Cell-Cell Interaction: A Method to Upgrade the Neural Cells Function

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Abstract

Neural cells being dopaminergic can be used for cell replacement therapy of Parkinson's Disease (PD). PD results when Dopamine release in the brain becomes less due to the death of neural cells. Therefore, replacement of neural cells in the brain if can be done from outside, is believed to restore the Dopamine level that can combat the PD-related symptoms. Neural stem cells (NSCs) is a better choice than many other cells that can also be thought for the same purposes (recently reviewed by Chakraborty and Diwan). Further, equipped with the systems in maintaining the controlled level of dopamine, these hNSC cells do not cause any future dopamine–associated problems, like dyskinesia, motor neuron defect in the individual. However, NSCs grow very slowly and senescence occur after few passages, therefore practically may not be feasible to collect many cells for the treatment of a number PD patients. Here we will discuss an option to modify the cells for its better growth and survival length as well as it's dopaminergic ability. Cell-Cell interaction are commonly known to modify the cells, and may be considered for the above purpose.

Key words:

Human Neural Stem Cells. Melanocytes. Cell-cell Interaction. Dopamine. Parkinson's Disease

Introduction

Dopaminergic Neural cell's death in the Substantia Nigra (SN) region in the brain is the ultimate cause of having Parkinson's disease (PD) [1,2] The number of PD cases in the world is growing substantially [3]. No such curative treatments are yet available, except some palliative treatment like DOPA supplementation as a precursor of Dopamine [4]. However, longtime use of DOPA supplement can cause dyskinesia, motor neuron defect, etc [5]. In recent days, neural stem cells (NSCs), induced pluripotent stem cells (iPSCs), and also other DOPA-producing cells like Melanocytes have been considered for using as a cell therapeutic regiment for PD treatment [6,7].

However, in a recent review by Chakraborty and Diwan (2019) have shown many evidences in support of hNSCs for PD cell therapy [8]. In brief, hNSCs being equipped with both Tyrosine hydroxylase, a key rate limiting enzyme for Dopamine production, as well as its scavenging enzymes (DAT and MAO-B), can efficiently control the physiologic level of that neurotransmitter [9]. Therefore, cell therapy of PD with hNSCs should be a better approach than Levo-dopa therapy itself, as that way any possibilities of having dyskinesia, motor neuron defect at the long run can be avoided. Furthermore, hNSCs can produce brain-derived neural factors (BDNF) and Glial-cell derived neural Factors (GDNF) which can influence the growth and Dopamine production ability of hNSCs in an autocrine manner[10-12]. However, hNSCs is a slow growing cells and senescence occurs after a few passages rendering a low level of cell-supply for treatment purpose [13].

Here we will review whether and how hNSCs could be modified to a better growing cells with increased survival length along with differentiation and Dopamine producing ability, using cell-cell interaction approach.

A: Cell-Cell interaction is vastly studied in cancer biology. Cancer cells not only interact with themselves but also respond to tumor microenvironment (TME) containing growth factors, cytokines, and extracellular matrix proteins [14-16]. The interactions between normal and cancer cells can be either tumor-suppressive [17-22]. Cancer-associated fibroblasts can promote growth and invasion of the cancer cells [23]. Further, Cancer cells elongate blood vessels in TME by interaction with endothelial cells [24]. Overall, cell-cell communication in the Tumor Microenvironment (TME) is the biggest barrier to challenge the disease [25]. Cancer cells can modify the host cells to have tumor-supportive traits, and the modified host cells by interacting with cancer cells contribute to tumor progression. Therefore, understanding cell–cell interaction within TME can provide insight into cancer biology, and also in identifying new therapeutics.

B: Cell–Cell interactions for Neural cell modification: The classical neuronal synapses exhibit many similarities with the immune synapses required for cell-cell adhesion and close membrane apposition. In addition, activation of cell surface receptors in both the cases leads to intracellular signal transduction [26]. Recent studies have shown that dendritic cells (DC) and naïve T-cell interaction results the release of serotonin (5-HT) in mice as well as in humans [27,28]. Together, it appears that Cell-Cell interaction contribute to coordinated cellular behavior and complex biological functions in tissues, such as, embryonic development, neurotransmission, wound healing, inflammation, and many more [21,29].

B-1: In Neuron formation: Neurons and axons certainly have the opportunities to interact with each other during path-finding [30]. There is plenty of time for commissural neurons and their axons to interact with each other, although there have been no studies addressing this possibility so far.

Under ischemic conditions, an important aspect of remodeling involves fractalkine receptor (CX3CL1/CX3CR1) mediated signaling to promote microglial hagocytosis of apoptotic neurons [31]. Similarly, more extensive neuronal cell loss was evident in a toxic model of Parkinson's disease (PD) and a transgenic model of amyotrophic lateral sclerosis (ALS) with CX3CR1-/- mice (Chemokine receptor knockout mice) than CX3CR1+ littermate controls. Augmentation of CX3CR1 signaling may protect from microglial neurotoxicity, however penetration of CNS by CX3CR1 antagonists could increase neuronal vulnerability. This response also promotes neurogenesis and generate neuroblasts. These neuroblasts migrate to the olfactory bulb for differentiate into interneurons. NSPCs (neuronal stem/progenitor cells) when activated they migrate to the ischemic lesion and proliferate at that site [32]. This dual effect is also observed in other signaling proteins, such as HMGB-1 (High mobility group box 1) protein which belongs to DAMP family (damage-associated molecular pattern proteins (DAMPs), induces inflammatory/deleterious effects in the early stage of stroke, but promotes neurogenesis and angiogenesis in the chronic recovery phase [33].

Other incidence of cell–cell interactions are also noticed under stress conditions. Metabolic disturbances cause deficits in axonal energy in glial cells and that are closely related to neurodegenerative disease, like PD and AD. Oligodendrocytes under normal conditions, supply lactate to neurons through monocarboxylate transporter 1 (MCT1), but it's dysfunction may cause neuronal/axonal damage [34]. In an amyotrophic lateral sclerosis (ALS) mouse model as well as in human subjects, oligodendrocytes exhibit MCT1 deficiency—a phenomenon would likely lead to a disruption of the trophic support to neurons (axons)[35].

B-2: Cell-Cell Interaction for Dopamine production: Dopamine, a major monoamine neurotransmitter in CNS, involved in various functions like

movement, endocrine regulation and cardiovascular function, etc. In the periphery, dopamine is the primary precursor of adrenaline neurotransmitter of the sympathetic nerve system, and noradrenaline the adrenomedullary hormone. In dopamine-producing cells, tyrosine is converted to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (TH), followed by DOPA decarboxylation to dopamine. TH is activated by cAMP [36]; and five types of dopamine receptors, D1 and D5, couples with the Gs class of G proteins, can stimulate cAMP formation, while D2, D3 and D4 form couples with the Gi class of G proteins, leading to a decrease in intracellular cAMP formation [37].

Leukocytes can release Dopamine which acts as an autocrine and paracrine immune modulator. The synthesis and storage of Dopamine in monocyte-derived dendritic cells (Mo-DCs) can be enhanced by forskolin, an inducer of cAMP [38]. Further, in naive CD41 T cells, dopamine increase cAMP levels via D1-receptors and shifts T-cell differentiation to Th2.

In hemi Parkinsonian rat model, the phosphorylation level of DARPP-32kDa (a dopamine- and cAMP-regulated phosphoprotein), is elevated in the lesioned striatum by DOPA. DARPP-32 being an important component of dopamine signaling, inhibits the dephosphorylation of PKA- targeted proteins, and continues the D1DR-mediated signaling [39,40].

C: Selection of Partner cell for interaction with hNSCs: Now the question is what should be the partner cell to be used for interaction with the Neural cells.

C-1: Human ES cells: The use of human Embryonic stem cells (ES cells) for cell-replacement therapy is still at an early stage. In transplantation studies, hES cell-derived neurons did not show any integration into the host brain and result no functional recovery in the PD animal models [41]. Further, they also cause teratoma into the host brain once transplanted there , and ethical problems too, concerning the use of hES cells in human.

C-2: Neural progenitor cells: Neural progenitors cells (NPC) are multipotent and present in the brain. NPCs can migrate towards a lesioned area, differentiate into neurons and make synaptic contacts with the local neurons. These demonstrate that NPCs could be used as a future cell therapeutic tool for neuro-degenerative disease. However, Jain and colleagues have shown that transplanted NPCs in the 6-OHDA-lesioned PD animal model, can migrate to the lesioned area but not being influenced by the loss of DA in the SN. Further, the presence of neural progenitor cells in the SN region is still in dispute.

C-3: Other progenitor cells: Bone marrow derived adult progenitor cell due to their accessibility, also could be considered as a candidate for cell-replacement therapy. They may be low in number during collection but are able to Trans-differentiate. Recently, these cells were shown to generate neurons in the mice brain in vivo. Cogle and colleagues have found hippocampal neurons containing a Y chromosome in all sex-mismatched female bone marrow transplantation patients. This study results support that hemopoietic cells can indeed trans-differentiate and can take place in human too, indicating its impact for therapeutic use. However, some different explanations against this hypothesis were made describing that no new neurons from these stem cells but occasionally fusion with the host neurons could be possible.

C-4: Melanocytes: Melanocytes are Neural-crest originated cells, and a component of skin and produces melanin. These cells contains melanocrtin receptor (MC1) and releases the second messenger, cAMP. cAMP and/or its inducer are known to increase Dopamine production and Dopamine or its precursor Dopa can increase also cAMP level via D1-receptor mediated signaling. Therefore, a cross-talk can be expected between the neighboring cells producing dopamine and/or cAMP [42].

Our approach: Melanocytes being considered possibly as a better partner cells over others discussed above, we aim to study whether melanocyte has any influence on neural cells proliferation, survival length, Differentiation, along with its axon Production, Dopamine production/secretion, secretion of neural factors BDNF/GDNF, an intimate property of Neural cells.

As a method Co-culture experiment would be adopted for cell– cell interaction. Melanocyte (hNMCs) and human Neural Stem Cells (hNNSCs) should be plated into the same dish, that are commonly used in vitro models. This methods are quite similar to co-culture of cancer cells and endothelial cells, fibroblasts and immune cells, that are often used in various studies to know the insight of cell–cell interactions.

Analysis at specified time points will be carried out as follows: Cell Glo assay for cell proliferation; Light Microscopy for Cell morphology, Axon production; Immunofluorescent Microscopy for Nestin, Tubulin III (Tuj1) expression; ELISA for measurement of Dopamine, BDNF and GDNF Secretion.

Discussion

The human body is estimated to be composed of more than 200 different types of cells, and cells with specialized functions form functional units such as organs (brain, heart, liver, etc.), skin, bone, blood, and muscle, by coordinating their behavior through communication with other cells.

Cell–cell interaction is a complex phenomenon; a single cell can interact with many other cells through physical contact, surface receptor-ligand interaction, cellular junctions, and secreted stimulus from neighboring cells or those of distant organs. Interactions via secreted factors such as protein or peptide-based growth factors and cytokines; small molecules and metabolites has been extensively studied.

More recently, interactions involving extracellular vesicles have emerged as another way of interaction. In addition, cell–cell interactions are affected by their physiological environments, including physical properties of the surrounding extracellular matrix and its biochemical properties, like levels of oxygen (hypoxia) or nutrients (energy deprivation). In humans and other mammalian systems, lipoxin (LX) biosynthesis is an example of LO–LO (lipoxygenases) interactions via transcellular circuits. LXs are a separate class of local mediators produced from arachidonic acid and that gives them distinct and potent biological roles [31].

Together, it appears that cell-cell interaction can contribute to a coordinated cellular behavior and also complex biological functions in tissues, such as, neurotransmission, embryonic development, wound healing, inflammation, etc.

Parkinson's disease (PD) is a neurodegenerative disease characterized by gradual onlet of tremor, slow movement, and cognitive impairment in the elderly people. The biochemical features of Parkinson's disease are primarily death of neural cells in subatantia nigra (SN) region in the brain and the disease is sporadic without any specific etiology. A modified neural cells transplantation in the brain is expected to be a curative approach.

Conclusion

Since in neural cells, cAMP–Tyrosine hydroxylase pathway exists and can be controlled by dopamine receptors, one can predict that dopamine released by Neural cells may induce cAMP formation in an autocrine manner via D1 receptor. That cAMP can further induce neighboring melanocytes to produce Dopa, a precursor of dopamine production by neural cells.

In summary, we are approaching seemingly to a logical direction to demonstrate any influence of melanocytes might have on neural cells for its differentiation, dopamine production and releasing abilities of neural factors, like BDNF and GDNF. Production of BDNF /GDNF are vital for neural cells survival. Our experimental results only can prove our hypothesis, and therefore may open up a modification tool for upgrading neural cells before transplantation in Parkinson's cases for their cell therapy.

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Conflict of Interest

The authors report no conflicts of interest.

Ethical Approval

Nothing needed

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