Cellular repair strategies in Parkinson's disease

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting 0.7% of the elderly population (defined as over 65 years of age). PD is clinically characterized by resting tremor, muscular rigidity, hypokinesia and postural instability. These motor symptoms result largely from the deficiency or dysfunction of dopaminergic neurons in the substantia nigra. Histopathological analysis reveals depletion of dopaminergic neurons as well as eosinophilic intracytoplasmic inclusions (Lewy bodies) in surviving neurons of the substantia nigra and other brain regions. The molecular pathogenesis is linked to protein misfolding by compromised alpha-synuclein and/or related proteins (synucleinopathy). Therefore, successful therapy of motor symptoms aims for the restoration of dopaminergic neurotransmission. Pharmacological drug treatment is usually effective only at an early stage of the disease but cannot halt progressive neuronal degeneration. With recent developments in stem cell technology, cell repair or replacement approaches came into focus. Here, we review new therapeutic strategies resulting from the innate propensity of the adult brain to generate new neurons, either by pharmacological stimulation of endogenous adult stem cell population or exogenous cell transplantation modalities.

Keywords: stem cells, neurogenesis, transplantation, neurodegeneration, alpha-synuclein

Introduction

Parkinson's disease (PD) is an adult-onset, progressive, neurodegenerative movement disorder affecting the aged (senescent) population in the Western world [Thomas and Beal, 2007; Trenkwalder *et al.* 1995]. Both sporadic and genetic forms of PD are characterized by progressive degeneration of neurons in the striato-nigral system. In addition to the dopaminergic cell population, other groups of neurons degenerate, including cholinergic cells in the nucleus basalis, the serotonergic system of the raphe nuclei, noradrenergic neurons in the locus coeruleus, autonomic ganglia, amygdala, hippocampus, olfactory bulb, temporal cortex and cingulate cortex [Harding and Halliday, 2001]. The neuropathological hallmark is the formation of Lewy bodies (Figure 1) and Lewy neurites [Shults 2006; Takeda *et al.* 1998; Trojanowski *et al.* 1998; Spillantini *et al.* 1997; Wakabayashi *et al.* 1997]. These inclusions contain alpha-synuclein, ubiquitin and synaptic as well as cytoskeletal

components. Clinically, the striatal dopaminergic deficit leads to resting tremor, muscular rigidity and bradykinesia. Current pharmacological treatment is symptomatic and enhances dopaminergic neurotransmission. However, drug treatment is most effective only during the early course of the disease without halting the progressive loss of pigmented dopaminergic neurons in the substantia nigra pars compacta or improving other deficits related to compromised, nondopaminergic neuronal populations. Furthermore, life quality of PD patients is often hampered by nonmotor symptoms such as olfactory deficits, cognitive impairments, depression and autonomic dysfunctions. To accurately diagnose PD and effectively treat it, the understanding of its molecular pathogenesis is mandatory.

The etiology of PD is thought to be caused by a combination of environmental (toxins, lifestyle and aging) and genetic factors [for reviews, see Meredith *et al.* 2008; Terzioglu and Galter, 2008;

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Figure 1. Neuropathological findings in Parkinson's disease. (a) Pigmented neurons within the pars compacta of the substantia nigra. This neuronal subpopulation constitutes the major reservoir for dopamine in the human brain. Extracellular pigment deposits (arrowheads) indicate substantial neuronal cell loss in PD. Hematoxylin-eosin staining. Scale bar=100 μm. (b) An eosinophilic intracytoplasmic inclusion body (Lewy) is visible in this pigmented neuron (arrowhead). Hematoxylin-eosin staining. Scale bar=20 μm, applies also for C. (c) Alpha-synuclein immunoreactivity specifically detects intracytoplasmic Lewy bodies in this neuron (arrowhead).

Sulzer, 2007]. In recent years, several genes have been linked to familial forms of PD [for reviews, see Belin and Westerlund, 2008; Gasser, 2007]. The identification of these genes and the evaluation of their molecular functions were a major step forward in understanding the disease pathogenesis. In fact, the analysis of genetic but also of toxin-induced PD animal models revealed common intersecting molecular pathways associated with mitochondrial dysfunction, oxidative damage, abnormal protein accumulation, cytoskeletal dysfunction and neuroinflammation.

Interestingly, and despite the major contribution of these animal models to the understanding of PD, they also confront us with the issue that no single animal model for PD created to date mimics comprehensively the clinical and structural phenotype of the disease: nonmotor symptoms, slowly progressing motor deficits, loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies. This also indicates the lack of our knowledge towards the molecular pathogenesis, which will be required to allow specific 'targeted' molecular therapeutic interventions, and results in the fact that, at present, it remains impossible to stop the disease progression or to restore lost functions. However, animal models were instrumental in the development of current symptomatic as well as neuron replacement therapies in Parkinson's disease. Indeed, the fascinating progress in stem cell biology during the last decade in

combination with the development of appropriate animal models has opened new avenues for cell repair and replacement strategies.

Dopaminergic neurons and the molecular basis of their development

Notwithstanding, experimental or therapeutic engineering of dopaminergic cells, either obtained from adult, fetal or embryonic stem cells, or by 'pharmacological' stimulation of the endogenous regenerative capacity of a given brain area (i.e. striatum; see Figure 2), will substantially rely on the precise understanding of developmental signaling mechanisms involved in the induction, specification and maintenance of dopaminergic neurons in the substantia nigra, the cell population degenerating and in need of replacement in PD patients. Recently, substantial advances have been made to unravel the genetic network regulating these processes by using different animal models [reviewed in Smidt and Burbach, 2007; Prakash and Wurst, 2007, 2006; Castelo-Branco and Arenas, 2006].

Initially, the development of the ventral midbrain is regulated by the isthmus, a signaling center located at the junction between the prospective mid- and hindbrain and determined by the opposing location of two transcription factors: orthodenticle homeobox 2 (Otx2) and gastrulation and brain-specific homeobox protein 2 (Gbx2). Major signaling molecules at this center are

Figure 2. Cell repair strategies in Parkinson's disease. Striatal connections are received from the substantia nigra (SN) in normal brain (a). Cell death of dopaminergic neurons in the substantia nigra (as induced by a unilateral 6-OHDA lesion) leads to a dopaminergic deficit in the striatum as well as in the subventricular zone (b). Growth factor treatment in this animal model induces migration of neural progenitor cells residing in the subventricular zone towards the striatum (c).

fibroblast growth factor 8 (Fgf 8), sonic hedgehog (Shh) and wingless type 1 (Wnt1). Furthermore, the initial establishment of the dopaminergic progenitor domain in this region *in vivo* is dependent on a genetic network regulated by Wnt1. Later in development, Wnt1 also appears to initiate the differentiation of the postmitotic progeny of the dopaminergic precursors by regulating the expression of midbrain dopaminergic-specific transcription factors. In parallel to this Wnt1-regulated genetic network, a second genetic cascade regulated by Shh is involved in the induction and specification of the dopaminergic phenotype. In addition to an involvement in the establishment of the dopaminergic progenitor domain, the Shh-controlled cascade is apparently responsible for the induction of proneural transcription factors required for the acquisition of generic neuronal properties by the midbrain dopaminergic progeny. Further molecular pathways thought to play a role in the initial development of dopaminergic neurons involve the transcription factors pentraxin-related protein 3 (PTX3, also known as PTX3), engrailed 1 (EN1), engrailed 2 (EN2), nuclear receptor related 1 protein (NURR1) and the signaling molecules transforming growth factor β (TGF β) and retinoic acid. Interestingly, many of the transcription factors described above have also been identified in being essential for the maintenance of the dopaminergic phenotype in adults. Further trophic factors involved in dopaminergic

neuron maintenance constitute glial cell line-derived neurotrophic factor (GDNF), brain-derived growth factor (BDNF), fibroblast growth factor 2 (FGF2), fibroblast growth factor 20 (FGF20) and neurotrophins. The underlying intracellular mechanisms leading to their neuroprotective function remain, however, to be specified.

Taken together, during the last decade many molecular mechanisms underlying dopaminergic induction, specification and maintenance have been identified. The next step is now to understand the molecular codes of the different subsets of adult dopaminergic neurons. The knowledge of these data is instrumental for the development of new drugs to treat PD and to provide a functional cell-replacement strategy for this disease, be it exogenous or endogenous cell replacement.

Exogenous 'stem cell' repair strategies in Parkinson's disease – 14 years of expertise

As motor dysfunction is considered the most prominent and debilitating symptom and clearly linked to the dopaminergic deficit in the striatum, the major therapeutic focus aimed for many years was to replace the loss of dopaminergic neurons. As these dopaminergic cells in the substantia nigra project to the striatum, transplantation therapies using either dopaminergic or fetal

dopaminergic neurons were considered an ideal approach since the 1980s.

Stem cells are defined as immature cells with the ability to self-renew and differentiate into multiple cell types [Gage, 2000]. Different cell populations have been described as potential substrates for an exogenous cell repair strategy in neurological disorders, among them fetal dopaminergic neurons, neurons derived from embryonic stem cells (ESC), induced pluripotent stem cells (iPS), adult neural stem cells, and mesenchymal and umbilical blood stem cells transdifferentiated into dopaminergic neurons.

Dopaminergic neurons propagated and differentiated from ESC are a highly challenging option to treat parkinsonian symptoms in rodent animal models [Takahashi, 2007; Kawasaki *et al.* 2000; Lee *et al.* 2000]. Transplantation of ESC-derived dopaminergic neurons into primate models showed indeed amelioration of motor symptoms [Takagi *et al.* 2005]. However, reduced survival of cell transplants and, more importantly with respect to clinical safety, the oncogenic potential of undifferentiated ESC contaminated within the transplanted cell suspension remains an unmet challenge.

The ability to derive pluripotent cells from adult human tissues opens important opportunities in research for synucleinopathies like PD. Recently, Yamanaka and colleagues [Takahashi *et al.* 2007] and Yu and colleagues [Yu *et al.* 2007] demonstrated that expression of specific transcription factors induces adult human fibroblasts to express many of the characteristics of human embryonic stem cells. In a recent study another milestone was achieved: human iPS cells were induced to differentiate into dopamine neurons of midbrain character and were transplanted into a 6-OHDA rat model of PD. The cells showed characteristics of midbrain neurons 4 weeks after surgery. Histological analysis also showed teratoma formation, indicating that this current method still needs refinement [Wernig *et al.* 2008].

Adult neural stem/precursor cells reside within the subventricular zone of the lateral ventricle (SVZ) and the subgranular layer of the hippocampal dentate gyrus, which give rise to both neurons and glia even in adult stages [Doetsch, 2003; Gage, 2000]. Human hippocampal specimens can be obtained from epilepsy surgery and thus 'stem/precursor' cells have become

increasingly available for experimental studies. There are different protocols proving that adult stem cells can be expanded *in vitro* and differentiated into neuronal cell populations [Walton *et al.* 2006]. Cell transplantation into animal models further support their ability to anatomically and functionally integrate within the adult brain [Pluchino *et al.* 2003]. The oncogenic potential is generally assumed to be low in the adult neural stem cell population although recent findings indicate a tumorigenicity associated with rapid propagation cycles *in vitro* [Siebzehnrubl and Blumcke, 2008]. However, the study of adult human stem cells and their ability to differentiate into dopaminergic neurons will be mandatory not only for 'exogeneous' therapy strategies [Siebzehnrubl and Blumcke 2008]. These experiments are also important to confirm basic neurodevelopmental mechanisms of dopaminergic differentiation (obtained from animal models) in the human brain when targeting this cell population for an 'endogenous' regenerative approach (Figure 3; see also below).

As a third option, neural precursor cells can also be isolated from human fetal midbrain. Recent data prove their potential to differentiate into dopaminergic neurons, thus being a valuable alternative source for cell replacement strategies [Maciaczyk *et al.* 2008]. Indeed, fetal nerve cell grafts were implanted into the striatum of PD patients and were the first breakthrough of cell-based therapeutic strategies in the CNS. These cell-based approaches with transplantation of dopamine-producing fetal cells provided the central proof that transplanted neurons can survive, innervate the host brain and elicit clinical beneficial effects as demonstrated by motor improvements [Hagell and Brundin, 2001; Kordower *et al.* 1995; Lindvall *et al.* 1994]. In addition, PET-analysis even showed an increased fluoro-dopa uptake in the putamen [Hauser *et al.* 1999; Wenning *et al.* 1997] indicating that implanted cells were functionally integrated [Olanow *et al.* 1996; Kordower *et al.* 1995]. In a double blind trial published in 2001, however, only a subpopulation (younger patients) benefited from transplantation [Freed *et al.* 2001]. The second control study showed improvement in those PD patients with milder disease [Olanow *et al.* 2003] indicating that the time point for cell transplantation in PD patients will be another crucial selection criteria for the success of transplantation approaches. After initial

Figure 3. A dopaminergic cell engineered from human adult stem cells. Triple-immunofluorescence (d) of a tyrosine hydroxylase (TH) immunoreactive cell (b) co-labelled with antibodies against the neuronal marker MAP2 (a). Blue Hoechst labeling of a cell nucleus (c). This stem cell culture was isolated and expanded from a human hippocampal specimen obtained from epilepsy surgery (courtesy of Dr R. Coras; Dept of Neuropathology, Univ. Hospital Erlangen).

improvements in the first year, dystonia and dyskinesias recurred in 15% of patients who received transplants, even after reduction or discontinuation of levodopa substitution. This led to a complete halt of transplantation programs aiming to improve the neurosurgical transplantation techniques as well as the preparation methods for fetal cells [Freed *et al.* 2001]. In addition, limited access to suitable donor tissue, variability in the outcome and adverse side effects (graft-related dyskinesias) in some patients discouraged the continuation of this therapeutic option [Bjorklund *et al.* 2003]. While these trials were disappointing and led to a halt of transplantation trials in the US, open-label trials have continued with good success in individual patients [e.g. Mendez *et al.* 2005]).

Seven years later, three post-mortem studies examined long-term fetal transplant in a total of eight subjects with advanced PD. In these studies, most individuals who survived long-term after surgery showed only limited clinical benefits after transplantation [Kordower *et al.* 2008; Li *et al.* 2008; Mendez *et al.* 2008]. Strikingly, neuropathological analysis revealed alpha-synuclein inclusions within the transplanted cells in the striatum in two of the three groups. This is reminiscent of the work by Meyer-Luehmann and colleagues in AD mouse models, which demonstrated that deposition of aggregates can be induced in grafted cells [Meyer-Luehmann *et al.* 2008, 2006]. These reports raise several important questions: How was alpha-synuclein pathology transmitted to the grafted cells? What

induced the misfolding and aggregation of alpha-synuclein within the initially healthy fetal donor cell [Braak and Del Tredici, 2008]?

Several factors may have contributed to the spread of alpha-synuclein to the grafted cells, including lack of immunosuppression, cell preparations and surgical techniques. One alternative explanation may be linked to the endogenous spread of alpha-synuclein via striatal projections from the cerebral cortex and thalamic nuclei, affected by Lewy pathology in late-stage PD, as suggested by Braak and colleagues [Braak and Del Tredici 2008].

Did alpha-synuclein pathology affect the function of the graft? This is unlikely, as more than 90–99% of grafted neurons did not reveal any pathology [Li *et al.* 2008]. Instead, host PD progresses and the grafts may not continue to provide long-term benefits in some of these patients. To examine PD pathology in grafted neurons is an interesting option, although functionality and benefits to patients are even more important, and so far these studies do not suggest that the PD graft pathology should compromise functionality of the grafts. Taking these considerations together at present exogenous approaches need a deeper understanding of underlying graft–host interactions, integration mechanisms and immunogenicity of exogenously added cells, due to the limitations in cell sources or preparations of cells.

Endogenous approaches – future options for the treatment of PD

Despite several open-label and controlled trials of exogenous cell repair treatment, long-term evaluation of exogenous cell repair treatment is still pending and controversial. There are two important facts to be addressed that also consider nondopaminergic regions to be affected in PD: (1) there are several clinical deficits before the onset of motor symptoms that support early non-dopaminergic involvement: REM sleep behavior, subtle cognitive deficits, depression, olfactory dysfunction and constipation [for a review see Ahlskog, 2007]; (2) some brain areas that are associated with a subset of these functions, in particular the hippocampus and the olfactory bulb, contain stem- and progenitor cell populations and are regions of continuous generation of new neurons and represent, therefore, areas of long-living self-maintenance. As mentioned

above, neurogenesis occurs in the subgranular (SGZ) zone of the hippocampal dentate gyrus and the (SVZ) adjacent to the lateral ventricles. Adult neurogenesis involves three crucial steps: (1) asymmetric cell division of a stem cell, resulting in one daughter stem cell and one with the potential to develop into a neuron; (2) the second step is the migration of the newborn cell to its final and appropriate destination in the brain; (3) the final step involves the maturation of the cells into a neuron that forms both efferent and afferent connections within the brain. Importantly, disease processes may interfere at different levels during the generation and maturation of newly generated cells. In the dentate gyrus the newly generated cells differentiate into neurons in the granule cell layer and extend dendritic processes into the molecular layer and axonal processes towards their target area in CA3 [Zhao *et al.* 2006]. In the SVZ/olfactory bulb system, newborn cells arising in the SVZ normally migrate along the rostral migratory stream to the olfactory bulb where they differentiate into GABAergic and dopaminergic neurons [Ming and Song, 2005]. This pool of endogenous neural stem cells of the adult brain provides an alternative and attractive cell source for cell repair strategies. Furthermore, recent data encourage research efforts to target endogenous neural stem and progenitor cells for the treatment of early nonmotor symptoms in PD.

Neurotoxin-induced models of Parkinson's disease challenge adult neurogenesis

Several neurotoxin-induced animal models of PD have revealed severe alterations in adult neurogenesis, in particular decreased proliferation and/or survival of newly generated neurons. In 6-hydroxydopamine (6-OHDA) lesion models, which result in an acute cell death in the substantia nigra, a decreased SVZ proliferation was reported by several groups [Winner *et al.* 2006; Baker *et al.* 2004; Hoglinger *et al.* 2004]. Interestingly, as supported by a recent study, the proliferation rate is also affected in patients with PD, as is suggested by the decrease in the number of mitotic cells in the SVZ as well as in the hippocampus [Hoglinger *et al.* 2004]. Moreover, toxin-induced models show an increase in dopaminergic neurogenesis in the olfactory bulb glomerular layer, which has been described for the MPTP [Yamada *et al.* 2004] as well as for the 6-OHDA model [Winner *et al.* 2006]. This finding is of particular interest,

as an increase in dopaminergic olfactory neurons has been observed in the olfactory bulb of PD patients [Huisman *et al.* 2004] and parallels these experimental findings.

Does neurogenesis in the substantia nigra provide new dopaminergic neurons for Parkinson's disease?

This idea has stimulated several research groups. The fundamental question: does neurogenesis normally take place in the adult substantia nigra, or is such a process stimulated by damage or disease? Undoubtedly cell division takes place in the adult substantia nigra, but the majority of dividing cells appear to differentiate into different types of glial cells [Steiner *et al.* 2006; Chen *et al.* 2005; Lie *et al.* 2002; Mao *et al.* 2001]. One explanation may be that the microenvironment does not provide a suitable neurogenic niche to enable neuronal differentiation [Lie *et al.* 2002]. After all, there is still no unequivocal evidence that neurogenesis takes place in the human substantia nigra pars compacta of humans. If it does at all, the basal rate is not sufficient to compensate for the loss of dopaminergic neurons that occurs in PD [Yoshimi *et al.* 2005]. Three recent studies have once again suggested that neurogenesis may occur in the adult substantia nigra and, in one study, even restore lesion-induced behavioral deficits [Van Kampen *et al.* 2006, 2005; Shan *et al.* 2006]. A comprehensive review presents evidence that there are technical shortcomings in each of these three studies [Borta and Hoglinger, 2007].

Is the striatum the target region for endogenous replacement?

Another important focus of stem cell research has been looking to repopulate the dopamine depleted striatum. This approach seems compelling due to the close proximity of the SVZ containing the pool of endogenous stem- and progenitor cells. Several groups studied the effects of different growth factors or a combination of them; for example, GDNF, TGF β , platelet-derived growth factor (PDGF), epidermal growth factor (EGF), FGF2, liver growth factor and BDNF on striatal neurogenesis in rats with nigral lesions [Winner *et al.* 2008]. Interestingly, many of these factors are capable of inducing neuroblast migration to the dopamine-depleted striatum, but newly generated dopaminergic

neurons have not been identified [Reimers *et al.* 2006; Chen *et al.* 2005; Mohapel *et al.* 2005]. In conclusion, there seem to be direct dopaminergic effects on the endogenous stem- and progenitor cell population. Future studies are warranted to determine the interplay between dopamine-related mechanisms on the brain's regenerative potential and alpha-synuclein pathology.

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Conflict of interest statement

None declared.

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