Astrocyte Therapy in Parkinson’s Disease

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Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons. While neuronal dysfunction is central to PD, astrocytes also play important roles, both positive and negative, and such roles have not yet been fully explored.

astrocyte Parkinson’s disease

1. Introduction

The neurodegenerative and neuroprotective roles of astrocytes suggests that these cells might be a key piece of the puzzle in the elaboration of a disease-modifying treatment of PD. Indeed, astrocytes, as previously mentioned, have various positive effects such as the secretion of neurotrophic factors and the elimination of αS, and a key role in maintaining the equilibrium of the brain. However, certain reactive astrocytes are considered to have neurodegenerative effects. Thus, astrocytes should not be viewed as entirely positive, and this should not be overlooked in strategies involving astrocytes as part of a disease-modifying treatment. Therefore, a method, or a combination of methods, that would optimize the neuroprotective aspects of astrocytes but limit their neurodegenerative effects would be the most effective. Nevertheless, it should be noted that “astrocyte therapy” on its own is unlikely to definitively modify PD progression. Indeed, the full mechanisms of PD remain to be elucidated and all functions of astrocytes are still not fully understood or remain unknown. Additionally, αs is still likely to be the definitive player in the etiology of PD, which is considered a synucleinopathy [1]. Therefore, the best method might be to combine potential αS drugs, such as antisense oligonucleotides [2], with astrocyte therapy to optimize results; however, entirely halting αS production might be problematic. Current studies have shown that astrocytes can degrade at least a fraction of extracellular αS and prevent αS aggregation [3][4][5].

2. Promoting the Secretion of Neurotrophic Factors

Neurotrophic substances such as GDNF promote cellular survival. Therefore, artificially increasing the levels of these substances by injecting them into the bloodstream may offer certain benefits. Unfortunately, studies that have attempted to intravenously inject GDNF have failed [6][7], probably due to its difficulty in permeating the BBB to arrive at its targets. Furthermore, neurotrophins have a short half-life, which further complicates the development of an effective and realistic therapy. However, since astrocytes have been shown to naturally produce a variety of neurotrophins, a better way might be to develop a substance or method to stimulate or reactivate neurotrophin production. This would remove the need to find a way to allow neurotrophins, very large molecules, to traverse the BBB and might ensure a more even distribution of neurotrophins. Some authors have proposed the use of modified

viruses expressing genes encoding neurotrophins [8][9]. Bäck et al., precisely tested this paradigm by injecting a modified adeno-associated virus encoding CDNF into rats' striatum [8]. The results were mixed: CDNF was detected in the striatum and SN 12 weeks after injection, but there was no significant protection [8]. Similarly, in 2010, Marks et al., conducted a randomized controlled trial and found that the viral gene delivery for the trophic factor neurturin did not have any benefits [10]. Intriguingly, Cordero et al., found that the combination of CDNF and MANF overexpression by viral vectors conferred protection. This discrepancy in results is perhaps due to the fact that the dual overexpression of MANF and CDNF might confer more benefits than the expression of only one factor [11]. However, Cordero et al., used a 6-OHDA rat model [11], which is not a perfect representation of the etiology or development of PD compared to the controlled trial by Marks et al., involvingPD patients [10]. Furthermore, a possible reason may be the difference in the viral vector used, which might result in differences in gene expression or other diverging properties. Indeed, Cordero-Llana et al., used a lentivirus vector [11], while the two studies where the results were more modest used an adenovirus vector [8][10]. Therefore, since current studies seem contradictory, more research is needed on the best types of viral vector to use, as well as the efficacy of neurotrophin therapies.

3. Prevention of Astrocyte Conversion into a Pro-Inflammatory Phenotype and Inflammatory Response

Certain types of astrocytes secrete many inflammatory substances and are detrimental to neurons [12][13][14]. In PD, this conversion can be attributed to activated microglia [14]. A rational proposal would be to develop an inhibitor of this conversion. This seems to be a promising avenue since several preliminary studies discovered that certain molecules can inhibit reactive astrocyte activation. Capsaicin seems to be one of them, as discovered by Chung et al. [15]. Capsaicin, delivered through intraperitoneal injection, reduces the microglial expression of inflammatory cytokines, such as IL-1β in an MPTP rat model, through the TRPV1 receptors (capsaicin receptors) expressed in the brain [15]. Since inflammatory cytokines secreted by microglia activate reactive pro-inflammatory astrocytes [12], logically, pro-inflammatory astrocyte activation is reduced, as reported in [15]. However, these preliminary successes, while certainly encouraging, should be taken with a grain of salt. Simvastatin, an anticholesterol drug, was found to confer neuroprotection in neurotoxin models both in vivo and in vitro [16][17] in part due to its ability to prevent the conversion of astrocytes into a neurotoxic phenotype [16]. The results were encouraging, with Tong et al., reporting that an SH-SY5Y cell culture treated with simvastatin and 6-OHDA had a cell viability of 59.58 ± 5.80% in 24 h compared to only 47.34 ± 7.40% in SH- SY5Y cultures treated only with 6-OHDA; however, such success was not translated to success in clinical trials. In a 2022 randomized clinical trial involving 235 participants, Stevens et al., found that simvastatin was not effective as a disease-modifying drug and the drug takers had a worse performance in the MDS-UPDRS part 3 score by around 1.52 points in comparison to the control group [18]. The negative effect of simvastatin was supported by a 2017 case–control analysis showing that lipophilic statins, the group that simvastatin belongs to, are linked to an increased risk of PD [19]. There may, however, be an explanation for these seemingly conflicting data. The studies that found positive results were conducted either in in vitro tests, which did not completely simulate the complex dynamic of the real brain, or in in vivo tests, which used rat models induced with PD-like symptoms via neurotoxins [16][17]. Unfortunately, these models were shown to not

be completely accurate as they did not completely model all PD parameters [20]. This discrepancy in results, further highlights the imperfection of models such as 6-OHDA.

4. Astrocyte Graft

Astrocyte properties are not homogeneous throughout the entire brain and might vary significantly throughout regions [21]. Since PD mainly affects the neurons located in the substantia nigra, the introduction of astrocytes from different parts of the brain with different gene expression profiles that exhibit more neuroprotective behavior might help. One example is ventral midbrain (VM) astrocytes [3]. Yang et al., showed that this particular phenotype, when grafted into mouse brains, can inhibit intracellular and extracellular αS aggregation via numerous mechanisms. The transplantation of VM astrocytes can reduce αS accumulation and inflammatory cytokines in vivo while also restoring homeostasis of the brain [3]. This study convincingly showed the potential of utilizing astrocyte diversity. The benefits of astrocyte transplantation have also been confirmed in other studies in which cells differentiated into either astrocytes or astrocyte-like cells were beneficial once transplanted [22][23]. Indeed, after transplanting astrocyte-like cells into a 6-OHDA rat model, there was a marked enhancement in dopaminergic fiber density [23]. As our understanding of astrocyte heterogeneity grows, this method might become more appealing. While it is true that αS accumulation in astrocytes has been linked to a conversion into a more destructive phenotype [24][25], this property has not been observed in immature astrocytes [26]. This finding removes one potential risk of astrocyte graft: conversion into reactive pro-inflammatory astrocytes so long as the astrocytes are immature. Astrocyte graft can be combined with motor neurons to maximize its positive effects [3]. However, this technique is still rather experimental and certain aspects need to be improved before application. For instance, while it is true that, in the study conducted by Yang and colleagues, postnatal rodent astrocytes were utilized [3], there would be numerous ethical and logistical concerns about procuring human postnatal astrocytes on an industrial level. Therefore, human iPSCs should be prioritized. As the brain does not have full immune privilege contrary to what was previously theorized [27], there is still a certain response to the graft. This can be solved if the graft is autologous, but this technique, albeit more optimal compared with foreign iPSCs, is presently not as practical as in the case of DAergic neuron production [28]. Thus, further research is necessary. Furthermore, two other important questions to answer are whether there is a risk for glioma and what methods can be used to control excessive astrocyte proliferation. As of our current knowledge, no studies have been conducted on the risk of glioma in astrocyte grafts as most studies in this area involve rodents and not humans (difficulty translating results) and are not long-term. Moreover, while no excessive astrocyte proliferation has been reported in the scientific literature, this represents a question for this novel technique that must be answered for a successful clinical outcome. Since PD is clearly associated with a loss of DAergic neurons, it is logical to try to graft DAergic neurons as a way to replace the losses. However, certain data do not support the use of neuron grafting [29]. This may be due to the transfer of αS from the host to the graft, which stunts its potential effects [30]. However, since the astrocyte graft has been shown to prevent αS transmission, grafting neurons alongside astrocytes may prevent the neurons from developing αS aggregates, hence improving outcomes [3][31]. In summary, current evidence suggests that astrocyte grafts, particularly from certain parts of the brain, can reduce αS spread and may hold therapeutic value, especially when coupled with DAergic neuron grafts.

5. Astrocyte Reprogramming

Since PD's principal hallmark is a loss of DAergic neurons, replacing the dead neurons is a proposed solution. An exciting method to generate neurons is using microRNA (miRNA) to convert midbrain astrocytes into DAergic neurons [32]. This technique is particularly exciting as it is shown to work both in vivo and in vitro [33]. Indeed, Ghasemi-Kasman et al., converted astrocytes using a lentiviral particle carrying miR-302/367 and valproic acid with no detection of tumor [33]. Furthermore, this differentiation can be performed using other types of miRNAs (for a more detailed review of this, please refer to the review paper written by Wei and Shetty [32]). While this technique does appear to be promising, there are still some problems that need to be resolved. As astrocyte reprogramming does not resolve the αS problem, the new neurons will probably be infected with αS, as it is shown to spread [34]. Even more, as Wei and Shetty have noted, the newly reprogrammed neurons must be able to integrate into the existing neuronal network for positive results and in vivo programming might deplete astrocytes in the brain, thus limiting its efficiency [32].

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