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Seminars in Cell & Developmental Biology 18 (2007) 859–869

seminars in
CELL & DEVELOPMENTAL
BIOLOGY

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Review

Restorative cell therapy for Parkinson's disease: A quest for the perfect cell

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Available online 8 September 2007

Abstract

The development of a cell therapy for the neurodegenerative disorder Parkinson's disease is a realistic ambition. It is pursued by researchers and companies alike, and spans different donor tissue types of embryonic, fetal and adult origins. In this review, we briefly outline the past and current status of research and clinical trials with cell transplantation in Parkinson's disease. We discuss studies on donor tissue derived from embryonic ventral mesencephalon and assess the current research on various forms of stem cells of both embryonic and adult origins in the quest to develop a cell-based therapy for this debilitating movement disorder.
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Keywords: Parkinson's disease; Cell transplantation; Restorative medicine; Ventral mesencephalon; Neural stem cells; Adult stem cells; Embryonic stem cells; Review

Contents

1. Introduction

Parkinson's disease (PD) is the second most prevalent motor neuron movement disorder and affects 150 in 100,000 [89]. It results in a reduced quality of life. The symptoms are largely due to the loss of dopaminergic neurons in the substantia nigra (SN) pars compacta within the midbrain [89]. These neurons innervate the caudate nucleus and the putamen [76], which are areas of the brain that primarily control voluntary motor function. The most prominent symptoms in this disease are progressive development of bradykinesia, rigidity, postural instability and a resting tremor. Alterations of the serotonergic, GABAergic and cholinergic pathways and noradrenergic pathways are also evident in PD [76]. Currently, the major forms of treatment include oral

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1084-9521/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcdb.2007.09.004

administration of the dopamine precursor levadopa (L-Dopa), in combination with a peripheral dopa decarboxylase inhibitor, with the aim of restoring dopaminergic neurotransmission in the failing nigrostriatal pathway. Levadopa crosses the blood-brain barrier, is then converted into dopamine, mostly by spared dopamine neurons and released from nigrostriatal dopaminergic nerve terminals; thus stimulating postsynaptic dopamine receptors [47]. Some evidence also indicates that residing serotonergic neurons may also convert L-Dopa into dopamine [4,33]. However, the treatment is coupled to unwanted side effects such as L-Dopa-induced dyskinesis and often, in later stages, psychiatric disturbances [24,47]. In addition, L-Dopa loses its effectiveness as the remaining native neurons further degenerate and cannot synthesize and release enough dopamine from the administered L-Dopa [76]. Typically patients then fluctuate between a state when they are immobile (called "off") and periods in which they are able to move or even have dyskinesias ("on" periods). Eventually, the time spent in "on" diminishes and the patients spend almost all of their time in the "off" state and end up bedridden. In addition to L-Dopa therapy, other means to boost the ailing dopaminergic neurotransmission are used, for example, directly acting dopamine agonists and inhibitors of monoamine oxidase B (MAO-B) and catechol-*O*-methyl transferase (COMT), which prevent the breakdown of dopamine [32]. Alternately, surgical intervention, such as deep brain stimulation of the subthalamic nucleus can change neuronal activity in the basal ganglia in a manner that facilitates movement [99]. Unfortunately, none of these treatments are restorative, nor can they alter the natural history of the disease. As a consequence, the patients always exhibit progressive worsening over time. Cell replacement is therefore considered an exciting alternative for brain repair in PD, although the technique still remains at an early stage of development. This approach aims to replace the failed nigrostriatal pathway, which may allow patients to acquire long-lasting benefits from the treatment. In our quest for the perfect cell, we aim to generate a dopaminergic neuron that may produce and secrete dopamine. It must form extensive axonal outgrowth and form synapses, which interact with host neurons. It must also be able to autoregulate dopamine release and in the ideal world, this dopaminergic neuron is immunologically compatible. In this review, we outline different cell sources for transplantation (Fig. 1), briefly describe the outcome of previous clinical trials and outline the future perspectives for cell therapy treatment for PD.

2. Use of ventral mesencephalic tissue: a historical perspective

The two first studies showing the therapeutic benefit of transplanted embryonic ventral mesencephalon (VM) in experimental animals was published in 1979 by Perlow et al. [69], and by Bjorklund and Stenevi [9]. These studies indicated that

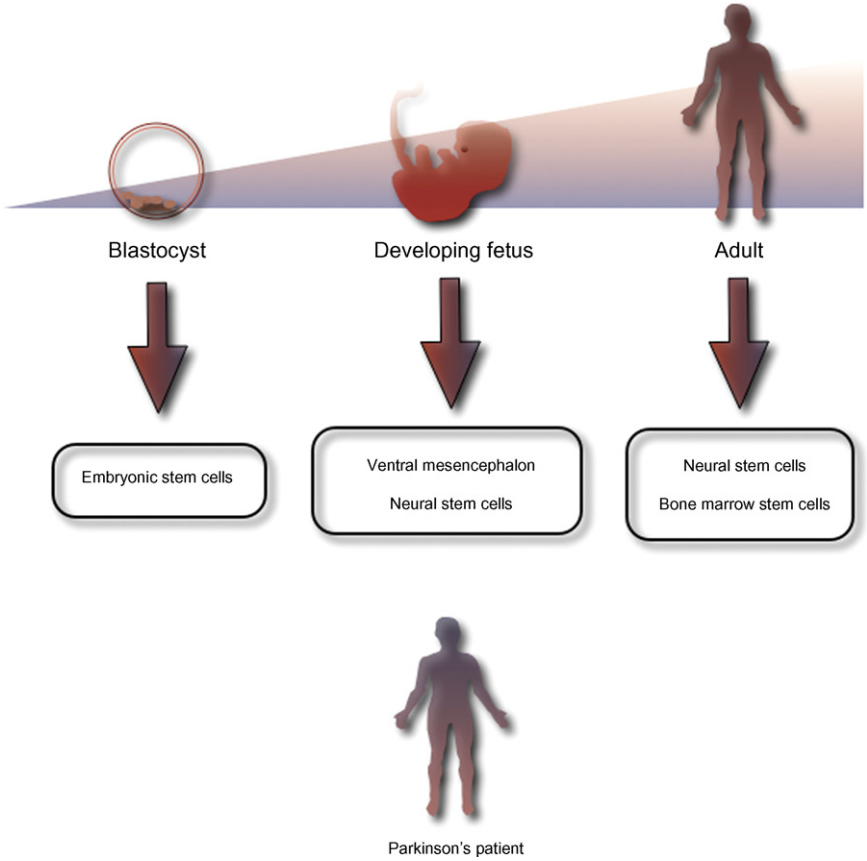

Fig. 1. Current sources of cells considered useful for research and development of cell therapies for treatment of Parkinson's disease may be derived from embryonic, fetal and/or adult origins.

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