Perinatal Tissue-Derived Stem Cells in Neurodegenerative Diseases Treatment

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Stem cells exert neuroprotective and neurodegenerative benefits through different mechanisms, such as the secretion of neurotrophic factors, cell replacement, the activation of endogenous stem cells, and decreased neuroinflammation. Several sources of stem cells have been proposed for transplantation and the restoration of damaged tissue. Over recent decades, intensive research has focused on gestational stem cells considered a novel resource for cell transplantation therapy.

Keywords: gestational stem cells ; neurodegenerative diseases ; Parkinson's disease ; Huntington's disease ; Alzheimer's disease ; amyotrophic lateral sclerosis ; cell transplantation therapy

1. Introduction

Neurodegenerative diseases (NDDs) refer to a heterogeneous group of pathological conditions characterized by the loss of neurons in the brain or spinal cord usually associated with a wide spectrum of clinical presentation including cognitive, psychiatric, and motor deficits [1]. NDDs can be triggered by either acute or chronic events. Acute cases, such as ischemic stroke and traumatic brain or spinal cord injuries are caused by a traumatic event leading to the loss of neurons at the site of damage. On the other hand, chronic cases are linked to the more selective loss of cell populations like dopaminergic neurons in Parkinson's disease (PD) and motor neurons in amyotrophic lateral sclerosis (ALS) [2][3][4][5]. Most NDDs are characterized by an accumulation of misfolded proteins (proteins with altered physicochemical properties), which represent a hallmark of the disease. Examples of protein accumulations are (i) a-Synuclein (a-syn), a small 14-kDa protein, encoded by the SNCA gene, which is the primary constituent of Lewy body deposits present in the brain of subjects affected by PD [6]; (ii) ubiquitinated protein inclusions of a transactive response DNA-binding protein of 43 kDa observed in the motor neurons of individuals with ALS [7][8]; (iii) Aβ plaques, consisting of 39- to 42-aa-long Aβ peptide fragments and neurofibrillary tangles, formed by tau oligomers which, in Alzheimer's disease (AD), are shown to be present outside and inside neurons, respectively [9][10]; (iv) mutant huntingtin protein aggregates reported as one of the main features of Huntington's disease (HD) and present in the cytoplasm and in the nucleus of the nervous cells throughout the brain [11]; (v) prion protein PrPSc accumulation, a 253-amino acid protein encoded by the gene for PrP (PRNP) located in chromosome 20, which also shows a synaptic pattern of deposition and is detected in the so-called "prion diseases" [12]; (vi) FET proteins, a protein family which includes FUS, the fused-in sarcoma protein, EWSR, the Ewing sarcoma RNA-binding protein 1, and TAF15, the TATA-binding protein-associated factor 15 (TAF15) [13], reported to form cytoplasmic aggregates found in neurological diseases, such as frontotemporal lobar degeneration (FTLD) and ALS [14][15].

Unfortunately, no successful treatment for NDDs has been developed so far. Due to the complex nature of NDD pathophysiology, a multimodal therapeutic approach may be needed. This aims to replace lost nervous cells, remove toxic deposits, and guarantee a safe environment essential for the survival and plasticity of these cells. In recent years, cellular therapy has been considered a novel potential therapeutic strategy for the treatment of NDDs [16][17][18].

Different cell types, such as embryonic stem cells (ESCs), adult stem cells, and induced pluripotent stem (iPS) cells have been tested for their ability to replace damaged cells and to restore tissue function after transplantation [19]. In the last few years, perinatal tissue-derived mesenchymal stem cells (MSCs), including placenta-derived, chorion, and umbilical cord-derived MSCs, have raised great interest due to the large accessibility, their ability to differentiate in several cell lineages (**Figure 1**), the absence of tumorigenicity after transplantation and, importantly, the lack of ethical problems initially limiting the availability of ESCs [20][21]. The isolation of stem cells from fetal material does not raise ethical concerns since these tissues are considered medical waste immediately after delivery and are readily accessible. Research material can be

collected from tissues obtained from invasive diagnostic and treatment procedures throughout the pregnancy, planned terminations, and after the full-term vaginal delivery or cesarean section.

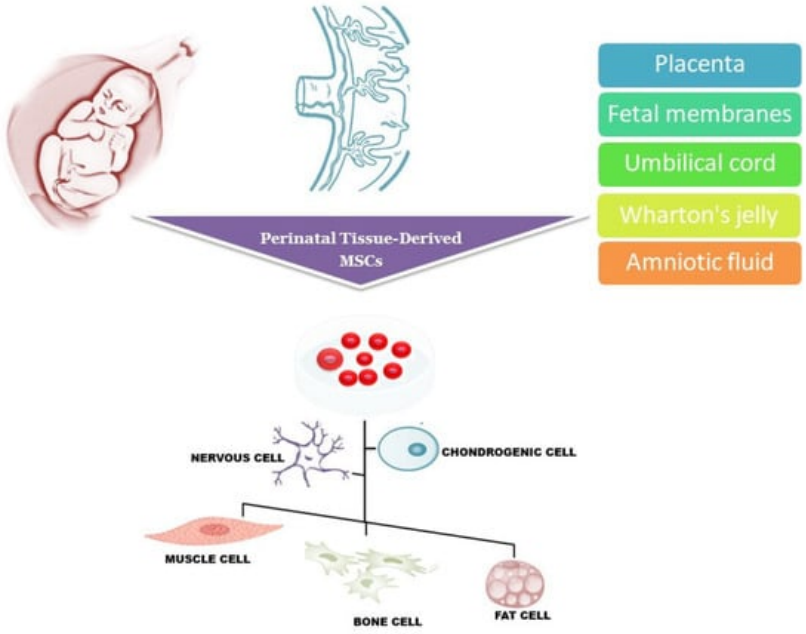

Figure 1. Perinatal tissue-derived stem cells, which can be isolated from placenta, fetal membranes, umbilical cord, Wharton's jelly, and amniotic fluid, can differentiate into several cell lineages, including muscle, nervous, chondrogenic, bone, and fat cells.

2. Cell Therapy in Alzheimer's Disease

AD is the most prevalent cause of dementia, accounting for 50–70% of dementia cases worldwide [22]. The disease is characterized by the deterioration of cognition, function, and behavior, with an insidious onset, usually beginning with the loss of memory of recent events, and a slow progression [22][23]. Most patients are affected by the sporadic form of the disease (>95) for which several genetic risk factors have been identified, whereas a small number of subjects present inherited mutations affecting the processing pathways of the amyloid-β (Aβ) peptide [24]. Two main pathological features characterize AD. One is the extracellular Aβ plaques (also known as "senile plaques"), composed of Aβ peptides of 39 to 42 aminoacidic residues [25][26]. The other one is the intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein, which assemble to form the so-called "paired helical filaments" [27]. The consequence of these biological alterations is neurodegeneration leading to synaptic and neuronal loss and ultimately to macroscopic atrophy. Other pathological processes including astrogliosis, microglial activation, and cerebral amyloid angiopathy are frequently found and contribute to the disease onset and progression [28][29][30][31].

The risk of AD is estimated to double every 5 years after the age of 65 [22] and the number of subjects affected by AD is predicted to triple by 2050, reaching millions of patients by 2050 [32], thus significantly contributing to the increase in the risk of disability. Both the socioeconomic and family burden of AD have prompted the World Health Organization to declare AD as a global health priority [33].

Despite the dramatic worldwide impact of AD, there are still no therapeutic approaches able to effectively reverse or counteract the progression of the disease. So far, only acetylcholinesterase inhibitors such as donepezil, galantamine, rivastigmine, and the N-methyl-Daspartate receptor antagonist memantine are available in the US and EU. Aducanumab is a human IgG monoclonal antibody targeting Aβ fibrils and soluble oligomers aimed at clearing the Aβ plaques and contributing to slow AD development [34][35]. This drug, considered the first disease-modifying treatment for AD, has been approved under the fast-track pathway by the US Food and Drug Administration. On the contrary, the European Medicines Agency recently recommended the refusal of its marketing authorization due to the conflicting results from the two phase III clinical trials that have concluded (EMERGE and ENGAGE) [36][37][38]. Indeed, the Committee for Medicinal Products for Human Use stated that the risk–benefit balance was unfavorable [39]. The company withdrew the application on 20 April 2022 [39]. In this scenario, the development of novel therapeutical approaches emerges as an urgent need.

Several pieces of experimental evidence support the idea that the transplantation of MSCs is associated with an improvement in synaptic plasticity [40][41][42][43][44][45][46]. MSCs have also been reported to ameliorate cognitive performance in different animal models of NDDs, including AD [47][48][49][50][51][52][53], thus suggesting that this can

represent a promising therapeutic strategy. The standard source of human MSCs preferentially used for clinical applications is represented by bone marrow (BM). Although BM cell harvesting is considered a safe procedure, it is invasive and requires the need for general anesthesia, with related potential complications and risks [54]. Moreover, other complications may be present including the frequent presence of acute and/or chronic pain at the sites of aspiration, anemia, vasovagal reaction, and infection [55]. To try to overcome these challenges, a device for a rapid, poorly invasive harvest of BM for both autologous and allogeneic use, called “MarrowMiner”, has been developed and recently approved by the US Food and Drug Administration [56].

On the other hand, gestational tissue-derived human MSCs, which (i) can be easily obtained in large amounts; (ii) do not need crude procedures; (iii) and do not raise ethical concerns have been increasingly considered a valid and suitable source of MSCs for clinical applications. Among gestational tissues, human umbilical cord (hUC) is considered one of the best sources of MSCs for the reasons reported above, but also for their low immunogenicity and high proliferative capacity associated with a very low potential to generate tumors [57][58]. Thus, hUC-MSCs have gained much attention and interest for their use in regenerative medicine [59] and as an attractive novel therapeutic approach in different NDDs, including AD [60][61].

3. Cell Therapy in Huntington’s Disease

Huntington’s disease (HD) is a progressive neurodegenerative disorder. It is an autosomal dominant genetic disorder that shows pathological and clinical features. Both neuronal malfunction and cell death probably cause progressive motor disability, which includes chorea, bradykinesia, incoordination and rigidity, cognitive impairment, behavioral change, and psychiatric disorders. In particular, the death of GABAergic medium spiny neurons (MSNs) is involved in the onset of HD manifestation [62][63].

Huntington’s disease is caused by a CAG triplet repeat expansion in the Huntington gene, which encodes an expanded huntingtin (HTT) protein. This protein is essential for embryonic development, and it is involved in cellular activities, such as vesicular transport and recycling, endocytosis, endosomal trafficking, autophagy, and transcription regulation; however, its normal function(s) is still incompletely understood. In the general population, the CAG repeat length is of 16–20; 40 or more CAG repeats are pathogenic. Individuals with an expanded HTT allele can become symptomatic at any time point in their life. In the vast majority of cases, the clinical course of HD slowly begins in adulthood, typically in the mid-40s. The disease is inherited in an autosomal dominant manner with age-dependent penetrance and individuals at risk can be identified before clinical onset by predictive genetic testing. Longer CAG repeats predict an earlier onset, while the length of the CAG repeat seems to contribute less to the rate of progression [64].

The pathological signature of HD is the formation of intranuclear inclusion bodies, which are large aggregates of abnormal HTT in neuronal nuclei, cytoplasm, dendrites, and axon terminals [65]. Mutant HTT causes the decreased transport and release of corticostriatal BDNF. An increased stimulation of extrasynaptic glutamate receptors occurs and the reuptake of glutamate by glia is reduced. As a result, excitotoxicity and enhanced susceptibility to metabolic toxic effects take place. Finally, activated microglia produce increased inflammatory activity [66]. Epidemiologically, HD shows a prevalence of 5–7 per 100,000 in most White populations. It is a fatal disease; death generally occurs 15–20 years from its onset [63], and there is no effective cure yet. At present, most drugs a

For these reasons, stem-cell-based regenerative medicine is gaining increasing interest in HD treatment. Cell-based therapies aim to restore brain functions by replacing lost/dying neurons as well as giving neurotrophic aid to diseased tissue.

Several studies suggest the potential efficacy of MSCs in the treatment of HD [67][68][69][70][71]. A recent meta-analysis confirmed the positive effect of MSCs on HD animal models overall, as reflected in morphological changes, motor coordination, muscle strength, neuromuscular electromyography activity, cortex-related motor function, and striatum-related motor function, while cognition was not changed by MSC therapy [72]. Among different MSC sources, bone marrow MSCs were the most investigated cells and were effective in improving motor coordination. However, while capable of reducing behavioral and histological deficits in the R6/2 mouse model of HD, bone marrow-derived MSCs did not generate new neurons following transplantation in the mouse striata. For this reason, stem cells from other sources, mainly from gestational stem cells, are gaining interest.

Glial cell line-derived neurotrophic factor (GDNF) and BDNF are principal mediators involved in HD neuropathology [73]. GDNF has also been shown to provide striatal neurons with neuroprotective support against excitotoxic lesioning in the quinolinic acid (QA) lesion rodent model of HD. However, GDNF has demonstrated only the partial protection of the

GABAergic striatal neurons from QA-induced cell death. These results probably reflect GDNF difficulties in achieving efficient delivery to striatal neurons in vivo, thus limiting the potential of this factor in counteracting the neurodegenerative process of HD [74]. McBride and colleagues [75], using the alternative 3-nitropropionic acid (3-NP) animal model of HD, demonstrated that the delivery of GDNF to the striatum using a recombinant adeno-associated viral (AAV) vector could protect striatal neurons from degeneration. This suggests that the neuroprotective actions of GDNF on the striatal neurons involve not only the protection against excitotoxicity but may be also effective against mitochondrial inhibition. It has been reported that GDNF may provide striatal neuroprotection by promoting the expression of various antiapoptotic factors, including X-linked inhibitors of apoptosis, bcl-2, and bcl-xL [76][77].

BDNF is reduced in HD neural cell models, and genetic and pathogenetic mouse models of HD and in human post-mortem material [78], and the over-expression of BDNF has been verified to improve the HD phenotype in the mouse model [79]. A possible mechanistic link between BDNF with HD has been established. BDNF is essential for the corticostriatal pathway, and cortical BDNF is involved in the survival and differentiation of striatal neurons both at physiological and pathological levels. Moreover, the normal huntingtin protein contributes to the physiological control of BDNF synthesis and transport in the brain. Both these processes are disrupted in HD patients, who have huntingtin mutant protein. Several lines of evidence show that HD patients, together with being affected by the toxicity of mutant huntingtin, also are characterized by decreased normal huntingtin activity, which may reduce cortical BDNF gene transcription [80]. Altogether, all these lines of evidence indicate that HD involves profound changes in BDNF levels and that attempts to restore these levels are therapeutically interesting. Results of BDNF supplementation are promising but this approach raises several different problems, mainly related to the unstable nature of BDNF, which only in small amounts can cross the blood–brain barrier.

In HD patients, early studies have mostly shown that BDNF blood levels were decreased compared with controls [81][82][83]. Ciammola et al. further observed a significant association between the BDNF level and the clinical severity of the disease and cognitive performance [81]. However, these findings were not sustained by other studies. Zuccato and colleagues found no difference in the BDNF levels in serum and plasma in a large cohort of patients [84]. Other studies with plasma samples have confirmed this finding [85][86] and further detected no significant associations between the plasma BDNF and clinical signs of HD [87][88]. Overall, the current evidence does not support the value of BDNF as a robust biomarker of HD. Peripheral BDNF levels did not decrease as expected; this may be partially due to the region-specific secretion properties and its complex originations. It has been reported that a BDNF decrease mostly occurred in the striatum, but not in the cortex, thus suggesting that the cortex was unaffected, or even compensated for the deficit. While the BDNF level changes remain conflicting in blood, interestingly, the analysis of the DNA methylation level at BDNF Promoter IV in the whole blood revealed a significant association with anxiety and depression symptoms, but not with any motor or cognitive performances. This relationship between DNA methylation alterations of BDNF Promoter IV and neuropsychiatric symptoms deserves further validation [88].

4. Cell Therapy in Parkinson’s Disease

Parkinson’s disease (PD) is caused by the loss of dopaminergic neurons in the substantia nigra of the brain. PD is more typically diagnosed in elderly patients and affects about 1–2% of the population over 70 years of age. Current pharmacological treatment includes the administration of dopamine precursors that improve the symptoms but cannot impede the disease progression.

Concerning transplantation, dopamine replacing could follow two different protocols: (1) the in vitro pre-differentiation of stem cells toward dopaminergic neurons and (2) in vivo differentiation toward dopaminergic neurons after implantation. From the studies reported in the literature, the mechanisms of stem cell therapy on PD can be classified into two repair categories: (a) a direct repair pathway that includes the increase in endogenous neurogenesis through the differentiation of cells transplanted into neurons and/ or integration with neural circuits of the damaged brain [89][90][91]; (b) indirect repair through trophic factors as stem cells express several neurotrophic factors able to promote the neuronal differentiation of local stem cells. Several studies have shown functional improvements and neuroprotective and neurodegenerative effects after gestational stem cell transplantation to animal models of PD. In a rat model of PD [92][93][94], it has been shown that undifferentiated UC-MSCs prevented the degeneration of 48.4% of dopamine neurons and 56.9% of dopamine terminals from loss. Other investigators have described the functional benefit of differentiated hUC-MSC transplantation towards dopaminergic neurons able to alleviate motor symptoms [95][96][97][98]. Two interesting studies have used the combination of a particular cocktail, such as choroid plexus epithelial cell-conditioned medium, knockout serum replacement, and Lmx1a (a gene of homeodomain family members and neurturin (NTN) to facilitate the conversion of UC-MSCs to dopamine neurons. After cellular transplantation in animal models, such as hemiparkinsonian rhesus monkeys, improvements in behavioral deficits were detected [99].

The application of human amniotic fluid stem (hAFS) cells in PD was pioneered by Donaldson in 2009 [100]. It was reported that undifferentiated cells did not promote the development of fully differentiated dopaminergic neurons in culture or after transplantation into the PD rat brain. After a few years, different preclinical data showed that CD44+AFS cells induce the regeneration of dopaminergic neuron cell-like cells, increase migration distances, and improve animal behavior in a rat model of PD. These results reinforce the necessity of further studies to investigate the potential therapeutic effect of hAFS cells and support their use in clinical therapy [100].

Taken together, these findings provide evidence that a number of challenges and problems regarding cell-based therapies must be addressed: (i) the long-term survival of stem cells in the host brain; (ii) the active integration of transplanted cells into a local neural network; (iii) a low risk of side effects; (iv) the physiological release of dopamine in the brain of patients.

5. Cell Therapy in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease and is characterized by the loss of both upper and lower motor neurons. ALS has an incidence that varies between 1.2 and 4.0 per 100,000 individuals per year and it predominantly occurs in males [101]. The exposure of females and males to sex hormones has been shown to influence the disease risk or progression. Therefore, the correlation between genetics and sex has been widely investigated in ALS preclinical models and in large populations of ALS patients carrying the pathological expansion of a hexanucleotide repeat in chromosome 9 open reading frame 72 (C9orf72), which is the most common genetic mutation identified in familial ALS [102].

Current progress in regenerative medicine has proposed cell-based therapy as a novel treatment to cure ALS. Despite being in the early stages of clinical translation, numerous preclinical studies have investigated the neuroprotective mechanisms of stem cells in animal models. Most promising for this purpose are hUC-MSCs, which can survive readily after transplantation and have good migratory potential [103][104]. In 2008, Rizvanov et al. transplanted genetically modified hUC-MSCs in transgenic G93A mice adopted as an ALS animal model. The results obtained demonstrated that transplanted cells successfully grafted into nervous tissue and could differentiate into endothelial cells, forming new blood vessels. In this report, it was hypothesized that the neuroprotective effect could be derived from the delivery of various neurotrophic factors by newly formed blood vessels [105]. Similar data were confirmed by other groups that have focused their attention on the combined effect of the gene/ stem-cell approaches. In addition, multiple studies have labeled hUC-MSCs to detect transplanted cells in vitro and in vivo by magnetic resonance imaging (MRI) after intraspinal injection in a transgenic mouse model of ALS [106][107][108]. In line with these promising findings, over the years, several labeling strategies have been proposed. In this regard, it was described for the first time the paramagnetic labeling of hAFCs and their subsequent long-term tracking in a murine model of ALS. Surprisingly, the presence of double tracers has not altered the survival of hAFCs but has allowed for a correlation between in vivo and ex vivo data at different moments [109]. This study describes the therapeutic potential of hAFSCs in the treatment of ALS; however, additional preclinical trials are required to elucidate their benefits in clinical therapy for motor neuron disorders. Among the gestational stem cells, hAECs have also been proposed as an attractive source in cellular treatment for ALS. These stem cells are a heterogeneous population, containing several undifferentiated progenitor cells, which have not been extensively investigated. They constitute an ethically acceptable alternative to embryonic stem cells, with a comparable multipotentiality and a very low immunogenic response. The finding that hAFCs express and release numerous cytokines and neuro-glial factors [110] further promotes their application in the field of NDDs. A single preclinical study has reported the beneficial effects of their transplantation in terms of extended survival, the improvement of motor function, and decrease in neuroinflammation [111].

Although several studies have shown that MSC transplantation results in disease improvement, the mechanisms by which the beneficial effects of MSC therapy arise are not entirely understood. Several mechanisms of repair and support, including cell replacement, trophic factor or gene delivery, and immunomodulation have been observed, sometimes in tandem [112]. Some studies have shown the ability of MSCs to differentiate into cells with neuron-like morphology, gene expression, and protein expression [113][114]. However, this phenomenon is still controversial, mainly due to the lack of evidence of functional synapse formation between trans-differentiated MSCs, and their therapeutic contribution is still uncertain. MSCs express or can be stably transduced to overexpress trophic factors which may promote endogenous restorative or regenerative processes, such as neurogenesis, gliogenesis, and synaptogenesis [115]. MSCs may play several immunoregulatory roles which may contribute to their beneficial effects in ALS. They reduce the proliferation of B cells, T cells, and natural killer cells, and impair the maturation of dendritic cells. Then, they can also affect immune cell function by reducing (i) antibody production by B cells, (ii) the activation of dendritic cells and T cells, and (iii) the secretion of natural killer cells [112]. In the central nervous system, MSCs migrate to areas of inflammation, reducing it. In experimental models of ALS, MSCs attenuate microglial activation and reduce astrogliosis [116][117][118].

6. Functional Differentiation of MSCs towards Neuronal Lineage in Neurodegenerative Diseases: An Unmet Clinical Challenge

The potential efficacy of MSCs to restore neurological functions in NDDs depends on neurogenic differentiation, cell replacement, and the secretion of neurotrophic factors [119]. Unfortunately, the direct transplantation of MSCs at the injury site or injection into the vascular system frequently translates, within several days, into their death, due to natural senescence [120], the hostile microenvironment, and (or) nutrient deprivation [121]. Thus, even if the transdifferentiation of MSCs into neurons provides a practical technique for NDD treatment, it is limited by the unmet challenge of getting well-differentiated and mature neurons. The use of a single or combination of growth factors has been adopted to guide the differentiation of MSCs into a neuronal lineage. Growth factors, including Epidermal Growth Factor (EGF), Fibroblast Growth Factor, basic (bFGF), and Platelet-derived Growth Factor (PDGF), engage various cell surface receptors and a variety of signaling pathways, which often crosstalk, leading to an unexpected biological outcome [122].

New strategies for the differentiation of MSCs into neurons, which could eventually be used to treat patients who are in need, are recently developing. These include (i) highly specific systems for MSC differentiation into neurons directed by local electrical stimuli [123], and (ii) MSC-based gene delivery strategies [124]. Since the inherent characteristics of neurons is to transmit electrochemical signals throughout the nervous system, electrical stimulation could significantly promote the neural differentiation of stem cells or neuron maturation [125][126], with different potential advantages, such as rare immune response, controllable parameters, low damage, easy implementation, localized induction, and synergy with other inducers. Thus, most studies have used external electric fields generated by electrodes or large electrical signal-generating devices to directly induce stem cell differentiation [127][128]. However, this is an invasive approach with an increased risk of wound pain and infection, unsuitable for nerve repair in humans [129]. Thus, recently, increasing research has focused on the development of an implantable, low-cost, non-invasive wireless stimulation system [130][131][132][133] and on the use of stimulus-responsive materials, such as graphene, which has been shown to promote MSC neural differentiation [134].

The transfection of MSCs with genes that promote cell resistance to hypoxia/ischemia, oxidative stress, and acute or chronic inflammation or with genes enhancing neurotrophy and neuroprotection may increase cell survival in vivo and, importantly, facilitate neuronal replacement and repairing, and the reconstruction of neural circuitry, thus potentially restoring neurological function [124]. The main tools for gene delivery include viral-based methods, which allow for the construction of stably transfected MSCs, with a more sustained gene expression time, and nonviral-based methods, always sustaining only a transient gene expression in MSCs [124]. In addition to the stable long-term expression of integrated genes, virus-based methods for gene delivery also have the advantage of a high infection efficiency, but potential disadvantages that can also reduce safety include immunogenicity, the risk of gene integration and the insertion of mutations, and lethal and carcinogenic risks. On the other hand, non-viral-based methods, which include physical methods (such as sonotransfection and electroporation) are characterized by a high transfection efficiency but they can be associated with high cytotoxicity and a lack of targeting. Moreover, non-viral-based methods can be difficult to apply in vivo [124].

7. Immunological Response in Cell Therapy for Neurodegenerative Diseases

The well-documented immunomodulatory and regenerative properties of MSCs are the reason why they are being used for the treatment of many diseases, including NDDs. Moreover, as reported before, they have been considered “immune-privileged cells”, as they do not activate aggressive immune responses. For this reason, MSC treatments are performed without considering the histocompatibility and without preventing possible immune rejections [135]. However, several studies have provided evidence that mismatched MSCs are immunogenic: mismatches in HLA antigens between donor and recipient lead to serious complications such as graft failure, transplant rejection, or graft versus host disease (GVHD).

Several critical factors could impact the immune response and should be taken into consideration when implanting cells to treat neurodegeneration [135]. The first is the transplantation procedures: although these are becoming minimally invasive and extremely accurate, immunosuppression is needed to overcome the inflammation and morbidity associated with the procedure. However, immunosuppression therapy could cause toxicity and worsen the clinical scenario; thus, it should be accurately selected and monitored [136][137][138]. Other factors include the cell type used [fetal tissue, ESCs, iPSCs, neural progenitor cells (NPCs), MSCs], the presence of genetic modifications, and the degree of mismatch between the donor and recipient. The compatibility of the major histocompatibility complex (MHC), known in humans as human HLA, represents an important factor: the degree of mismatch between donor and host increases the risk of immune rejection,

ranging from the absence of rejection to the need for immunosuppressive therapy throughout the lifespan. MSCs seem to be more compatible with the host's immune system due to their low levels of MHC I and the lack of MHC II molecule expression [139][140].

Figure 2 summarizes the main strategies to restrain the immunological response following cell therapy for NDD. Among them, the graft of autologous material from an identical donor twin is associated with the lowest immunogenic risk. However, currently, obtaining this type of transplantation for patients with NDD, such as PD or HD, is not easy. Possible realistic alternatives have been proposed [135]. Among them, the selection of the donor based on HLA compatibility with the host, which has to be accompanied by treatment with immunosuppressive drugs, has been proposed; in this context, the generation of cell banks could increase the availability of HLA-matched cells [141][142][143].

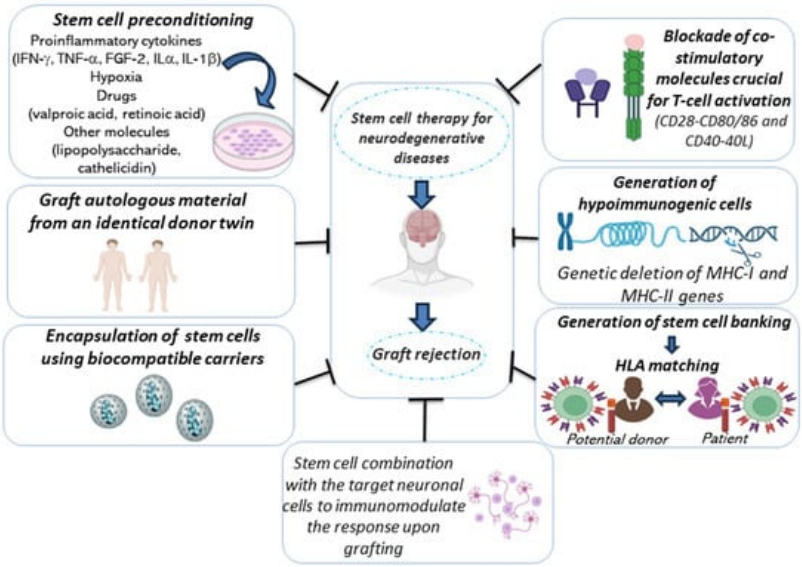

Figure 2. Strategies to overcome graft rejection in cell therapy for neurodegenerative diseases. Created in Biorender.com.

Tolerance induction approaches include the blockade of co-stimulatory molecules that are crucial for T-cell activation, such as CD28-CD80/86 and CD40-40L [144]. However, the immune tolerance strategy mainly developed in mouse models must be re-evaluated in the context of the human immune system. The use of stem cells in combination with the target neuronal cells to immunomodulate the response upon grafting has also been proposed. In animal models, this approach can delay allograft rejection and preserve the functionality of the graft [145][146][147]

In conclusion, up until now, the occurrence of the immune response when considering cell therapy for NDDs has remained an open challenge. The immune response may impair the survival of grafted cells and, therefore, their functionality. Thus, immunosuppression is needed to overcome the inflammation and morbidity associated with the procedure, and this could cause toxicity and worsen the clinical scenario. Most clinical assays in the field are not performed based on clear and feasible guidelines for monitoring the immune response.

8. Large-Scale Production of Human Mesenchymal Stem Cell Manufacturing for Clinical Uses

The clinical uses of MSCs are limited by technical problems associated with mass production, high manufacturing cost, and contamination. The production of MSCs on a large scale is further complicated by the need for manufacturing processes able to provide a high therapeutic quality and purity of cells according to the current GMP standards. Several expansion methods to obtain appropriate numbers of cells with preserved therapeutic quality have been proposed [148]. However, currently, an ideal method for the expansion of MSCs on a large scale remains an important challenge.

The most used approach for the large-scale manufacturing of MSCs for clinical use is represented by standard bioreactor systems [149]. This automatic system of cell cultures allows for the growth of large numbers of adherent cells, providing reduced labor costs and improvements in cell quality, a central issue when scaling up the processes. Bioreactors can enable the frequent feeding of the culture; thus, they maintain the levels of metabolites necessary for cell expansion under control and allow for a faster and safer expansion of MSCs compared to conventional cultures [150].

In this system, the main process parameters to be controlled include temperature, pH, pO2, pCO2, microcarrier suspension, and shear stresses [148]. Therefore, it is necessary to develop online control systems that ensure that product characteristics remain unchanged. Another major limitation to the therapeutic use of MSCs is the composition of culture

media, which hinders the validation of GMP-compliant processes. To date, a large number of laboratories use culture media supplemented with fetal bovine serum (FBS) to expand MSCs, but this option will be not applicable in the future. FBS has a not well-defined composition, and it may promote interspecies cross-contamination. Proposed alternatives include human platelet lysate (hPL), but the potential risk of disease transmission and its limited availability reduce its application to large-scale production. Alternatively, new GMP-compliant, commercially available, chemically well-defined xenogeneic-free media that support MSC growth would constitute a more cost-effective and risk-reduced approach. However, some changes in morphology, phenotype, potency, and cellular senescence have been reported, thus suggesting that methods for MSC culture need to be further optimized to enhance batch-to-batch consistency in the cell manufacturing process [151].

The challenge of the future in the field of the MSC manufacturing process is to harmonize it for different clinical conditions and to work to obtain a unique ‘off-the-shelf’ MSC product. Ideally, this product should be derived from freely available tissue sources, such as umbilical cord tissue, which can be collected with non-invasive procedures. Moreover, it should be cultured in GMP- and regulation-compliant xenogeneic-free media and expanded in a closed automated bioreactor system. Then, it should be delivered ‘off-the-shelf’ as a cryobanked product suspended in a chemically defined, dimethyl sulfoxide (DMSO)-free media. DMSO is an efficacious and economical cytoprotective agent, but its use can be associated with negative effects on humans depending on concentration, administration, and dose. Finally, the final cryobanked product should not require further manipulation at the bedside. Nevertheless, there is the need to repeat pre-clinical safety and efficacy studies when changes are introduced into the bioprocess.

As reported above, in recent years, several strategies have been designed to improve the therapeutic potential of MSCs, which, in Europe, are considered advanced therapy medicinal products (ATMPs). However, the manufacture and handling of these cells for their use as ATMPs is still poorly studied, and a large part of the available data is not related to industrial processes. Up until now, the MSCs used to obtain ATMPs could only be isolated in authorized centers with processes which are standardized around the world. In contrast, the optimal protocols for culturing isolated MSCs are not standardized. This constitutes a major open challenge to improve their therapeutic properties. Cell culture conditions, such as the cell density, time of culture, and culture medium composition represent bottlenecks that need critical controls [150].

9. Conclusions

Cell-based therapies have been proposed as a promising tool in the treatment of several human NDDs. Remarkably, preclinical studies have demonstrated encouraging results on the functional benefit of cell transplantation in the neurological field and several efforts have been undertaken to successfully apply cell therapy in NNDs. However, to date, this approach has remained experimental and most of the undertaken clinical trials have not been properly designed to assess efficacy and to confirm the promising results about the safety. One of the challenges when considering cell therapy for NNDs is the immune response, which can compromise the survival of grafted cells, impairing their integration and, therefore, their functionality. For this reason, in recent years, in vitro strategies have been developed to evaluate the potential immunogenicity of cell therapy. Funding agencies and the neuroscience community should invest in this kind of strategy to improve and standardize preclinical studies for the development of cell therapies. Good well-standardized in vitro models may provide access to understanding some mechanisms that are difficult to assess in animal models. In fact, the molecular mechanisms underlying the beneficial effect of cell therapy are still largely unidentified. There are some concrete pieces of evidence to support the hypothesis that the transplanted cells produce neurotrophic factors, enhance neuronal plasticity, and activate local progenitors and cell replacement (**Figure 3**).

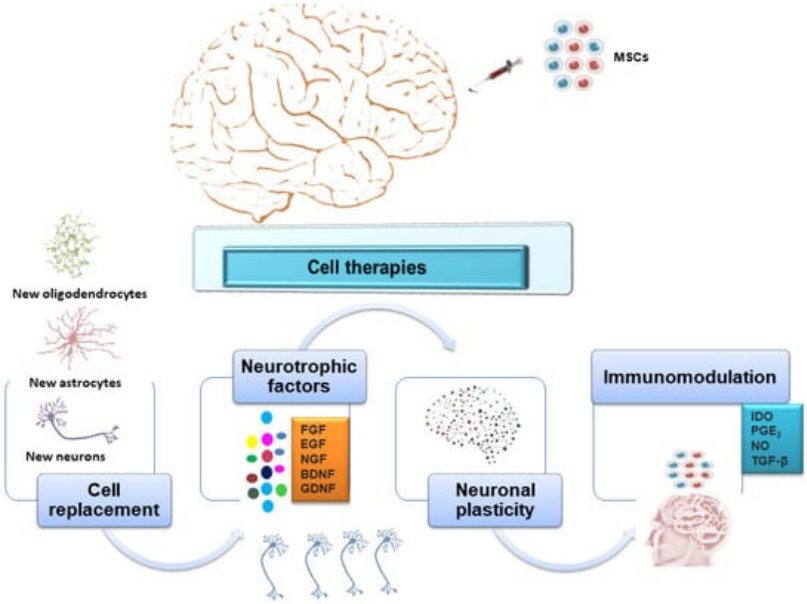

Figure 3. Mechanisms underlying the functional benefits of MSC transplantation in the neurological field can be associated with their capacity to activate local progenitors and cell replacement, to produce neurotrophic factors, including Fibroblast growth factor (FGF), Epidermal Growth Factor (EGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), enhance neuronal plasticity and the immunomodulation mediated by several factors, including Indoleamine 2, 3-dioxygenase (IDO), prostaglandin E_2 (PGE_2), nitric oxide (NO), transforming growth factor (TGF)-β these limitations.

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