·Minireview·

How to improve the survival of the fetal ventral mesencephalic cell transplanted in Parkinson's disease?

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Abstract: It has been extensively confirmed that fetal ventral mesencephalic cell (VMC) transplantation can ameliorate the symptoms of Parkinson's disease (PD). But there are still several problems to be resolved before the extensive clinical application of this technology. The major limitations are the poor survival of grafted dopamine (DA) neurons and restricted dopaminergic reinnervation of host striatum. Some attempts have been made to solve these problems including use of some trophic factor and co-transplantation with neural/paraneural origins. The purpose of this review is to overview advances of the means improving the survival of grafts and their current limitations.

Keywords: Parkinson's disease; cell transplantation

1 Introduction

Parkinson's disease (PD) is a chronic neural degeneration disease caused by selective loss of dopamine (DA)-secreting neurons in the substantia nigra (SN) and the subsequent degeneration of striatal dopaminergic fibers. This specificity of cellular degeneration has made PD the most accessible therapeutic application for cell transplantation[1]. Intrastriatal transplantation of fetal ventral mesencephalic cells (VMC) has been attempted in rodent[2] and nonhuman primate model[3] as a potential treatment of PD. To this day, a number of patients have received VMC implantation and shown various degree of improvement of functional deficits[4]. However, the clinical efficacy of neural transplantation has not reached a level to justify its use as a routine therapeutic procedure for PD. The major limitations are the poor graft survival, restricted sprouting of dopaminergic fibers, and ethical issues linked to the minimum of initial human fetal tissue number required in cell replacement strategy[5]. Studies in both rats and humans suggest that only 5%-20% of the DA neurons harvested from embryo actually survive the grafting procedure[6]. From available data, it seemed that the detrimental triggers including hypoxia/ischemia, less trophic factor surpport, and oxidative stress may exert the most impact on DA grafts survival[7].

At present, a bulk of attempts have been made to counteract these problems by utilizing trophic factor[8], antioxidants[9], antiapoptotic agents[10], co-transplantation approach[11], immunodepressive drugs[12] and gene transfer technology[13]. In this review, recent findings with regard to the approaches improving the survival of the grafts in PD are described.

2 Current neuroprotective strategies

2.1 Trophic factors It has been well verified that the survival and differentiation of developing neurons are affected to a large extent by the trophic factors produced by the developing organism. The expressions of these factors are dynamic and often with distinct temporal periodicities. Consequently, the trophic milieu experienced by neurons which develop *in situ* will be quite different from that encountered by fetal neurons which are removed from their normal environment and transplanted into the mature nervous system[14]. Therefore, some scholars have suggested that one possible explanation to the low survival of grafts may be the deficiencies in the trophic environment provided by host brains[15]. Several identified and unidentified neurtrophic factors have been investigated for their potential to improve embryonic VMC survival in culture and the following transplantation.

2.1.1 Glial cell lined-derived neurotrophic factor Glial cell

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line-derived neurotrophic factor (GDNF), which belongs to the transforming growth factor-β superfamily, has been originally identified as a trophic molecule for midbrain dopaminergic neurons. GDNF exerts its neuroprotective and neural restorative effects on DA neurons via the tyrosine kinase receptor c-Ret and the ligand binding component GDNF-family receptor α1(GFRα1)[16]. It is well documented that GDNF can reduce dopaminergic neurons apoptosis, increase the survival and differentiation of fetal dopaminergic cell *in vitro*[17]. It has also been shown that GDNF can increase dopaminergic cell survival, graft-derived fiber outgrowth and overall functions of the graft after neural transplantation in rodent model of PD[18]. But the effect depends on the juncture and the dose of the GDNF addition. Winkler C and his colleagues found if grafts were exposed to GDNF continuously as mature dopaminergic neurons, their ability to improve spontaneous motor behavior in parkinsonian rats may be impaired. This study also indicate that intrastriatal administration of GDNF at the time of or shortly after grafting is highly effective in initially promoting the cell survival and the fiber outgrowth from the grafts[19].

2.1.2 Erythropoietin Erythropoietin (EPO), which is well known as a hematopoietic cytokine with functions in erythrocyte development[20], has received considerable recent attention as neuroprotective therapy for central nervous system (CNS) injury[21]. EPO and EPO receptors have been verified expressing extensively within the CNS, in cultured neurons and astrocytes[22]. In the research of Csete *et al*., EPO receptor has been reported to be colocalized with tyrosine hydroxylase (TH), the rate-limiting enzyme of the DA synthesis, in all dopaminergic neurons of the adult rat SN as well as dopaminergic neuroblasts from the ventral mesencephalon, and exhibited neuroprotective effects against 6-hydroxydopamine(6-OHDA) exposure on cultured dopaminergic neurons[23]. Moreover, EPO was found to be able to induce the differentiation of neural stem cells to a dopaminergic lineage that may be efficacious than GDNF in this action[24].

In 2006, McLeod *et al*. found survival of grafts, TH-immunoreactive (TH-ir) dopaminergic fiber outgrowth and the ratio of blood vessel volume to graft volume increasing after hibernation with EPO and/or GDNF during cool storage prior to fetal VMC transplantation. They also indicate that EPO exerts its protective function through a 66-kDa cell surface receptor (EPO-R), which belongs to the cytokine receptor type I super family and induces signal-transduction pathways via the phosphorylation of non-receptor tyrosine kinase Jak-2/signal transducer, activating Stat 5a/5b, the Ras/mitogen-activated protein kinase (MAPK), and PI3-K/Art signaling pathways that are involved in the inhibition of apoptosis[25,26]. In addition, EPO may exert a depletion effect on accumulated iron, which has been suggested as another possible mechanism in the pathogenesis of PD[27]. Finally, since disruption of the blood-brain barrier (BBB) has been reported in PD, the well-known protective effect of EPO on the integrity of the BBB may promote its therapeutic effect on PD[28,29].

2.1.3 Other trophic factors Besides GDNF and EPO, there are also some other trophic factors used to improve the survival of the grafts, including brain derived neurotrophic factor[30], fibroblast growth factor (FGF)[31], nerve growth factor (NGF)[32] and so on. Although studies performed in different laboratories have convincingly established that exposure of DA grafts to some trophic factors during storage prior to transplantation or repeated injection of trophic factors into the implantation site will improve the grafts survival efficaciously, the optimal factors for support of DA grafts should be further identified. In addition, the proper dose and administration route of trophic molecule need to be investigated.

2.2 Antioxidants and antiapoptotic agents It has been suggested that the oxygen free radicals resulting from the inevitable cellular hypoxia and trauma during preparation and grafting of the VMC may provoke membrane lipid peroxidation, and consequently reduce the survival of DA neurons in the transplants[33]. The lazaroids, a group of compounds which have been developed for acute treatment of CNS injury, have been confirmed to improve the survival of grafted embryonic dopaminergic neurons by animal experiments[34]. Brundin and his colleagues found when tirilazad mesylate was administered to mesencephalic tissue prior to implantation and intravenously to patient for 3 d after surgery, the patients experienced the same improvement on functional performance and striatal [^{18}F] fluorodopa uptake as the previous patients who were implanted with twice much mesencephalic tissue[35].

Number of published studies has signified that counteracting apoptosis which triggered by oxidative stress, hypoxia, withdrawal of trophic factors, and anoikis may be another critical intervention points[7]. However, the inability of different experimenters to generate consistent improvement of implanted DA neuron survival has led to ar-

gument about the efficacy of caspase inhibitor[36]. One possible interpretation to the inefficacy of caspase inhibitor may be the majority of cell loss attributed to anoikis [apoptosis due to the detachment from the extracellular matrix (ECM) and neighboring cells] during tissue preparation and the first week following graft[37]. Marchionini and his colleagues have utilized the ECM molecule tenascin-C (tenascin) and antibody (Ab) to the cell adhesion molecule (CAM) L1 to specifically mimic the survival signals induced by cell-matrix and cell-cell interactions. Their findings further confirmed the view that cell density can dramatically influence the degree of stress placed on TH-ir neurons and consequently affect the success of survival strategies *in vivo*[38].

2.3 Co-transplantation with other cells

2.3.1 Olfactory ensheathing cells Olfactory ensheathing cells (OEC) are located in the olfactory nerve and in the first two olfactory bulb layers, and share properties with both glia from the peripheral nerveous system, Schwann cells, and a glial cell type from the CNS—the astrocyte[39]. Indeed, OEC are thought to be responsible for the continuous growth of new axons into the CNS tissue that takes place in adult mammalian olfactory systems. For this reason, many attempts to repair damage in injured CNS have relied on the use of OEC grafts. It has been demonstrated that OEC have the capacity to promote regeneration of CNS axons both *in vivo* and *in vitro*[40]. In this line, a recent study[41] sought to research whether co-transplantation VMC together with OEC had an effect on rat model of PD. Their results suggested that OEC may improve the survival of the VMC grafts and the growth of the axons. These findings were confirmed again by Johansson *et al*[11].

It has been speculated that the retrograde axonal transport of neurotrophic factors such as BDNF and GDNF secreted by OEC might lend contributory effect to this recovery. These neurotrophin could reach the target area through retrograde vesicular transport by binding to trkA/ret receptor complex[42]. In summary, OEC have been widely used in the field of the repair of the CNS injury, on account of their unique characteristics consistent with the inherent role of supporting neurogenesis throughout life. The present exciting outcome should stimulate more and more studies directed at characterizing the transplanted OEC at a cellular or molecular level.

2.3.2 Carotid body glomus cells The carotid body (CB) is a chemosensory organ located near the bifurcation of the common carotid artery and contains DA-rich, chromaffin-like glomus cells, which are neural crest-derived cells and release large amount of DA in response to hypoxic conditions[43]. CB is also known to express some neurotrophic factors, such as GDNF, BDNF and neurotrophin-3 (NT-3). In 2004, Shukla and his colleagues demonstrated the co-transplantation of the CB glomus cells with VMC in the 6-OHDA-lesioned rat model of PD. At twelve weeks post-transplantation, the rats co-transplanted with CB cells and VMC exhibited significant increase in TH-ir and attenuation in amphetamine induced circling behavior compared with CB cells or VMC transplanted alone rats. These results may be explained by the fact that CB cells provide higher DA levels and secret many growth factors simultaneously. Otherwise, the fetal VMC and CB can be obtained from the same fetal source, which may also reduce the initial number of fetuses required[44].

2.3.3 Other cells Fetal VMC has also been co-grafted with a wide variety of other tissues or cells, including peripheral nerve/Schwann cells[45], immature astrocyte[46], striatal tissue[47], Sertoli cells[48] and fetal kidney[49]. Motor function improvements were observed in all these research. The common mechanism underlying the increase in survival, fiber density and function may be the continuous support on the implanted fetal VM provided by neurotrophic factors.

2.4 Immunodepressive drugs The brain was once regarded as an "immunologically privileged site", the mechanisms underlying which are the absence of professional antigen-presenting cells (APCs), the sparse lymphatic drainage from the CNS, and the BBB[50]. It is clear now that the CNS does not display absolute immunological privilege, because activated lymphocytes can cross the BBB. Certain cells such as microglia may have an APC capacity and there is lymphatic drainage from the CNS into the deep cervical lymph nodes. In addition, in the context of neural grafting, there will be inevitable damage to the BBB[51]. Experimental studies in animal models also revealed that the allograft rejection of the brain following intracerebral transplantation was also found in the PD patients who accepted fetal dopaminergic grafts[52]. Data from some studies even demonstrated that inflammatory reactions could lead to not only poor graft survival and functional deterioration, but also the development of dyskinesias[53].

To date, there are no immunosuppressive drugs and protocols designed particularly for neural transplantation. Cyclosporin-A (CsA) is currently the most widely used

immunosuppressant drug in neural transplantation and has been deemed to be able to increase the grafts survival. However, it has many harmful systemic side effects and lead to the discussion whether application of immunosuppressive does more harm than good. In recent years, the neuroimmunophilin ligands have been investigated for their roles in neural transplantation. Two key drugs are tacrolimus (TAC) or FK-506, and rapamycin (RAPA) or sirolimus. In addition to their potent immunosuppressive effects, these drugs have also been found to have neuroprotective effects. Studies have shown that TAC increases the survival of dopaminergic cells in both cultures and grafting models in rodents. As well, the drug increases the length of neuritis extending from these cells[54]. Although immunosuppression may be a key issue in neural transplantation, the most effective protocols with the least side effects still need further evaluation.

2.5 Gene transfer technology Advances in molecular biology and virology in recent years enable the gene transfer technology to proceed forward and become a hot pot in the field of neural transplantation, thus augment the therapeutic efficacy. Gene transfer[55] and bcl-2 overexpression[56] were used for attempting to protect grafted dopaminergic cells from their apoptotic fate. No differences in cell survival between the bcl-2 overexpressing treatment groups and controls. However, TH-ir neurite extension was enhanced with bcl-2 overexpression. As a result, rats implanted with transgenic DA cells showed most rapid and pronounced decreases in drug-induced rotational behavior. These findings highlight the future of gene transfer technology as a strategy to augment dopaminergic neurons effectiveness after transplantation.

3 Summary

At present, fetal VMC transplantation in both animal models and patients of PD have showed improvement in functional deficits, but the low graft survival and innervation of the host striatum following neural transplantation are issues to be surmounted in order to achieve the optimal repair. Previous studies have provided encouraging evidences that neurotrophic factor, antioxidants, antiapoptotic agents and co-transplantations are useful for enhancing the functional integration of neural grafts into the impaired brain of the host. However, most of research is still in the stage of animal testing, their safe and long-term efficacy will require further detection and evaluation.

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如何提高帕金森病中脑细胞移植中的细胞存活率？

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摘要: 虽然胚胎中脑细胞移植对帕金森病的疗效已得到广泛证实，但在这项技术广泛应用于临床之前仍有一些问题亟待解决。其中主要是移植物存活率低和宿主纹状体神经支配恢复有限。迄今为止，人们尝试了很多方法来解决这些问题，包括神经营养因子的广泛应用，以及神经和(或)非神经来源组织的联合移植。本文将对目前的胚胎中脑细胞移植术中所用的神经保护手段及其局限性进行简要的介绍。

关键词： 帕金森病；细胞移植