNpc development and maintenance [69]. Moreover, overexpression of *Pitx3* in ventral mesencephalon-derived NPCs improves motor function in a 6-OHDA PD model [70]. As previously mentioned, Pitx3 is necessary for *Nurr1*-mediated transcription, an important mechanism in DA neuron development and maintenance. As such, *Pitx3* mutations may increase susceptibility to PD by a downstream effect on *Nurr1* activity and the subsequent reduction in the numbers of DA neurons formed in the SN during brain development,

Endogenous α -synuclein has also been implicated in DA neuronal development [71]. In this study, Garcia-Reitboeck and colleagues describe a reduction in the number of DA neurons in the SN of mice with a spontaneous deletion of the *SNCA* gene, as well as in *SNCA* knockout (KO) mice, visible as early as E13.5. Their results demonstrate that α -synuclein is necessary for the embryonic development of at least a subpopulation of DA neurons and suggest that PD-related *SNCA* mutations may also lead to a reduction in the number of DA neurons in the developing brain, long before DA neuronal degeneration even starts. Interestingly, in this scenario, reduced levels of α -synuclein contribute to an increased PD risk, although more commonly, it is elevated α -synuclein levels that are associated to PD. This would suggest that only a balanced, optimal dosage of α -synuclein is beneficial for DA neuron formation and maintenance, while too high as well as too low levels are detrimental. Additionally, the function of α -synuclein as well as the dosage effects of this protein might be different during embryonic development or adulthood (see further discussion of *SNCA* below).

In the developing mouse brain, PINK1 protein expression is evident at E15 and increases significantly just before birth at E19 [72], coinciding with a period of increased neurogenesis in the brain [73]. PINK1 has recently been shown to interact with and phosphorylate the embryonic ectoderm development polycomb histone-methylation modulator, redistributing it to the mitochondria, resulting in a favorable change in transcription regulation for neuronal differentiation [74]. *PINK1* downregulation in zebrafish results in delayed brain development, enlarged ventricles and a moderate decrease in TH-positive neurons in the diencephalon, likely due to an increase in apoptosis as evidenced by an increase in active Caspase 3 in these embryos [75].

LRRK2 expression in the developing mouse brain is particularly strong in the ventricular zone and SVZ of the telencephalon during the period of neurogenesis (E11.5 to E17.5) [76]. Furthermore, *LRRK2* is expressed in NSCs isolated from both the DG and SVZ of E18.5 mice. The LRRK2 protein may interact with the regulator of neurite outgrowth during embryonic neurogenesis, CRMP2 [77] and numerous studies have demonstrated that mutant LRRK2 overexpression decreases neurite length/outgrowth, while LRRK2 deficits result in an increase of neurite length and arborization [78–94]. Moreover, LRRK2 has been shown to bind Wnt signaling components (the DVL proteins) and play a role in the canonical Wnt/ β -catenin signaling pathway, an important pathway for neurogenesis and in particular the development of DA neurons [83, 95, 96].

Neuronal developmental defects are also visible in the absence of the PD-related gene, *VPS35*, discussed in more detail in the “[Function of PD Genes in neural stem cells](#)” section below. Briefly, *VPS35* knockdown (KD) in mouse embryonic hippocampal neurons results in shortened apical dendrites, reduced dendritic spines and swollen commissural axons [97].

Lastly, brain-derived neurotrophic factor, known to regulate the differentiation and survival of midbrain DA neurons [98], displays reduced mRNA expression in the SNpc of PD models [99, 100].

Evidence for deregulated adult neural stem cell activity in PD

Neurogenesis in the PD brain

Adult neurogenesis has been described in the human brain in both the SVZ and the SGZ [46, 47, 101]. Unfortunately, few studies have been done to examine neurogenesis in the post-mortem PD brain and those that have been conducted present conflicting findings.

A first group of studies has demonstrated that post-mortem PD brains display deregulated adult neurogenesis. In these studies, cell proliferation appears to be decreased in the SGZ and SVZ of PD patients. The number of proliferating cell nuclear antigen (PCNA)-positive adult NSCs in the SVZ and Nestin-positive precursor cells in the OB are decreased in the PD-affected post-mortem brain [102] and a decrease in NSCs correlates with the progression of PD, while L-Dopa treatment appears to increase NSC numbers [103]. Moreover, EGF and EGFR levels are also decreased in the PD striatum and the prefrontal cortex of PD patients [104] and EGFR-positive neural stem/progenitor cell numbers are decreased in the SVZ of PD patients [105].

Other groups, however, have demonstrated no change in NSC proliferation in the PD-affected brain, such is the case in one study that examined NSC proliferation in the SVZ of PD patients and control brains [106]. NSCs have been identified in the SVZ of the aged human brain [107, 108] and in the SVZ of PD patients [106]. NPCs have been isolated from post-mortem human cortex and SN of PD patients [109, 110] and neurospheres have been obtained from the SVZ of a PD brain, indicating the presence of adult NSCs [106]. However, idiopathic human PD multipotent NPCs isolated from the SN appear to lack key factors required for neuronal differentiation as they must be co-cultured with embryonic stem cell-derived neural precursors to obtain neurons [110].

Neurogenesis defects in PD animal models

Mainly, two animal models for PD have been used to study neurogenesis: acute lesions formed by either 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. Both experimental models replicate the DA neuron degeneration observed in PD and result in motor phenotypes. Although neurogenesis in both the SVZ and the SGZ has been shown to decline with age in rodents [111–113], whether this phenomenon is exacerbated, inverted or unchanged in PD animal models is still up for debate.

In one study, MPTP administration in the mouse brain decreased the number of proliferating cells in the SVZ and the corresponding DA neuron denervation decreased the number of PCNA-positive progenitor cells in the SGZ [102]. In later studies, MPTP administration was shown to induce apoptosis of migrating neuroblasts (NBs) from the SVZ [114, 115]. Conversely, MPTP treatment has also been shown to increase proliferation in the SVZ and the SGZ [116] and to increase neurogenesis in the SN and OB [116–119] of mice. Yet in another study, no change in proliferation or neurogenesis was observed. While MPTP treatment in mice induced DA denervation of the striatum,

no change in proliferation of the SVZ progenitors was observed [106].

In macaque monkeys, MPTP treatment has been shown to deplete DA innervation in the SVZ and reduce the number of proliferating cells in this area [120]. In another study focusing on another brain region, MPTP treatment in the macaque revealed no increase in DA neurogenesis in the striatum [121].

In a number of studies, 6-OHDA treatment leads to decreased proliferation of neuronal precursors in the SVZ, visualized by a decrease in the number of PCNA-expressing cells in the SVZ of treated rats [102, 122] or a decrease in the number of BrdU-labeled cells in the SVZ of treated mice [123]. In the OB, 6-OHDA treatment results in decreased BrdU labeling in the granule cell layer (the site of integration for neural progenitors originating in the SVZ) but increased BrdU labeling in the glomerular cell layer with a concomitant increase in DA neurons in the OB, suggesting that DA differentiation is increased [122–124]. On the other hand, 6-OHDA treatments in rats have also increased proliferation in the SVZ [125–127]. It is noteworthy that, although proliferation appeared to be increased, these cells could only differentiate into astroglial cells and not neurons and thus neurogenesis would appear to be deregulated in these models as well [125]. Finally, examination of Dcx-positive NPCs in the SN of mice revealed no change after 6-OHDA injections [128].

Regulation of NSC activity by PD-associated neuroinflammation

Chronic neuroinflammation has been observed in both PD patients' brains and in animal models of PD [129–132], but how this inflammation affects neurogenesis is only just being elucidated.

Inflammation-related proteins and molecules such as TNF- α , inflammatory cytokines and nitric oxide negatively regulate neurogenesis [133–136], while neurogenesis is increased in the hippocampus and SVZ by anti-inflammatory drug treatment in the focal traumatic brain injury and Japanese encephalitis models for acute neuroinflammation [137–139].

In the 6-OHDA PD model, treatment with anti-inflammatory drugs (minocycline or specific COX2 inhibitors) activates NSC proliferation in the SVZ and oligodendrogenesis and/or astrogliosis in the affected striatum and in the SN and even induces a functional regeneration as shown by rotational behavior experiments [128, 133].

Finally, the inflammatory response and microglia activation in a MPTP model of PD are partially mediated by the chemokine receptor CX3CR1 [140], a known regulator of adult neurogenesis [141].

Regulation of neurogenesis by dopamine

Dopamine appears to also play a role in the control of neurogenesis. Indeed, dopamine receptors have been observed on both neurospheres derived from rodent SVZ precursors [102, 142, 143] and in vivo on progenitor cells of the SVZ in mice and rats [102, 144, 145]. Moreover, DA fibers have been described in close proximity to EGFR-positive cells (progenitor cells) in the post-mortem human brain [102]. These DA fibers likely originate from SN cells, as has been described for non-human primates [120].

An experimentally reduced dopamine level in mice decreases precursor cell proliferation in both the subependymal zone and in the SGZ; this effect can be reversed by a selective D₂-like receptor agonist (one of two subfamilies of DA receptors, including the D₁, D₂ and D₃ DA receptors) [102]. Correspondingly, experimentally induced dopamine loss decreases SVZ proliferation and EGFR-positive adult NSCs via D₂-like receptors [102, 105, 122, 123, 146]. It appears that dopamine can also exert its effects on neurogenesis, at least in part, via the D₃ receptor. Activation of the D₃ receptor in rats increases proliferation in the SVZ, RMS and possibly in the SN [147] and also stimulates OB neurogenesis [145]. In vitro studies have demonstrated that dopamine can also stimulate cell proliferation in neurospheres through the D₃ receptor and may also stimulate neurogenesis [142].

Function of PD genes in neural stem cells

Studies of PD-related genes, in particular in NSCs, progenitor cells and iPSCs have suggested that these genes may be important in the regulation of stem/progenitor cell proliferation, maintenance and differentiation. Below, we outline the state of the art of this topic for the most common PD-related genes (reviewed in Table 1).

SNCA (PARK1/PARK4)

The *SNCA* gene (4q21), located at the PARK1/4 locus, encodes the protein α -synuclein. Several PD-related *SNCA* mutations have been identified. The A53T [148], A30P [149] and E46K [150] mutations as well as gene duplications [151] and triplications [152] are the *SNCA* genetic variations responsible for the onset of an autosomal dominant form of PD, while other PD-associated mutations such as the A18T, A29S, H50Q and G51D mutations may also contribute to PD progression [153–155].

α -Synuclein is a highly conserved protein that is abundantly expressed in the adult brain, but its precise function is still unknown [156, 157]. Certain studies have, however,

described an involvement of α -synuclein in normal brain function [158], synaptic plasticity [159, 160] and the regulation of the presynaptic vesicular pool [161, 162], including DA release [163]. α -Synuclein has also been described as a chaperone and described to contribute to SNARE complex formation [164]. α -Synuclein is a natively unfolded monomer but it is able to switch from a helical to a β -sheet structure, aggregate and form fibrils [156, 157]. In PD brains, α -synuclein is the predominant protein found in Lewy Body inclusions [165, 166] and the misfolding and aggregation of this protein into neurotoxic species is considered central in PD pathogenesis [167].

An increasing number of studies reveal that α -synuclein plays an important role in neurogenesis. When the *SNCA* gene is differentially expressed or bears mutations or the α -synuclein protein forms aggregates, the neuronal stem cell pool is negatively regulated and the survival of newly generated neurons is decreased. The aforementioned suggests that there is a link between neurogenesis, *SNCA* and neurodegenerative diseases. If decoded, the details of this relationship could provide a valuable tool for designing potential therapies for patients with neurodegenerative diseases such as PD.

Overexpression of wild-type *SNCA*

Adult mice overexpressing human wild-type *SNCA* under the PDGF promoter were used to investigate adult NSC proliferation, migration and differentiation [168]. Although no difference in the number of PCNA-positive proliferating SVZ or DG cells could be observed between the transgenic and the control mice, a significant reduction of newly generated (BrdU positive) neurons was apparent in the OB and the DG. In particular, DA neurogenesis in the OB was severely impaired as was evident by the fact that the number of TH/BrdU double-positive cells was reduced more than half in the mice overexpressing *SNCA*. This effect observed in the OB was accompanied by increased cell death in the granule layer of the DG and in the OB [168].

In vitro, *SNCA* overexpression reduces the number of secondary neurospheres formed and affects NSC morphology and cell cycle progression, leading to their accelerated differentiation [169]. However, when the authors used the same virus to overexpress *SNCA* in vivo, no effect was seen on the proliferation of SVZ NSCs, an observation that agrees with previous study mentioned. Instead, they observed a delay in the migration of NSCs through the SVZ/RMS/OB system, evident by an increased number of NSCs that remained in the neurogenic niche [169].

A subsequent study using mice overexpressing human *SNCA* under the tet-off system investigated if impaired OB

Table 1 Effect of PD-related genes in NSCs and on neurogenesis

Gene	Phenotype	Observed effect	References
SNCA	Overexpression	<i>Adult</i>	[168]
		– proliferation in SVZ and DG	
		↓ neurogenesis in OB and DG	
		↑ cell death in OB and DG	
		<i>Embryonic</i>	[169]
		↓ formation of secondary spheres	
		↓ cell cycle entry of NSCs	
		↑ differentiation of NSCs	
		<i>Adult</i>	
		– proliferation in SVZ, RMS and OB	
		– cell death in SVZ, RMS and OB	
		– differentiation of NSCs into DA neurons in OB	
↓ NSC migration through the RMS			
<i>Adult</i>	[71]		
↑ DA neurons in SN			
<i>Adult</i>	[184]		
↓ dendritic length of neurons in DG			
↑ spine density of neurons in DG			
↓ mushroom spines of neurons in DG			
<i>Adult</i>	[172, 173]		
↓ neurogenesis in DG			
↑ cell death in DG			
<i>In vitro</i>			
↓ neurogenesis			
↑ cell death			
↓ neuronal differentiation			
Knockout	<i>Adult</i>	↑ neurogenesis in DG	[184]
		– BrdU ⁺ newly generated cells in DG	
		– proliferation in DG	
Mutant	A30P	↓ neurogenesis in OB	[175]
		– proliferation in SVZ	
Mutant	A53T	<i>Adult</i>	[174]
		↓ neurogenesis in OB	
		↑ cell death in OB	
		<i>Aged mice</i>	
		↓ proliferation in SVZ	
		↑ cell death in SVZ	
		↓ neurogenesis in OB	
		↑ cell death in OB	
		<i>Adult</i>	[172]
		↓ neurogenesis in DG	
		↑ cell death in DG	
		<i>In vitro</i>	
↓ neurogenesis			
↑ cell death			

Table 1 continued

Gene	Phenotype	Observed effect	References	
<i>LRRK2</i>	Knockout/knockdown	<i>Adult</i>	[94]	
		– proliferation in DG		
		– BrdU ⁺ newly generated cells in DG		
		↑ early differentiating neurons (DCX ⁺ cells) in DG due to delayed maturation		
		↑ dendritic arborization and dendritic length		
		<i>In vitro</i>	[197]	
		– NSC proliferation		
		↑ neuronal differentiation		
		↓ ROS and cell death of differentiating neurons		
		<i>In vitro</i>	[198]	
	↑ (accelerated) neuronal differentiation			
	<i>Adult</i>			
	↑ early differentiating neurons (DCX ⁺ cells) in DG			
	<i>In vitro</i>	[199]		
	↓ DA neuronal differentiation			
	↑ cell death			
	Mutant	G2019S	<i>Adult</i>	[86]
			↓ proliferation in DG, SVZ and RMS	
			↓ survival of newly born neurons in OB and DG	
			↓ dendritic arborization and spines	
			<i>In vitro</i>	[200]
			↓ neural differentiation	
			↓ proliferation (clonal expansion)	
			↑ susceptibility to proteasomal stress	
		R1441G	<i>In vitro</i>	[197]
			– NSC proliferation	
			↓ neuronal differentiation	
			↑ ROS and cell death of differentiating neurons	
<i>VPS35</i>	Knockout/knockdown	<i>Adult</i>	[97]	
		↓ dendritic arborization and spines		
		<i>In vitro</i>	[197, 218] [199]	
		↓ neurite length		
<i>PINK1</i>	Knockout/knockdown	<i>In vitro</i>	[250]	
		– DA neuronal differentiation		
		<i>Adult drosophila</i>	[254]	
		↓ proliferation		
		<i>In vitro (human NSCs)</i>		
	↓ proliferation			
	Mutant	Q456X	<i>In vitro</i>	[251, 253]
			– DA neuronal differentiation	
<i>Parkin</i>	Knockout/knockdown	<i>In vitro</i>	[276–278]	
		– DA neuronal differentiation		
<i>DJ-1</i>	Knockout/knockdown	<i>In vitro (ESCs)</i>	[300]	
		↑ sensitivity to proteasomal stress and ROS		

– no effect is observed, ↑ increased, ↓ decreased

neurogenesis caused by *SNCA* overexpression could be rescued when the transgene is silenced [170]. As in the case of Winner et al., the authors demonstrated a decrease in NSC proliferation in the SVZ and in the generation of new neurons in the OB. When *SNCA* overexpression was ceased, the amount of new cells in the granule cell layer was increased but these cells did not manage to become neurons. On the other hand, glomerular layer neurogenesis was partially restored. It is worth mentioning that the amount of newly TH-positive cells was also reduced when the transgene was active and upon its silencing, the number of TH-positive cells was increased up to 89 % in the glomerular layer of the bulb [170].

A broader investigation concerning α -synuclein was performed in silico; mice overexpressing human wild-type *SNCA* were used to perform a transcriptome analysis of the striatal brain region [171]. The expression of many genes implicated in apoptosis, cell cycle progression, neurogenesis and synaptic function were impaired, demonstrating that indeed α -synuclein is involved in many different cell processes that, when deregulated due to differential *SNCA* expression, may influence neurogenesis. Indeed, rat hippocampal NPCs and mouse ESCs overexpressing *SNCA* display impaired neuronal differentiation and survival, an effect that is mediated by increased p53-mediated repression of Notch-1 signaling [172, 173].

Overexpression of mutated *SNCA*

OB neurogenesis during aging was investigated in mice that overexpress either human wild-type (WT) or A53T mutated *SNCA* [174]. Among these animals, only the aged mice bearing the *SNCA* mutation showed a significant decrease in proliferation of the SVZ NSCs. In addition, both transgenic mice revealed a reduction in the total number of newly generated neurons accompanied by an increase in apoptosis of neuronal progenitor cells in the OB. Newly generated TH-positive cells were decreased in both groups but the effect was more profound in the mice overexpressing the mutant form of *SNCA* [174]. This study demonstrates a correlation between aging and neurogenesis in the context of WT and mutant *SNCA* overexpression, showing that the A53T mutation produces more deleterious effects with respect to proliferation of NSCs and the survival of both stem cells and newly generated neurons.

Transgenic mice overexpressing the A30P mutant form of *SNCA* display no difference in proliferation in the SVZ, compared to control mice [175]. However, in the OB, the amount of newly generated DA neurons is decreased in the mutant mice. More recently, the same group investigated the effect of the mutation on hippocampus plasticity and found that the survival of new hippocampal neurons is dramatically decreased in these mice [176]. The cause of

this decrease in newly formed neurons has not been investigated in this model. As such, it would be interesting to investigate if the decrease in neurons in this model is also due to decreased survival (increased apoptosis), as was the case for the A53T *SNCA* overexpression mouse model. In addition, the *SNCA* mutant mice present behavioral changes such as an increase in anxiety. Olfactory deficits and behavioral changes such as increased anxiety are also examples of non-motor symptoms of PD patients, suggesting a role for *SNCA* variations in non-motor deficits of PD.

Finally, mice expressing a truncated form of human *SNCA* (1–120 *SNCA*) under the control of the TH promoter in an endogenous null background developed inclusions in the SN, motor abnormalities, redistribution of SNARE proteins and impaired exocytosis [177, 178]. Recently, these mice were used to generate a new transgenic line by crossing them with WT mice. Compared to WT or to the 1–120 *SNCA* transgenic line, a significant increase in the number of SN DA neurons was observed [71]. The group, however, did not investigate the correlation between the increase of TH-positive neurons with increased neurogenesis nor did they investigate the proliferation, differentiation or survival potential of these cells, which would be an interesting point for future research. If these questions are answered, they might unveil an interesting mechanism or point to a certain direction concerning the specific function of α -synuclein in neurogenesis of the SN.

The sum of these studies demonstrates the deleterious effects of *SNCA* overexpression in the mouse brain. In vitro, WT *SNCA* overexpression leads to a decrease in proliferation. Overexpression of WT *SNCA* in vivo decreases the number of newly generated TH⁺ neurons via increased apoptosis of newly generated neurons and a decrease in cell migration through the RMS. Moreover, the decrease in the number of newly generated TH⁺ neurons is even more pronounced and is accompanied by a clear decrease in SVZ NSC proliferation when a mutated form of *SNCA* is expressed. Neurogenesis is a vital ongoing process in the adult brain and its disruption, via the deregulated expression or function (incurred by genetic mutations) of *SNCA*, could contribute to the non-motor deficits observed in patients with PD.

Interestingly, olfactory deficits have been described in mice overexpressing WT *SNCA* and olfaction impairment is an early non-motor symptom of PD. In one study, mice overexpressing *SNCA* under the Thy1 promoter displayed impairments in a number of olfactory functions [179]. In another study, mice overexpressing the human WT *SNCA* gene via the mouse *SNCA* promoter displayed olfactory deficits such as odor detection impairment, olfactory memory deficit and impaired odor discrimination [180, 181]. OB neurogenesis was also examined in the latter

experiment but no difference in the number of newly generated neurons in the OB, based on BrdU labeling assays, was detected. Instead, it is likely that the olfaction deficits observed in *SNCA* transgenic mice are due, at least in part, to impaired growth and branching of dendrites and the subsequent failed stable integration into the OB of newly born DA neurons during adult neurogenesis, leading to a decrease in cell survival, as has been described for an A30P *SNCA* overexpressing mouse [182, 183].

Reduced expression of *SNCA*

Neurogenesis in the adult mammalian brain has also been investigated in the $\alpha\beta$ -*SNCA* double knockout (DKO) mouse in the second neurogenic niche of the brain, the DG. These mice display increased neurogenesis in the DG but lack any apoptosis phenotype. When human *SNCA* is introduced (either as a transgene or a retrovirus), a substantial impairment in hippocampal neurogenesis and in dendrite development and morphology is observed [184]. In this study, the group investigated if there was an increase in the newly generated neurons by injecting the mice with BrdU. In addition, they used Caspase 3 staining to examine if the increase that they saw in the new neurons was balanced by increased apoptosis but they did not find any difference of cell death between the DKO mice and the wild type. These observations indicate that the results obtained indeed represent an increase in neurogenesis. It would be interesting to investigate the second adult neurogenic niche of this mouse to examine the effect of *SNCA* ablation on proliferation of the SVZ stem cells, their migration and the number of newly generated neurons in the OB.

Finally, in another study, surprisingly, the number of TH positive neurons is profoundly reduced in the SN of developing homozygous and heterozygous *SNCA* knockout embryos compared to WT embryos, suggesting that endogenous *SNCA* plays an important role in the embryonic development of DA neurons [71].

Altogether, the majority of the above-described experiments suggest that overexpression of *SNCA* (either WT or mutant forms) decreases the number of newly generated neurons in the DG, OB and SN of the adult brain, including DA neurons in the latter two brain regions. This decrease in DA neurogenesis has been attributed to a multitude of factors, depending on the study, including decreased NSC proliferation in the SVZ, decreased survival of newly generated neurons (increased apoptosis) in the DG and in the OB as well as decreased cell migration through the RMS. Moreover, the $\alpha\beta$ -*SNCA* double KO mouse displays increased neurogenesis in the adult DG. By contrast, one study describes a decrease in the number of newly generated DA neurons in the embryonic DG in the *SNCA* KO

mouse. These seemingly contradictory results hint at a differential effect of *SNCA* expression on neurogenesis, depending on the age of the animal (during embryonic development vs. in the adult neurogenic niches) or on the region of the brain being studied (SN vs. OB vs. DG). Moreover, it appears that *SNCA* expression levels need to be tightly regulated to avoid detrimental effects, as both increased and decreased expression of *SNCA* has been linked to an increase in PD risk.

It is obvious that there is a relation between cell proliferation, death and survival and that *SNCA* orchestrates, in an unknown way, cell fate decisions. In particular, it appears essential that *SNCA* expression and function be tightly regulated in the neuronal cells, as any changes in the expression levels (increased or decreased) or in the *SNCA* genetic sequence lead to defects in both embryonic and adult neurogenesis. In particular, the documented decrease in DA neurogenesis may suggest that individuals with *SNCA* mutations are born with less DA neurons and would therefore be more susceptible to PD. Still, PD symptoms would occur later in life due to the normal decline in neurogenesis with age. Mutant forms of *SNCA* would exasperate the neurogenesis decline; the accumulated decline in neurogenesis (from age and *SNCA* mutations) may bring it under a certain threshold, leading to the occurrence of non-motor symptoms.

LRRK2 (PARK8)

Mutations in the *LRRK2* gene (12q12), located at the PARK8 locus, are the most common cause of autosomal dominant PD, accounting for 1–40 % of all the cases depending on the populations, and up to 5 % of apparently sporadic cases [185, 186]. PD-related *LRRK2* gene mutations include R1441C, R1441G, Y1699C, G2019S and I2020T [187–191]. The G2019S and R1441G mutations, which increase kinase activity and decrease GTPase activity, respectively, are the two most common PD-associated mutations in *LRRK2* [192–194].

The *LRRK2* gene encodes for the leucine-rich repeat kinase (LRRK2) protein, a large and complex protein comprised of multiple domains, including a central catalytic tridomain with GTPase and kinase activities surrounded by several potential protein–protein interaction domains [187, 188]. Despite the knowledge regarding *LRRK2* protein structure and its mRNA and protein expression, the precise physiological function of LRRK2 remains unclear.

LRRK2 shows widespread expression throughout the brain at both the mRNA and protein level [76]. In the mouse brain, *LRRK2* mRNA is first detected at E16 and increases as development progresses through postnatal

periods [195]. It is a ubiquitous protein expressed in various brain regions and various cell types, including neurons and glial cells. *LRRK2* has been described to display robust expression in areas with “high proliferative and migratory activity as well as sites of differentiation and cell death” [76]. In particular, it is expressed in the main neurogenic niches of the mammalian brain: the ventricular zone, SVZ and hippocampus [195]. Moreover, *LRRK2* co-localizes with the migrating NB marker PSA-NCAM [195]. Altogether, the expression pattern of *LRRK2* suggests a role for this protein in CNS development and neurogenesis.

Reduced expression of *LRRK2*

Although *LRRK2* KO mice do not appear to exhibit any alterations in neuronal function or survival [196], the different NSC gene expression profiles in the presence or absence of *LRRK2* expression demonstrate that the absence of *LRRK2* protein affects a number of different cellular processes, including genes implicated in cell cycle regulation, ribosome biosynthesis, proteasome function and mitochondrial oxidation or reduction processes [197].

LRRK2 loss of function does not affect NSC self-renewal in in vitro cultures, nor does it affect cell proliferation in the adult DG of *LRRK2* KO mice [94, 197]. *LRRK2* deficiency has, however, been linked to an increase in neuronal commitment in vitro and an increase in immature NBs due to delayed neuronal maturation in the adult DG [94, 197, 198]. In fact, neuronal differentiation appears to be closely linked to *LRRK2* protein expression levels, as even a 50 % decrease of this protein’s expression levels in *LRRK2* heterozygote ESCs appears to accelerate retinoic acid-induced neuronal differentiation [198]. This was visible through a differential gene expression analysis that revealed accelerated silencing of ESC pluripotency markers and downstream targets as well as increased expression of voltage-gated ion channels and neurotransmitter receptors or transporters in *LRRK2* heterozygous cells 7 days after retinoic acid-induced neuronal differentiation. This effect may be mediated through the alleviation of *let-7* miRNA (a key pro-differentiation miRNA, discussed further below) suppression via *Lin28*. Indeed, the reduction in *Lin28* expression was also exaggerated in *LRRK2* heterozygous cells compared to WT cells during differentiation.

The sum of these studies demonstrates that *LRRK2* is implicated in early neuronal differentiation and appears to negatively regulate this process. Of note, another study utilizing siRNA-mediated KD of *LRRK2* in NPCs did not observe a difference in the number of total neurons after neuronal differentiation but instead observed a difference in the number of TH⁺ neurons, suggesting a reduced capacity of these cells to differentiate into DA neurons

[199]. Varying the expression levels of *LRRK2* may, therefore, differentially affect the genesis of specific neuronal populations.

Overexpression of mutated *LRRK2*

Overexpression of PD-related mutant G2019S *LRRK2* protein produces defects in adult neurogenesis, at the level of cell proliferation and generation of newborn neurons. Indeed, transgenic mice overexpressing the PD-associated human *LRRK2* G2019S protein display a significant decrease in the number of proliferating (BrdU positive) cells in the adult DG, SVZ and RMS and decreased neurogenesis (BrdU and NeuN positive) and DA neurogenesis (BrdU, NeuN and TH positive) as well as decreased survival of newly generated neurons in the OB [86]. The *LRRK2* G2019S mutation may contribute to the hippocampal and SVZ-related age-dependent non-motor symptoms via dysfunctions in the NSC pool and in their neural derivatives at early stages of maturation. Indeed, *LRRK2* G2019S iPSC-derived NSCs in culture, especially at late passages, display increased susceptibility to proteasomal stress and a passage-dependent decrease in clonal expansion and neuronal differentiation capacities [200].

LRRK2 regulates microRNAs

microRNAs, also known as miRNAs, are short (20–25 nucleotides) endogenous RNAs that regulate gene expression at the mRNA level. Briefly, pre-miRNAs are recruited to the miRNA-induced silencing complex, containing at least the Dicer protein, the double-stranded RNA-binding domain protein transactivation-responsive RNA-binding protein and a member of the Argonaute family [201]. The pre-miRNA is then processed by Dicer [202] and the mature miRNA guides the miRNA-induced silencing complex to the target mRNA sequence, via complementary base pairing, to downregulate its expression through translational repression, mRNA degradation or mRNA cleavage [203]. Several miRNAs are specifically enriched in the brain and the necessity of miRNA regulation for normal brain development has been the subject of several recent reviews [204–206]. What is more, miRNAs are regulators of NSC proliferation and differentiation and several studies have linked deregulated miRNA expression or function in the brain or in NSCs with PD pathogenesis (reviewed in [207, 208]).

Although miRNAs were initially described to function upstream of protein expression by targeting the mRNA of disease-associated genes to direct their posttranscriptional repression, more recent studies have demonstrated that some disease-associated proteins are also involved in the regulation of miRNAs pathways. For example, in

Drosophila, pathogenic LRRK2 antagonizes *let-7* and *miR-184**; transgenic flies carrying the equivalent of the human G2019S mutation displayed increased inhibition of *let-7* and *miR184** activity [209]. Furthermore, the effect of pathogenic LRRK2, at least on *let-7* inhibition, was dependent on its kinase activity, evident by the fact that the introduction of kinase-inactivating mutations abolished the observed effect. *let-7* and *miR184** are implicated in the repression of E2F and DP, respectively. These transcription factors are involved in cell cycle control and survival. As such, their repression results in a reduction in locomotor activity and an enhanced neuronal degeneration phenotype, suggesting another mechanism of miRNA pathway regulation in LRRK2-associated PD.

Additionally, Bahnassawy and collaborators investigated miRNA regulation by the R1441G mutation, the second most common PD-associated LRRK2 mutation. They showed that expression of R1441G LRRK2 in murine NSCs leads to a downregulation of *let-7a* and *miR-9*, although LRRK2 deficiency did not affect microRNA expression levels [197]. Altogether, these studies point to an important role for the LRRK2 gene in the pathogenesis of PD, mediated through miRNA regulatory pathways and point to future possible targets in the search for new therapeutic strategies for PD.

LRRK2 is involved in Wnt signaling

In addition to its role in the regulation of NSC differentiation, LRRK2 has been suggested to play a role in neurogenesis. Correspondingly, Berwick and Harvey have proposed that LRRK2 functions as a scaffolding protein that plays a role in numerous signaling pathways, thus linking LRRK2 to neurogenesis and to the function of post-mitotic and mature neurons [210]. The canonical Wnt/ β -catenin pathway is part of the signaling mechanisms involved in the regulation of embryonic and adult neurogenesis, and in particular in the development of DA neurons. It plays a role in the regulation of axonal guidance, dendritic morphogenesis and synapse formation. Wnt cascades have been implicated in PD and deregulated Wnt signaling represents a feasible initiation event in neurodegeneration [211].

LRRK2 has been associated to Wnt signaling via its interaction with key components of the Wnt signaling pathway, such as DVL, the β -catenin destruction complex and LRP6 [95, 96]. Moreover, it has been demonstrated that pathogenic mutations of LRRK2 modulate its interaction with different Wnt pathway molecules, including DVL and GSK3, a component of the β -catenin destruction complex [83, 95]. Importantly, KD of LRRK2 results in enhanced canonical Wnt signaling [96]. This data suggest that LRRK2 plays a

central role in Wnt signaling, an essential pathway in NSC biology and neurogenesis.

Despite the growing body of knowledge concerning the LRRK2 gene and its PD-related mutations, the molecular and cellular implications of LRRK2 mutations during the onset and progression of PD still remain unknown. Given LRRK2's implication in neurogenesis and the parallels between neurogenic niches and brain regions implicated in non-motor PD symptoms, it is likely that LRRK2 mutations are responsible for some of the non-motor symptoms related to PD.

VPS35 (PARK17)

The VPS35 gene (16q12) is located at the PARK17 locus and codes for the vacuolar protein sorting 35 (VPS35). Recently, the p.D620N mutation in the VPS35 gene was identified as a novel cause of autosomal dominant late-onset PD by two research groups [212, 213] and five subsequent studies have identified this mutation in PD patients [214–217]. Moreover, PD-associated defects in RAB7L1 or LRRK2 lead to a deficiency of the VPS35 component of the retromer complex [218].

VPS35, along with VPS26 and VPS29, makes up the cargo recognition and binding subcomplex of the retromer, an important complex for the trafficking and recycling of lipids and proteins [219–221]. The D620N PD-related mutation in VPS35 displays a dominant negative missorting phenotype of retrograde transport of proteins dependent on the WASH complex [218, 222]. WT VPS35 regulates mitochondrial-anchored protein ligase transport from the mitochondria to the peroxisomes [223], suggesting that VPS35 mutations may produce mitochondrial defects in patients. VPS35 is also responsible for divalent metal transporter 1 transport [224]. Mutated VPS35 may, therefore, lead to divalent metal transporter 1 missorting and iron accumulation, similar to the iron accumulation described in PD patients and in the 6-OHDA mouse model of PD [225]. Finally, VPS35 is also hypothesized to influence the Wnt signaling pathway via deficient sorting of the Wntless protein, which leads to Wntless degradation [226–228] and Wnt/ β -catenin signaling is impaired in 6-OHDA-lesioned rats [229] and MPTP-induced mouse and monkey models [230].

As previously mentioned, Wnt signaling plays a role in embryonic and adult neurogenesis and has been linked to PD. As such, the PD-related VPS35 mutation (D620N) may also have an effect on neurogenesis in the PD brain. Little is known about the role of VPS35 in neurogenesis partly because homozygous KO mice die early during embryonic development, before E10 and before the onset of neurogenesis [231]. In one study focusing on Alzheimer's

disease by Wang et al. [97], VPS35 was shown to promote apical dendritic growth and maturation and axonal protein transport in developing mouse hippocampal neurons. The authors demonstrated that embryonic hippocampal CA1 neurons with reduced VPS35 expression (via electroporation with microRNAs) display shortened apical dendrites, less dendritic spines and swollen commissural axons. The authors suggest that these observations reflect a defective protein transport in developing mouse neurons via impaired retrograde trafficking of beta1-secretase and altered beta1-secretase distribution. Similarly, KD of VPS35 or overexpression of D620N VPS35 in rat primary cortical cultures leads to a reduction in neurite length [218]. It will be interesting in the future to see if this protein also plays a role in the development or maintenance of other neuronal types in the adult brain as well as during embryonic neurogenesis. One could hypothesize that the dominant negative VPS35 mutant may drastically decrease the survival of newly generated neurons by inhibiting proper retrograde transport of important trophic factors and by inhibiting normal neurite outgrowth.

Of note, in a non-neuronal system, the mouse intestinal epithelium, although depletion of VPS35 does reduce Wntless protein levels, it did not affect stem cell proliferation in intestinal epithelium-derived cell cultures but did slightly reduce the growth rate of in vitro organoids derived from these cultures [232]. Given its role in Wnt signaling, it is not surprising that the loss of normal VPS35 function results in a decreased proliferative phenotype. It will be interesting to see if this phenotype is reproduced or even exaggerated in other systems such as during development of the CNS, in which Wnt signaling is required for long-distance gradient formation to guide NB migration and to establish neuronal polarity. Recalling that Wnt signaling has been implicated in the development of mid-brain DA neurons, we can then hypothesize that disruption of Wnt signaling via the D620N VPS35 mutation has the potential to decrease the number of DA neurons formed during embryonic development, resulting in fewer DA neurons at birth, thus increasing an individual's susceptibility to PD. Moreover, defects in adult neurogenesis caused by a disruption in Wnt signaling are likely to contribute to the non-motor symptoms observed in PD.

Finally, the D620N VPS35 mutation has also been shown to impair the autophagic process via missorting of the autophagic protein, Atg9, thought to contribute to autophagosome formation [222]. Several studies using mice deficient for autophagy-related genes have outlined the importance of the autophagic machinery in embryonic development of the CNS [233–236]. In particular, autophagy is necessary for proper neuronal differentiation [237, 238]. It will be interesting in the future to evaluate if impaired autophagosome formation caused by the PD-

related VPS35 mutation also leads to impaired neurogenesis via defects in neuronal differentiation.

PINK1 (PARK6)

More than 50 mutations in the PINK1 gene (1p36), located at the PARK6 locus, have been identified in PD-affected patients [239–243] and these mutations are believed to account for up to 1–8 % of sporadic cases with early onset [244].

PTEN-induced putative kinase 1 (PINK1) is a serine/threonine kinase protein localized to the mitochondrial matrix and the intermembrane space [245, 246]. Under normal conditions, it is rapidly degraded but when the mitochondrial membrane is compromised, PINK1 is stabilized at the outer mitochondrial membrane where it recruits the E3-like ligase protein, Parkin, which in turn ubiquitinates other matrix surface proteins and targets the damaged mitochondria for autophagic degradation [247, 248].

PINK1 transcripts are ubiquitously expressed in the murine brain, including brain structures in which neurogenesis still occurs in the adult such as the hippocampus [249]. *PINK1* expression has also been confirmed in human NSCs using RT-PCR. Interestingly, *PINK1* expression increases 100-fold following differentiation to DA neurons [250]. In the latter study, the authors created a stable *PINK1* KD human NSC line using RNAi methods to study this proteins' function in NSC-derived mature DA neurons. Although *PINK1* expression was reduced by >90 % in the selected clone, these NSCs displayed a similar DA neuron differentiation efficiency as the WT controls, suggesting that PINK1 is not necessary for DA neuronal differentiation.

In another study, the role of PINK1 was examined in human iPSCs derived from a patient with a PD-associated *PINK1* mutation (Q456X) that results in a premature stop codon and results in a 80–90 % reduction in *PINK1* mRNA levels compared to human iPSCs derived from a healthy family member [251, 252]. iPSCs derived from the fibroblasts of the PD patient were comparable to WT iPSCs; they displayed a high expression of the pluripotency markers OCT4a, Tra-1-60, NANOG and SSEA-4 at both protein and transcript levels; the iPSC-derived embryonic bodies were able to differentiate into the three embryonic germ layers; and the iPSCs displayed a normal karyotype. Once again, the decreased expression of *PINK1* in the mutant iPSCs did not impede DA neuronal differentiation, as was demonstrated by a slightly higher number of TH-positive neurons in the *PINK1* mutant-derived cells.

Similar observations were made in a third study done by Cooper and colleagues in 2012 in which human iPSCs

were again derived from patients with the Q456X *PINK1* mutation [253]. Supplementary results to validate the cellular model confirmed that the *PINK1* mutant iPSCs are able to differentiate into all the neuronal lineages including DA neurons and display normal karyotyping. As only one *PINK1* mutation has been studied with respect to neurogenesis defects, future studies will be needed to determine if other *PINK1* mutations affect DA neurogenesis or DA neuronal differentiation.

All the above studies focused on DA neuron differentiation in cells with reduced, but not absence of, *PINK1* expression. By contrast, in drosophila neuroblasts (dNB) and mammalian NSCs, *PINK1* deficiency is inversely related to dNB maintenance and cell proliferation [254]. The number of type II dNBs, which contain transit-amplifying intermediate progenitors and are similar to mammalian NSCs, was significantly reduced in *PINK1*-null Drosophila mutants. Moreover, RNAi KD of *dPINK1* blocks activation of mTORC2 and formation of ectopic NBs. In human NSC cultures, shRNA KD of *PINK1* significantly inhibited cell proliferation. This effect appeared to be regulated by a non-canonical Notch signaling involving PINK1, mTORC2 and phosphorylated AKT, in which Notch directly interacts with PINK1 at the mitochondria. Indeed, Notch signaling is implicated in neuronal precursor cell proliferation and loss of function mutations of Notch leads to early neuronal differentiation and a decrease in the number of neuronal precursor cells [255, 256].

As previously mentioned, the PINK1 protein is important for mitochondrial quality control via autophagic degradation of damaged mitochondria. Mitochondria may play a role in stem cell proliferation by reducing mitochondrial oxygen levels, a phenomenon that enhances both ESC and NSC proliferation and differentiation potential [257–259], and by reducing mitochondrial Ca^{2+} levels, that are increased, along with mitochondrial fusion, during neuronal differentiation [260]. Loss of normal mitochondrial function may also contribute to the observed decrease in proliferation in the *PINK1* KD experiments.

Although little research has been done to date on the implication of the PINK1 protein in neurogenesis, the little data thus far would suggest that the PINK1 loss of function mutations results in a decrease of NSC proliferation. Moreover, conditional *PINK1* KO mice display impaired olfaction [261], which is a non-motor symptom of PD and a phenotype that can be attributed to impaired neurogenesis.

Parkin (PARK2)

Parkin deletion mutations are a common cause of early-onset PD and over 100 mutations have been identified to

date [262–266]. The Parkin gene, located at the PARK2 locus (6q25.2-q27), is mutated in up to 50 % of all familial PD cases and in 10–15 % of sporadic early-onset PD [267].

The *Parkin* gene, located at the PARK2 locus, codes for the protein Parkin, an E3 ubiquitin ligase enzyme that is involved in proteasome-mediated and autophagy-mediated degradation of several substrates, particularly mitochondria [268]. During membrane depolarization or in the presence of reactive oxygen species, Parkin is recruited to the mitochondrial membrane by PINK1 and ubiquitinates mitochondrial proteins, targeting them for autophagic degradation [269]. PD-related mutations in *Parkin* result in the loss of its ubiquitin ligase activity [268]. *Parkin* KO mice display decreased levels of proteins involved in mitochondrial function or oxidative stress [270] and *Parkin* KO Drosophila display a mitochondrial pathology [271]. Given its role in mitochondrial quality control, *Parkin* mutations may act similarly to PINK1 loss of function and affect neuronal differentiation, via abnormal mitochondrial activity. Moreover, the Parkin protein ubiquitinates the neuronal cell fate determinant TRIM32, which in turn regulates NSC differentiation [272–275]. However, the experimental evidence for a role for Parkin in neuronal differentiation, outlined below, is contradictory.

Parkin KO ESCs display the same efficiency of in vitro neuronal differentiation as the WT ESCs, in particular the expression of the DA neuronal marker, TH, was the same in both WT and KO ESC-derived neurons [276]. RT-PCR analysis of these neurons revealed similar amounts of all transcripts examined, including the transcription factors Nurr1 and Pitx3, the enzymatic proteins TH and AADC, and the DA receptor, D2R.

In other studies, iPSCs derived from *Parkin* mutation related PD patients with homozygous or heterozygous deletions for a variety of different exons were created and compared to control iPSCs. Again, the mutant iPSCs displayed the same human pluripotent stem cell markers as their WT counterparts and were capable of generating embryonic bodies as well as neurospheres and differentiating into DA neurons [277, 278].

On the other hand, the drosophila Parkin protein has been shown to interact with clueless [279], which regulates atypical protein kinase C (aPKC) activity, a protein that is involved in NB asymmetric division, giving rise to both NBs and newly generated neurons [280]. Interestingly, both clueless and *park* (drosophila Parkin gene) mutants display similar Parkinsonian phenotypes and mitochondrial defects [279] as well as a similar NB phenotype, namely mislocalized cell fate determinants [281]. Furthermore, aPKC has been previously shown to regulate the neuronal cell fate determinant TRIM32 [272]. Together, these results suggest that, in *Drosophila*, Parkin is involved in

the same neurogenic pathway as clueless, although further studies will be necessary to confirm this hypothesis.

Finally, *in vitro* experiments have shown that, in SH-SY5Y cells, PINK1 phosphorylates Parkin and activates its E3 ubiquitin ligase activity, which in turn adds K63-linked polyubiquitination chains to nuclear factor-kappaB (NF- κ B), activating NF- κ B signaling [282], a known regulator of embryonic and adult neurogenesis and neuronal differentiation. PD-related mutations in *PINK1* (G309D, L347P) disrupt PINK1 kinase function [283–285] and are unable to phosphorylate Parkin and therefore unable to activate NF- κ B signaling, suggesting that neurogenesis may also be disrupted in these PD genetic models. These findings and the subsequent effect on neurogenesis will need to be confirmed in *in vivo* models of *PINK1* and *Parkin* mutations.

Although very little evidence exists linking PD-related *Parkin* mutations to neurogenesis and non-motor symptoms of PD, clearly this protein is implicated in several neurogenesis-related pathways, including mitochondrial quality control in neuronal differentiation, TRIM32 ubiquitination in cell fate determination, regulation of aPKC in stem cell renewal regulation and NF- κ B signaling in adult neurogenesis and neuronal differentiation.

DJ-1 (PARK7)

Over 10 different mutations in the *DJ-1* gene (1p36.23), located at the PARK7 locus, are responsible for 1–2 % of early-onset cases of autosomal recessive PD [286–288].

Originally identified as an oncogene, *DJ-1* is thought to act as a molecular chaperone protein [289–291], an oxidative sensor and antioxidant [292–294] and in the regulation of gene transcription [295]. *DJ-1* mutations can reduce DJ-1 protein synthesis or increase DJ-1 protein degradation [296]. In the cell, DJ-1 is expressed in the nucleus and the cytosol [297, 298]. Nuclear DJ-1 forms a complex with RNA-binding proteins and DNA-binding proteins that regulate gene transcription [295], while cytosolic DJ-1 can be found in several pools, including in the intermembrane space and matrix of the mitochondria.

DJ-1 is expressed in the cytosol of Nestin-positive cortical NSCs cultured from E14 rats, as well as *in vivo*, in the same cortical region and in rat NSC-derived neurospheres during proliferation [298]. DJ-1 may protect NSCs during proliferation through its antioxidant activity. Indeed, DJ-1 plays a role in the protection against oxidative stress and oxygen–glucose deprivation in human NPCs in culture [299] and *DJ-1* deficiency in murine ESCs causes increased sensitivity to oxidative stress (increased apoptotic cell death after H₂O₂ treatment) and to proteasomal inhibition (increased sensitivity to the proteasomal inhibitor

lactacystin) [300]. These results underline the importance of this protein in the protection of these highly proliferative cells against accumulation of deleterious ROS or accumulating proteins.

DJ-1 protein expression has also been described in both midbrain- and hippocampal-derived NSC neurospheres, in cells within the neurospheres as well as in cells migrating from the spheres [301]. During differentiation of cultured NSCs, DJ-1 expression increases gradually although the percentage of neuron-specific enolase NSE/DJ-1 colocalisation in neurons was less than 5 %, while the percentage of glial fibrillary acidic protein/DJ-1 colocalisation in astrocytes increased gradually to 85 % at day 7 of differentiation [297]. This is in accordance with the fact that, in the brain, DJ-1 is expressed mainly in astrocytes [302]. By contrast, another study has demonstrated a high level of DJ-1 expression in ESCs and a downregulation of DJ-1 expression to null amounts in these cells as they differentiate to cardiomyocytes [303], suggesting that any role for this protein in differentiation is likely specific to neural lineages. DJ-1 may play a role in NSC differentiation by acting as a scavenger of ROS, since controlled generation of ROS can stimulate differentiation via regulation of redox-sensitive transcription factors important for neurogenesis such as NF- κ B and AP-1 [304, 305].

Conclusions

The studies described in this review demonstrate a link between defects in NSC characteristics, neurogenesis and PD. It suggests that some of the non-motor symptoms observed early in PD are likely due to defects in embryonic neuronal development as well as defects in adult neurogenesis. Furthermore, they underscore that PD has a strong developmental component. A better understanding of the interplay between deficits in embryonic and adult neurogenesis and PD onset and progression will be key to the development of better treatments for this debilitating disease. In particular, the adult SVZ contains a source of endogenous NSCs that are capable of differentiating into DA and non-DA neurons. As such, treatments that can restore impaired neurogenesis in PD patients could provide a source of endogenous repair. It may be time to change the way we look at this neurodegenerative disease, to start considering the possibility that PD starts much earlier than DA neuron degeneration and to consider that developmental and adult neurogenesis are key players in onset and progression of this disease.

Acknowledgments This work was supported by the Fonds National de la Recherche Luxembourg (FNR). Jaclyn Nicole Le Grand and Laura Gonzalez-Cano are supported by fellowships from the FNR (AFR, Aides à la Formation-Recherche).

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