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Research Report

Cell therapy for Parkinson's disease: Functional role of the host immune response on survival and differentiation of dopaminergic neuroblasts ☆

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder, whose cardinal pathology is the loss of dopaminergic neurons in the substantia nigra. Current treatments for PD have side effects in the long term and do not halt disease progression or regenerate dopaminergic cell loss. Attempts to compensate neuronal cell loss by transplantation of dopamine-producing cells started more than 30 years ago, leading to several clinical trials. These trials showed safety and variable efficacy among patients. In addition to variability in efficacy, several patients developed graft-induced dyskinesia. Nevertheless, they have provided a proof of concept that motor symptoms could be improved by cell transplantation.

Cell transplantation in the brain presents several immunological challenges. The adaptive immune response should be abolished to avoid graft rejection by the host. In addition, the innate immune response will always be present after transplanting cells into the brain. Remarkably, the innate immune response can have dramatic effects on the survival, differentiation and proliferation of the transplanted cells, but has been hardly investigated.

In this review, we analyze data on the functional effects of signals from the innate immune system on dopaminergic differentiation, survival and proliferation. Then, we discussed efforts on cell transplantation in animal models and PD patients, highlighting the immune response and the immunomodulatory treatment strategies performed. The analysis of the available data lead us to conclude that the modulation of the innate immune response after transplantation can increase the success of future clinical trials in PD by enhancing cell differentiation and survival.

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects more than 1% of people over the age of 60. PD's patients suffer several motor symptoms as bradykinesia, rigidity, resting tremor and postural instability (Lesage and Brice, 2009; Obeso et al., 2010). The principal feature of this disease that accounts for most of its motor symptoms is the progressive loss of dopaminergic (DA) neurons (DAn) located in the *substantia nigra pars compacta* (SN) (Lesage and Brice, 2009; Obeso et al., 2010). At the moment, approved treatments include pharmacological replacement of dopamine and electrical inhibition of specific areas such as the sub-thalamic nucleus. Oral intake of DA precursors or agonists can control motor-symptoms in PD patients. However, the continuous use of anti-PD medications in mid- or end-stage PD patients can lead to undesired side effects such as drug-induced dyskinesias, motor fluctuations and autonomic disturbances, among others, that severely affects their quality of life (Piquet et al., 2012). Thus, there is an urgent need to develop therapeutic strategies that prevent cell death of DAn or can replace the DAn lost (Lesage and Brice, 2009; Obeso et al., 2010; Piquet et al., 2012).

More than 30 years of pre-clinical and clinical efforts have provided proof of concept that the transplantation of DA neuroblasts in the striatum can alleviate parkinsonian symptoms (Wijeyekoon and Barker, 2009). Still, the clinical efficacy achieved with this strategy is variable. The efficacy of this therapy relies on several factors including age of the patient; number, preparation and storage of the DA neuroblasts transplanted; transplantation site; host immune response and presence (or not) and type of immunosuppressive treatment, among others. In addition, it was observed that some patients suffered side-effects as graft-induced dyskinesia from these interventions (Barker et al., 2013).

In all, the available information indicates that, although cell therapy had provided benefits and the safety parameters required were fulfilled, further refinement is needed in order to obtain an established treatment (Hauser et al., 1999; Piccini et al., 1999; Freed et al., 2001; Khanna et al., 2007; Roskom et al., 2009; Piquet et al., 2012, Barker et al., 2013; Lindvall, 2013). Illustrating this point, there is an on-going multicentric effort conducted in 14 institutions in 5 European countries to test the efficacy and safety of the transplantation of fetal ventral mesencephalic cells containing DA neuroblasts (VM cells) in PD patients (Barker, 2010).

As stated above, the host immune response to the transplanted cells and its modulation by immunosuppressive treatments can influence the success of cell therapy against PD. The immune response can modulate different processes such as the survival, proliferation, differentiation and engraftment of the transplanted cells. Certainly due to the impact on functional engraftment, the immune response to the graft needs to be fully studied in order to refine possible future cell-based therapies. However, there is a major lack of information on this issue.

The aim of this review is to discuss the available data on the possible functional consequences of the host immune response to the transplanted DA neuroblasts in Parkinson's disease focusing on the potential use of stem cell technology.

2. The brain immune privilege and the functional effects of the immune response on cell proliferation, differentiation and survival

An immune response to transplanted cells in the brain is similar to others in that it involves an innate and adaptive response, but differs significantly from other organs. The brain is considered an immune privileged site due to the presence of the blood brain barrier (BBB), the low or absent expression of MHC molecules, an immunosuppressive environment mainly due to the expression of anti-inflammatory molecules such as TGF-beta and the lack of dendritic cells, among other factors (Perry et al., 2010; Roca et al., 2011). This immune privilege favors antigenic ignorance and delays or inhibits antigen recognition and the subsequent adaptive immune response, but is very far from being absolute (Lowenstein et al., 2007; Perry et al., 2010). For example, non-activated immune cells can cross an intact BBB (Lowenstein et al., 2007; Perry et al., 2010).

Immune privilege of the brain is one of the bases for claims that cell transplantation will not elicit an immune response of a sufficient degree to affect transplanted cells into the brain. We believe that this view is an oversimplification. Cell transplantation may or may not elicit an adaptive immune response depending on several variables, but will trigger, irremediably, an innate immune response with undoubted physiological consequences, reviewed in Mathieu et al. (2010). Most of the available studies are focused on the adaptive immune response because this decides whether a graft will survive or not after transplantation. But the innate component of this immune reaction has been hardly studied.

This is in contrast with the dramatic effects of molecules related to the innate immune response on the survival, proliferation and differentiation of adult stem/progenitor-derived neuroblasts (reviewed in Mathieu et al., 2010). For example, overall, it is assumed that pro-inflammatory molecules such as Interleukin(IL)-1beta or Tumor necrosis factor(TNF)-alpha, can exert anti-neurogenic effects, while anti-inflammatory cytokines such as Transforming growth factor beta, IL-4 and IL10 can have pro-neurogenic effects (reviewed in Mathieu et al., 2010). However, data on similar but not identical types of neuroblasts as the ones transplanted in PD models can be useful to propose hypotheses but not to ascribe effects of a given cytokine or chemokine to a DA neuroblast.

Scarce but valuable data on the functional effects of immune-related molecules on DA neuroblasts are available. Pioneer work by P. Carvey and colleagues showed that cells from embryonic rat mesencephalon can be differentiated into DAn using a combination of IL-1, IL-11, leukemia inhibitory factor, and Glial cell line-derived neurotrophic factor (GDNF) (Carvey et al., 2001). IL-1beta can induce key molecules such as Nurr1 and Pitx3, followed by upregulation of tyrosine hydroxylase (TH) in midbrain-derived neural precursor cells already committed to the mesencephalic dopaminergic phenotype (Sabolek et al., 2009). TNF-alpha was shown to increase the efficiency of dopaminergic differentiation in cultures derived from E12.5 embryos, but promoted a decrease in DAn in cells cultures from E14 or E16 mice (Doherty, 2007). In addition, the TNF receptor