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Mini Review

Counting on Mesenchymal Stem Cells: A Hope for Treating Parkinson's Disease

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Abstract

Mesenchymal Stem Cells (MSCs) are reported to take part in tissue regeneration both at cellular and molecular levels. Here, we have reviewed the potential role of MSCs for the treatment of Parkinson's Disease (PD). MSCs, as such, their secretory neurotrophic factors and/or exosomes are found to be involved in partial reversal of the disease symptoms in case of animal model of PD. Since there is no proven long-term effective means for treatment of PD patients, it is extremely desirable that MSC-based cellular therapy is given due importance and more prospective pre-clinical and clinical trials are undertaken.

Keywords: Dopaminergic neurons; Cell therapy; Exosomes; Mesenchymal stem cells; Parkinson's disease

Introduction

MSCs, commonly known as mesenchymal stem or stromal cells and less popularly known as medicinal signaling cells, are group of cells having fibroblastic morphology with stem cell like properties [1]. MSCs were first isolated from the bone marrow as a Colony Forming Unit Fibroblasts (CFU-Fs) by Friedenstein et al. [2]. Afterwards, these cells were identified in different tissues like adipose, liver, skeletal muscle, pancreas, kidney, placenta, Wharton's jelly of umbilical cord, etc. [3]. The isolation of these cells were not only restricted to human, mouse and rat; but also from other animals such as buffalo, horse, sheep, dog, goat, etc. [4]. MSCs of different tissues have distinct origins, for example, embryonic MSCs are derived from neuroepithelium [5], whereas MSCs of skeletal muscle, pancreas, adipose tissue and placenta are perivascular in origin [6]. Similarly, dental pulp MSCs are known to be originated from glial cells [7]. Because of their diverse tissue origins, International Society of Cellular Therapy (ISCT) has recommended three minimal criteria for defining MSCs: a) plastic adherence, b) positive expression for CD73, CD90 and CD105 and negative expression for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II, and c) ability to differentiate into adipocyte, osteocyte and chondrocyte lineages [8]. It has been shown that besides mesenchymal lineage, MSCs can differentiate into other lineages, such as neurons, islet-like cells, lung epithelial cells, etc. [9]. MSCs are also shown to express a few neuron-specific genes and proteins, like MAP2, TUJ1, nestin [10,11]. Apart from their potential of neuronal differentiation, MSCs also secrete many trophic factors that are known to have anti-apototic, neuroprotective and immunomodulatory effects on the target cells [12]. Being immunomodulatory and hypoimmunogenic nature, MSCs have been considered as an ideal candidate for cell-based therapy [13].

Parkinson's Disease

It is a neurodegenerative disease with the hallmark of tremor, rigidity, bradykinesia and postural instability [14]. In 1817, Dr. James Parkinson in his famous book "An Essay on shaking palsy" described the disease as 'Shaking Palsy'. Later, it was renamed to 'Parkinson's Disease (PD)' by Dr. Jean Martin Charcot. In PD, neuro-degeneration occurs in nigro-striatal neurons that are projected from substantia nigra to caudate putamen. It was reported that the onset of disease was observed only after the degeneration of 43.2% tyrosine hydroxylase-positive cells of substantia nigra and 80.3% of dopaminergic transporter positive cells of striatum, thus considered a slow progressing disease [15].

Current PD treatment, involves medication of levodopa along with carbidopa and Deep Brain Stimulation (DBS). However long-term remission have not been observed as these procedures neither counteract the progression of neuron degeneration nor show effectiveness at the advance stages of the disease [16]. Above limitations has been the impetus on a cell-based therapy for PD patients [17].

Several attempts have been made by transplanting human mesencephalic tissue in caudate putamen of PD patients [18-20]. Study of long-term efficacy of these cells showed that patients were free from the pathological signs even after 14 years of transplantation [21] and the normal functional improvement continued till 18 years post therapy [22]. However, due to limited availability and ethical issue of using fetal mesencephalic tissues, alternate cell sources have been explored for the treatment of PD. In this regard Embryonic Stem (ES) cells, induced Pluripotent Stem (iPS) cells, neural stem cells and MSCs are most familiar. The use of ES cells is linked with the risk of tumour formation; moreover their clinical applications have been ethically restricted in many countries [23]. The iPS cells, on the other hand, besides inducing teratoma can also transmit concomitant illness to the patient [24]. Whereas, the neural stem cells are limited due to the shortage of donors [25]. Out of all the possible stem cells types that can be used for therapy, MSCs are considered highly promising owing to simple isolation and culture procedure, hypoimmunogenic (do not express HLA-II and but express HLA-G), immunomodulatory (secrete prostaglandin E2, TGF-β1, HGF, SDF-1α, indoleamine-2,3-dioxygenase, IL-4, IL-6 and IL-10), anti-apoptotic (secrete VEGF, HGF, IGF-1) properties, and ability to

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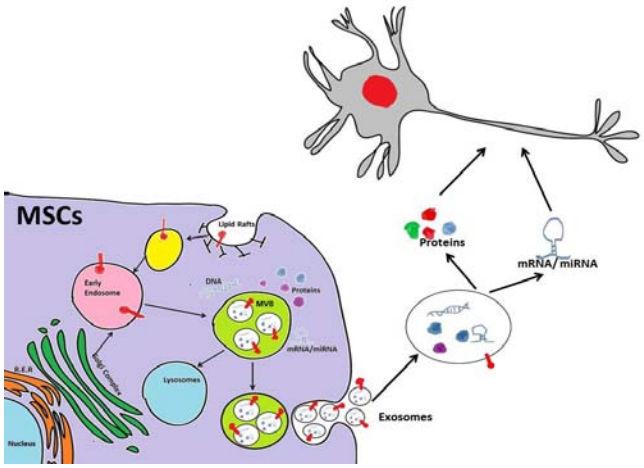

Figure 1: Exosomes are generated by a subgroup of late endosomes, called Micro Vesicle Bodies (MVBs) that by inward budding engulf proteins, lipids, mRNA and miRNA. Upon fusion with plasma membrane of the cells, these MVBs releases exosomes into the extracellular compartment that are internalised by target cells thereby mediate cell-to-cell communication.

differentiate into neuronal lineage [26].

Cell Therapy using Differentiated MSCs

Owing to transdifferentiation potential towards neuronal lineage, MSCs have been used to generate midbrain specific dopaminergic neurons. Different protocols were developed for the formation of dopaminergic neurons. Culture of MSCs in the presence of cocktail of growth factors (FGF2, SHH, FGF8) or with small molecules like forskolin or the combine use of DMSO and Butylated Hydroxyl Anisole (BHA) resulted change in cell fate [27-31]. Gene transfection of Notch Intracellular Domain (NICD) followed by treatment with FGF-2, forskolin and Ciliary Neurotrphic Factor (CNTF) resulted in the generation of dopaminergic neurons without the formation of glial cells in case of both rat and human MSCs [32]. The microRNAs (miR-29a, miR-9, miR-124) were also found to promote differentiation of MSCs into neuronal lineage [33-35]. The differentiation of MSCs into neuronal lineage has also been achieved by treating these cells with PC-12 cell-secreted exosomes containing miR-125b [36]. Recently neurons were successfully generated from human DPSCs (Dental Pulp Stem Cells) via intermediate neurosphere stage [37]. This intermediary neurosphere stage promotes cell-to-cell contact thereby playing a crucial role in neural commitment [38,39]. These differentiated cells when transplanted in PD model (6-OHDA lessoned mice, rat and monkey) not only effectively integrated in the tissue but also secreted dopamine in the striatum or caudate putamen of the recipients [28,40,41]. Although there have been many reports of successful differentiation of MSCs into dopaminergic neurons, detail characterisation of the cells at epigenetic level remains obscure. Moreover, it is of utmost importance to decipher the mechanism that directs cellular fate change. The stability of differentiated cells remains debatable as the various studies suggests that the use of small molecules like forskolin, induces transient differentiation [30,42,43]. This proposes a real challenge for using transdifferentiated cells in cell based therapy. Considering the efficiency of transdifferentiation, there is always a risk of having undifferentiated cells in the pool of differentiated cells, which when transplanted may cause undesirable side effects to the recipients [44-48]. This limitation was partially addressed by sorting dopaminergic primed transgenic stem cells expressing GFP under the control of either *Hes5 or Nurr1 or Pitx3*. Transplantation with Nurr1 based sorted cells showed the greatest number of DA neuron survivability [49,50].

Cell Therapy using Undifferentiated MSCs

Due to several properties attributed to MSCs, as mentioned above, direct use of MSCs has also become popular in cell therapy [51-53]. Human trials of MSCs in PD patients thus far have shown encouraging results [26,54]. The basis of the study was due to secretion of many trophic (e.g. SCF, LIF, FGF-2, VEGF, IL-6) and neuroprotective factors (e.g. NGF, GDNF and BDNF) by MSCs [55,56]. Furthermore, due to secretion of anti-apoptotic factors, these cells have been tested for their ability to restrict the progression of neurodegeneration. Bone marrow MSCs, when transplanted into a 6-OHDA rat model of PD, were not only found to secrete trophic factors like EGF, VEGF, Neurotrophin-3 (NT3), and BDNF without acquiring neuronal phenotype but also were effective in endogenous repair of the damaged neurons [57]. In another study, MSCs were able to exert neuroprotection in 6-OHDA rat model of PD via secretion of neuroprotective factor SDF-1α [58]. When transplanted into ventricles of E15.5 days mice, these cells generated both migratory neurons as well as radial glial cells [59]. A mean improvement of 17.92% during 'ON' and 31.21% during 'OFF' period on the basis of UPDRS (unified Parkinson's disease rating scale) was observed during allogenic transplantation of adult human bone marrow MSCs in PD patient [60].

Though MSCs transplantation has been designated safe by US-FDA [61], the biggest challenge associated with transplantation has been considered due to the risk associated with their maldifferentiation [46]. There is also a risk of propagation of Lewy-bodies from host to the grafted tissue in autologous therapy [62,63]. Moreover, MSCs can differentiate into Tumour Associated Fibroblasts (TAFs), thus may promote the formation of metastatic tumours [64]. To circumvent these problems, the current approach relies on the use of secretome or exosomes of MSCs.

Therapeutic Potential of MSC-Secreted Exosomes

MSCs secrete various paracrine factors either directly into the media or through exosomes when cultured on adherent plate [65]. Exosomes are a subclass of nano vesicles of sizes ranging from 50 to 100 nm with an average density of 1.15 g/cm^3 [66]. Exosomes have been isolated from the culture media by ultracentrifugation and characterised by assessing their size as well as the expression of CD9, CD63 and CD81 [67]. In addition to CD9, CD63 and CD81, MSCs derived exosomes also express CD29, CD44 and CD73 [65]. The generation of exosomes from MSCs and their uptake by the target cells are depicted in the Figure 1. The role of exosomes derived from MSCs was first reported in 2009 where it was shown to mediate cardioprotective effect in mice model of myocardial ischemia [68]. Exosomes serve as repertoire of protein, lipids, mRNAs as well as miRNA. Recently, miRNA profiling of human MSCs has revealed that the parent cells retain some miRNAs completely while gets devoid of others after secreting them via exosomes [69]. Exosomes

pre-treated with RNase were found to be completely ineffective in casting protective effect in a Kidney injury animal model [70]. Human adipose derived MSCs have been shown to secrete neprilysin-bound exosomes that helps in the degradation of both Aβ40 and Aβ42 in experimental model of Alzheimer disease [71]. In cerebral artery occlusion rat model, miR-133b present in MSCs derived exosomes promoted neurite outgrowth and functional recovery after stroke [72,73]. Genetically engineering MSCs to over-express GDNF along with modifying its 3' UTR to contain 25 nt binding site for miR1289 can prove effective in treatment of Parkinson disease [74-76]. MSCs when engineered to secrete exogenous miR-124 and miR-145 through exosomes, promoted neuronal differentiation of neural progenitor cells [77]. Low immunogenicity and high permeability towards blood brain barrier makes exosomes- mediated therapy less cumbersome. The major concern with exosomes-mediated therapy is to harness these vesicles in large quantities and their continuous delivery. Exosomes release from infected cells can carry infectious protein like abnormally folded Prion Protein (PrP), Scrapie (PrPsc) on their surface, which needs to be taken care prior to their therapeutic applications [78].

Conclusion

Due to limitation in current therapy for the treatment of PD, the new focus has been emerged in cell-based therapy. Dopaminergic neurons derived from different stem cell types (e.g. ESCs, iPSCs, NSCs); have shown remarkable therapeutic benefits in ameliorating parkinsonian phenotype in animal models and limited extent in human. Owing to the ethical and scientific issues associated with these cells, MSCs has become a popular choice for cell based therapy. Abundance and less invasive isolation procedure associated with MSCs, makes them ideal for autologous transplantation. Allogenic transplantation of MSCs and their derived cells are also possible due to their hypoimmunogenic and immunomodulatory properties. Transplantation of undifferentiated MSCs or dopaminergic neurons derived from MSCs remains a favourite option with a very high success rate. Ability to secrete many trophic factors and exosomes have made the use of MSCs more attractive in treatment of PD. Having small size and/or soluble nature, these secreted products can cross blood brain barrier, involve less complication in delivery, thus considered promising in the future.

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