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Stem Cells and Neurological Diseases

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Abstract

Now-a-days many human neurological diseases are not currently curable and result in devastating neurologic sequelae. In the last decade many laboratories are focusing on stem cell treatments for CNS diseases. Out of the many stem cell types that are being tested for neurological treatments, the most common are fetal and adult brain stem cells, embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells. So, now Patient-specific iPSC-based modelling of neurogenetic and neurodegenerative diseases is an emerging efficient tool for in vitro modelling to understand CNS diseases and to screen for genes and drugs that modify the disease process. So now-a-days a far more pragmatic approach in the short term might be to use stem cells as chaperones for degenerating nervous tissues, also, the targeted delivery of therapeutic agents could be achieved by modifying stem cells to release specific drugs at the site of transplantation. The exploitation and elucidation of this new 'stem cell pharmacology' has the potential to revolutionise treatment of neurological diseases investigations, and also aimed to replace damaged neurons and gliaby direct transplantation or recruitment of newly generated cellsin the adult. Now the next step is totranslate these exciting advances from the laboratory into clinically useful therapies.

Keywords: Stem cell technology, CNS, Parkinson's disease, Amyotrophic disease, Alzheimer disease.

Introduction

Most commonly occurring human neurological diseases such as stroke, neurodegenerative disorders, neurotrauma, multiple sclerosis (MS), Parkinson's disease and neuro-developmental disorders are caused by a loss of neurons and glial cells in the brain or spinal cord. These disorders usually cause morbidity and mortality as well as increase social and economic burdens of patients and their caregivers [1].Neural stem cell-based therapies are now being developedto treat a spectrum of neurological conditions once thought tobe incurable [2]. This review discusses some ofthe well-studied neural stem cell types and treatments for neuronalinjury and neurological disorders.

Stem cell plasticity; one cell for all diseases

Stem cells are known by the ability to renew themselves (self-renewal) through mitotic cell division anddifferentiate into a diverse range of specialized cell types [3].They are classified into three types according to theircapacity to differentiate into specialized cells (potency). These are totipotent stem cells, pluripotent stem cells(such as embryonic stem cells (ESCs) and induced pluripotentstem cells (iPSCs) artificially derived from a non-pluripotentcell, typically an adult somatic cell through

reprogramming [3]. ESCs can give rise to allcell types while adult stem cells(ASCs) are thought to be limited in differentiating intodifferent cell types of their tissue of origin. Isolation of ASCs from adult tissue is challenging because they are found in mature tissues however, ESCs can begrown in cell culture [72]. This difference is crucial for stemcell replacement therapies because large numbers of cellsare needed for therapeutic applications. The tissues derivedfrom the patient's own ASCs are currently believed less likelyto initiate rejection after transplantation. This is significantfor solving immune rejection problem of cell replacementtherapies.

The dawn of a new era: induced pluripotent stem cells (iPSCs)

Multipotent stem cells onlygenerate specific lineages of cells. Neural stem cells (NSCs)are multipotent stem cells which are derived from neuraltissues [4]. These cells are self-renewing and differentiate intolineage-specific neural precursor or progenitor cells (NPCs)that can give rise to all cell types (neurons, astrocytes, andoligodendrocyes) of the nervous system through asymmetriccell division. So using these stem cells clinical trials to treat neurological diseases has been started. In this regard, autologous bonemarrow stem cells and mesenchymal stem cells are usedfor treatment of amyotrophic lateral sclerosis. The first clinical trial of an embryonic stem cell-based therapy was authorized in 2009. It was based partly on landmark studies showing functional recovery in rats after spinal cord grafts of oligodendrocyte precursors derived from human embryonic stem cells (hESCs) [5], the U.S. Food and Drug Administration gave approval to Geron Corporation to begin the first clinical trial of hESC therapy aimed at regenerating myelin in patients with spinal cord lesions [6]. Afterwards, neural stem was approved to test a stem cell therapy in patients with amyotrophic lateral sclerosis.

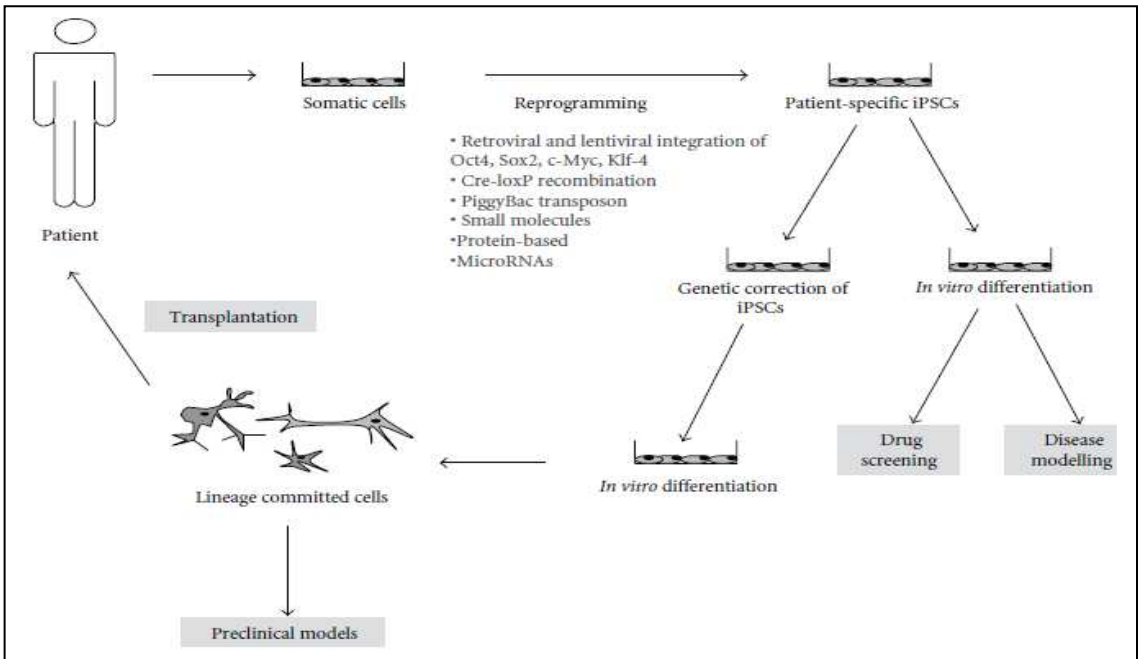

Figure 1. Potential applications of patient-specific pluripotent stem cells in neurological disease (Marchetto et al., 2010).

However, ethical concerns,immune rejection of grafted stem cells, and tumour formationlimit the use of human ESCs.So the development of iPSCs in recent years may bypass theethical controversies and rejection problem using autologousstem cells [7]. In many studies various neural cell types havebeen differentiated from human or rodent iPSCs generatedby the reprogramming of different somatic cells, mainlyskin fibroblasts [8-10]. IPSCs have also been differentiatedto NPCs [11, 12]. It has been found that in terms of cell morphology andpluripotency, iPSCs closely resemble ESCs. Several groups have

successfully generated a wide range of iPSCs from patients with neurodevelopmental and neurodegenerative diseases [13–15]. But before the transplantation process genetic correction of patient-specific iPSCs derived from the patients with neurogenetic disorders is required [73.] Patient-specific iPSCs also represent a valuable tool to dissect the poorly understood mechanisms of neurogenetic and neurodegenerative diseases [73].However the failure to translate the promising results of preclinical neuroprotection studies to the clinic setting may be due to many factors including species differences, brain complexity, age, patient variability, and disease-specific phenotypes that cannot easily be modelled in chosen nonhuman experimental systems [16, 17]. Cellular modelling studies and chimeric mouse models based on iPSCs may overcome these barriers [18, 19]. So, the patient-specific iPSCs may be most relevant cell source for drug screening and development as they take into consideration the patient's background, the affected cell type, and the developmental time [14, 20].

In this review, we consider several neurological disorders for which stem-cell based therapy has raised particular interest. We describe the ways in which stem cells might be used to treat these conditions, discussing the prospects for and problems of translating laboratory findings into clinically useful therapies.

Parkinson's disease

Parkinson's disease starts at a molecular level (a genetic defect and/or an environmental agent yield to a misfolding of proteins) with consequences at the cellular level (dysfunction of the ubiquitine proteasome system and mitochondria with free radical formation and protein aggregation leading to the apoptotic death of dopaminergic cells), which in turn produces biochemical and neurophysiologic disturbances, particularly dopamine deficiency in the striatum and in other nuclei, and increased firing rate with abnormal firing pattern in the sub thalamic nucleus (STN) and internal segment of the globuspallidus (Gpi). The clinical expression of all these disturbances is Parkinsonism [21]. The main symptoms of the disease are rigidity, poverty of movement (bradykinesia), tremor and postural instability. Current therapies mainly rely on the oral administration of L-dopa and dopamine receptor agonists, and on deep-brain stimulation in the subthalamic nucleus. However, these treatments are effective for some symptoms, but are associated with side effects and do not stop the progression of the disease. So, to be clinically competitive, a stem-cell-based therapy must lead to long-lasting, significant improvement in mobility, ameliorate currently intractable symptoms, or counteract disease progression.

In last twenty years, although the grafting of human fetal tissue-derived dopamine neurons into PD patients has shown some success in small-scale open clinical trials, but this has been tempered by practical limitations such as the use of human fetuses[75]. In efforts to overcome these constraints, expandable sources of stem cells have achieved preliminary success in investigations targeting treatment of PD [75].

For example, using mouse ES cells, two recent studies have demonstrated the potential utility of these pluripotent populations. Bjorklund et al., [22] showed that undifferentiated naive ES cells, when transplanted into rat models of PD as suspensions of single cells at low concentrations (1 ml of 1000–2000 cells at two striatal sites), spontaneously differentiated into midbrain-like dopaminergic neurons and were able to normalise motor asymmetry in these animals. However, the results were highly variable, with no graft survival in 24% of recipients in addition to frequent teratoma formation that led to death in 20% of transplanted animals. Afterwards, using an improved paradigm, directed differentiation of mouse ES cells into functional dopamine neurons has been achieved with transfection of nuclear receptor related-1 (NURR1 which plays an important role in the proper maintenance of dopamanergic system of brain, mutations can lead to dopamine dysfunction)

[74]followed by a multi-step in vitro growth condition-guided approach that takes into account known signals and gene expression patterns during central nervous system (CNS) development [23]. It was found that these differentiated neurons release dopamine, express many key dopaminergic markers and, when grafted into animal models of PD, integrate into the host striatum and significantly improve motor behaviour. Although Kim et al.,[23] enriched differentiated neurons to minimise undifferentiated dividing cells and did not observe teratomas, they cautioned that tumour formation remains a primary concern; thus, the long-term safety and functional benefits of these grafts must be carefully investigated. Moreover, human ES cells might require a different set of signals for dopaminergic maturation and survival in similar models.

Elucidation of the mechanisms underlying the therapeutic effects of stem cell transplantation, it was proposed that, in addition to neuronal replacement, undifferentiated neural stem cells might act as chaperones that offer neuroprotection and mediate rescue of degenerating host populations [76].Several studies indicated that in some cases, this has been linked to glial cell line-derived neurotrophic factor (GDNF), a potent growth factor with known 'dopaminotrophic' effects [24]for example, Ourednik et al.,[24], showed that unilateral grafting of immortalised cerebellar neural precursor cell lines (C17.2) into a bilaterally lesioned mouse model of PD, in which dopamine neurons survive but critical enzymes such as tyrosine hydroxylase (TH) downregulate, resulted in bilateral TH re-expression and functional recovery by two weeks after transplantation. Moreover, the majority of surviving TH-positive neurons in the substantianigrawas host-derived, rather than fromthe grafted precursors. In support of the study by Lie et al.,[25], none of the dopamine neurons incorporated bromodeoxyuridine, showing that they had not arisen from proliferating host stem cells. As most donor cells remained undifferentiated and widely dispersed throughout the mesencephalon, and also expressed GDNF, it was prposed that these immortalised neural stem cells might have the ability to establish suitable trophic environments and allow endogenous repair of dysfunctional dopaminergic neurons.

This finding was consistent with a previous study in which GDNFsecreting C17.2 cells exhibited neuroprotective effects on degenerating dopamine neurons in a different mouse model of PD [26]. Although these collective findings demonstrate the potential application of such cells in neurodegenerative diseases of a progressive nature, issues remain concerning the safety of immortalised neural stem cell lines; transformed populations have often resulted in cancers of various types, and tumours can be epigenetically induced by growth conditions [27,28]. Afterwards, increased survival of dopamine neurons was similarly observed in a rat model of PD by using non-transformed embryonic neural precursors that produce GDNF through lentivirusmediated genetic modification [29]. Recently, it was found that direct GDNF infusion into the putamen has shown significant clinical improvements with minimal side effects in five PD patients, following one year of chronic administration with programmable pumps [30]. So taken together, the use of stem cells in conjunction with growth factor treatment, as well as ongoing development of techniques to introduce foreign genes into cellular substrates [31], holds great potential for PD and side by side warrants further investigation.

Multiple Sclerosis

Multiple Sclerosis (MS) is defined as an autoimmune disorder in which aberrant immune responses lead to T-cell mediated focal myelin destruction and secondary oligodendrocyte and axonal damage. The current available disease-modifying therapies in MS are based on the idea that modulation of the autoimmune mechanisms will lead to a reduction of inflammatory infiltrates in the central nervous system (CNS) white matter. So, this reduction, in turn, should result in less demyelination and neurodegenerationand should therefore lead to suppression of clinical

manifestations [32].However these therapies are not sufficient for a permanent cure of the disease, so due to the limited effectiveness of the available therapies, the assessment of alternative therapeutic strategies in patients with aggressive clinical course is justified. We now know that bone-marrow transplantation is the standard treatment for several haematological malignant disorders and is being assessed for the treatment of severe forms of many autoimmune diseases including MS [32]. It was found that in patients, intense immunosuppressant therapy might eradicate the defective immune-system thus allowing the reconstitution of a CNS permissive/tolerant environment by a transplanted healthyhematopoietic stem cell compartment. These cells can beobtained from siblings or an unrelated donor closely matchedon HLA (allogeneic transplantation), an identical twin(syngeneic transplantation) or from the patient beforechemotherapy (autologous transplantation). The hematopoieticprogenitor cells can be directly harvested from the bone marrow or collected from peripheral blood. Thewell knownterm hematopoietic-stem-cell transplantation (HSCT) includes both sources. Regarding the mortality rate, allogeneic HSCT is associated with up to 40% mortality if the donor is not a sibling. By contrast, the mortality from autologous HSCT typically is less than 10% [32].Now-a-days HSCT has been so widely applied to MS patients and clinical efficacy appears so promising that the use of other sources for stem cells is today clinically insignificant, so this facilitated the procedure avoiding the issue of the embryonic stem cells (ES) and the related ethical concerns [33].

Recent studies indicated that Myelin-producing oligodendrocyte progenitor cells (OPCs) are abundant in the adult human brain. It was found that spontaneous remyelination occurs to varying degrees in the early stages of MS, and OPCs are also present in chronic demyelinated MS lesions.Recently, Back (2005),[34] showed that astrocyte derived hyaluronan accumulated in demyelinated lesions from MS patients and prevented the maturation of endogenous OPCs.

Afterwards, the transplantation of remyelinating cells represents another approach for treating myelin loss in MS. In this regard human adult and ES-cell-derived OPCs have been shown to myelinatedysmyelinated mouse brain and spinal cord after transplantation. However, a major obstacle is that the inflammatory environment could destroy the grafted OPCs and inhibit their maturation. So in this case, immunosuppressive and anti-inflammatory treatments might therefore be necessary. Another problem is that the demyelinated MS lesions are distributed across multiple locations throughout the CNS. So an effective therapy will require that these implanted OPCs should migrate to all these sites. Studies in this regard showed that, after systemic administration in mice, NS cells migrated to inflammatory demyelinating lesions, where some became OPCs and remyelinated axons[35]. However, most cells remained undifferentiated and suppressed proinflammatory mechanisms[36].

In order to establish the utility of human derivatives for direct remyelination, recent approaches have included prospective isolation of human progenitor cells from the adult postmortem brain, cell-sorting based on the expression of specific markers, and transplantation into demyelinated animal models. Recently, Windrem et al.,[37] reported that human cells could integrate into the host brain and replace lost myelin, although the functional effects of such transplants were not established. Thus, a direct correlation between grafted human cells and behavioural recovery is currently missing.

Stroke

Stroke is known to be caused by blockage of a cerebral artery that leads to focal ischaemia, loss of neurons and glial cells, and motor, sensory or cognitive impairments. It has been demonstrated that endogenous precursors proliferate and migrate in response to ischemic brain injury and to possess latent regenerative potential. Till now, no effective treatment to promote recovery exists, so a therapy

that produced even minor improvement would be valuable. Several studies indicated that transplanted cells from different sources, such as fetal brain, neuroepithelial or teratocarcinoma cell lines, bone marrow and umbilical cord, have yielded some improvement in animals and, in one clinical trial, in humans affected with stroke[38].

For enhancing the cell survival and function, mostly the grafts have acted by providing trophic factors [38]. For stem-cell therapy to be of major clinical value, human cells should be able to replace dead neurons, remyelinate axons and repair damaged neural circuitries. In doing so, human fetal neural stem (NS) cells were transplanted into the brains of stroke-damaged rats, resulting in the migration of new neurons towards the ischaemic lesion[39]. Similarly, some other studies showed that monkey ES-cell-derived progenitors transplanted into the brains of mice after stroke differentiated into various types of neuron and glial cell, re-established connections with target areas[40], and led to improved motor function[41]. Afterwards it was found that the therapeutic efficacy of such strategies could be improved further by genetically modifying the stem cells: for example, by over expressing an anti-apoptotic gene[42]. Interestingly, the stroke-damaged adult rodent brain has some capacity for neuronal replacement from its own NS cells. For several months after a stroke, NS cells can generate new striatal neurons that migrate to the site of damage [38, 43].

A lot of research has been carried out to establish whether endogenous neurogenesis contributes to functional recovery after stroke, and whether this occurs in humans. Also, because the regeneration of cortical neurons will be the basis for functional improvement in most stroke-damaged brains, we will also need to know whether the adult brain's own NS cells can be triggered to produce cortical neurons. So now effective therapies will depend on strategies to increase the survival of the new neurons and to enhance their incorporation into reorganizing neural circuitries.

In this regard, Nakatomi et al.,[44] reported that, following transient forebrain ischemia which induced selective degeneration of hippocampal CA1 pyramidal neurons, endogenous progenitors from the periventricular region and parenchyma produced new neurons that participated in hippocampal regeneration. It was found that significant recovery levels were noted 28 days post-ischemia, and could be considerably enhanced by treatment with epidermal growth factor and fibroblast growth factor-2. Moreover, regeneratedneurons undergo migration to the damaged striatum and express striatal-specific markers. Despite the promise of selfrepair in the adult brain through generation of new neurons, the overall level of endogenous self-recovery in this study was low, i.e. only 0.2% replacement was observed.

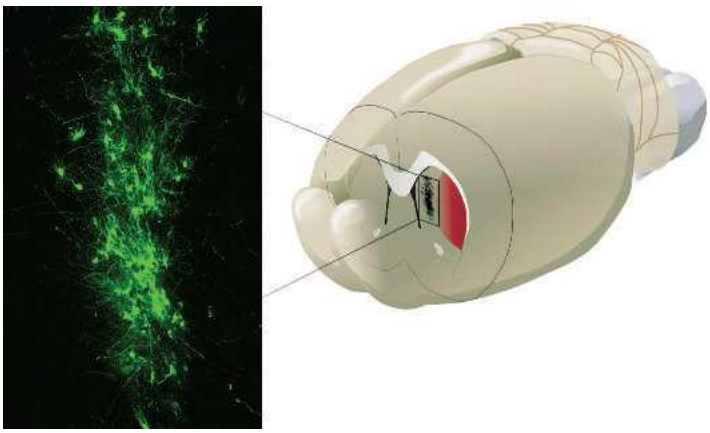

Figure 2. Transplantation of stem cells into injured brain. Human fetal NS cells labelled with green fluorescent protein survive for at least 1 month and differentiate into cells morphologically resembling neurons after grafting in close proximity to the stroke-damaged rat striatum (red area) (Lindvall et al., 2006).

Alzheimer's disease

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder that is characterized by memory loss and severe cognitive decline. It was found that the neuropathological

hallmarks of AD are the presence of amyloid β (Aβ) peptides in the form of amyloid plaques in the brain parenchyma, particularly in the hippocampus and cerebral cortex, leading to neuronal loss. It has been suggested that Aβplay an etiological, pivotal and likely causal role in the pathogenesis of AD [45, 46]. Therefore, a reduction of brain Aβ would have the potential to prevent and treat AD [47].

In AD, patients' memory and cognitive performance is progressively impaired; they develop dementia; and are likely to die prematurely. Current treatment includes the use of acetylcholinesteraseinhibitors to enhance cholinergic function, give only partial and temporary alleviation of symptoms. It was found that the pathological changes seen in AD offer an extremely problematic situation for cell replacement. Due to the widespread and progressive damage in the brains of patients with AD, it is unlikely that the mechanisms for instructing transplanted NS cells to differentiate into new neurons will be intact. Theoretically, cognitive decline caused by the degeneration of basal forebrain cholinergic neurons could be prevented by transplanting cholinergic neurons generated from NS cells in vitro.However, to provide long-lasting symptomatic benefit, this approach would require the existence of intact target cells within the patient's brain, and these are highly likely to be damaged. Since stem cells can be genetically modified and have migratory capacity after transplantation, they could be used for the delivery of factors that can modify the course of the disease. So in support of this approach, basal forebrain grafts of fibroblasts that produce nerve growth factor (NGF) which counteracts cholinergic neuronal death, stimulates cell function and improves memory in animal models have been of some benefit in patients with AD[48].

Recently, the therapeutic potential of bone marrow-derived mesenchymal stem cells (BM-MSCs) has been explored in various pathological conditions of the central nervous system (CNS) such as AD. In a study the feasibility of using the BM-MSCs, as a therapeutic agent for AD has been tested. In order to assess this possibility, an acutely induced AD model induced by injecting amyloid β (Aβ) into the dentate gyrus (DG) of hippocampus ofC57BL/6 mice was used. It was found that intracerebral transplantation of BM-MSCs into the brain of an induced AD modelreduced their Aβ levels when compared to sham-transplanted animals. Side by side the diminution of Aβ depositswas accompanied by the activation of microglia. In addition to these findings it was also found that, the activated microglia was located nearthe Aβ deposits, and their morphology was changed from ramified to ameboid as a sign of microglialphagocytosis. This study provides evidence that BM-MSCs can promote the reduction of Aβ through themicroglial activation in this acutely induced AD brain, suggesting a potential therapeutic agent against AD [50].

Huntington's disease

Huntington's disease (HD) is known as a fatal, intractable disorder that is characterized by chorea (excessive spontaneous movements) and progressive dementia. It is caused by the death of projection neurons in the striatum. In this case, stem-cell therapy aims to restore or preserve brain function by replacing and protecting striatal neurons, a strategy that might be insufficient

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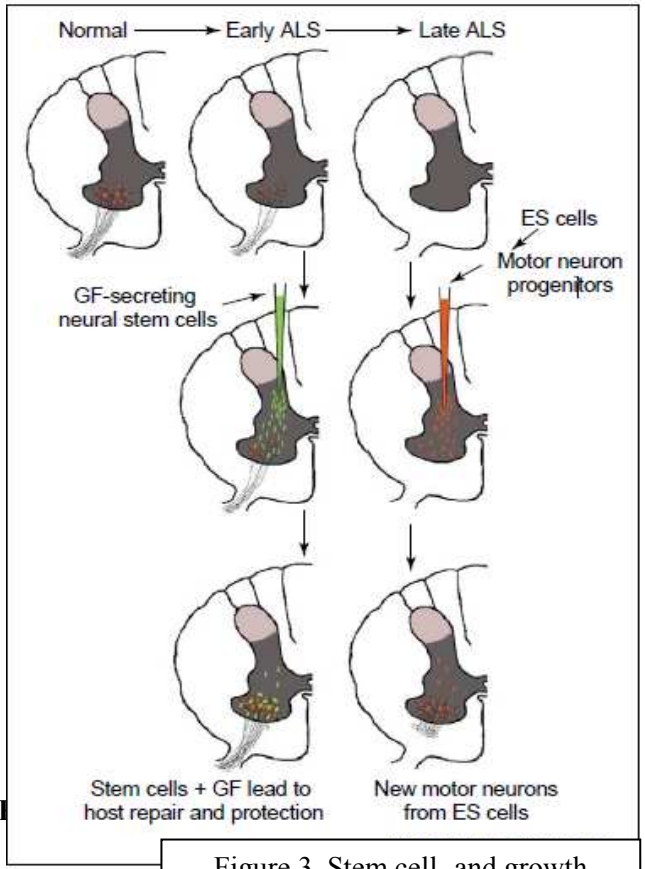

Figure 3. Stem cell- and growth factor (GF)-mediated repair of ALS (Klein et al., 2005)

because patients also suffer progressive neocortical degeneration. Several studies indicated that in animal models of HD, cell replacement using grafts of fetal striatal neurons promotes functional recovery, and some evidence from clinical trials indicates that this can also occur in patients[38]. By contrast, stem-cell-based approaches are still in their infancy, and the reconstruction of striatal neural circuitry has not been shown in animals. But recently human NS cells implanted into the brains of rats, were found to reduce motor impairments in experimental HD through trophic mechanisms[50, 51]. So now-a-days, using stem cells for the delivery of trophic factors and neuroprotection to prevent disease progression seems a more achievable clinical goal in HD than neuronal replacement.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal, progressive neurodegenerative disease that is characterized by motor neuron cell death in the brain and spinal cord accompanied by rapid loss of muscle control and eventual complete paralysis [52, 53]. In the present day, the only available therapy, riluzole (Rilutek), extends survival only by a matter of months but has shown reliable effects in several clinical trials. It was thought to work through the modulation of glutamate transmission, thereby reducing excitotoxicity[54], it is also possible that Rilutek increases trophic factor release from astrocytes [55].Since in amyotrophic lateral sclerosis (ALS), dysfunction and degeneration of motor neurons occur not only in the spinal cord (lower motor neurons) but also in the cerebral cortex and brainstem (upper motor neurons)so a stem-cell therapy must restore or preserve the function of both upper and lower motor neurons, and new neurons must become integrated into existing neural circuitries. So in this regard, recent reports have shown that it is possible to generate lower motor neurons in vitro from stem cells of various sources, including ES cells and those from the fetal CNS[56, 57]. Afterwards, it was found that mouse ES-cell-derived motor neurons establish functional synapses with muscle fibres in vitro[58, 59] and extend axons to ventral roots after transplantation into adult rats. But whether these neurons can integrate into existing neural circuitries and restore motor function has not been established. Although neuronal replacement in ALS patients seems a distant goal, using stem cells to prevent motor neurons from dying is a more realistic and shorter-term clinical approach. This prospect is supported by studies showing that human embryonic germ cells delivered into the cerebrospinal fluid of rats with motor neuron injury can migrate into the spinal cord and induce motor recovery, probably through neuroprotection. It was found that the efficacy of this approach could be improved by genetically modifying the stem cells to secrete molecules that promote motor neuron survival. A recent study showed that human cortical progenitors that were engineered to express GDNF survived implantation into the spinal cords of ALS rats and released the neurotrophic factor[60].

Epilepsy

Epilepsy is a defined as a common and diverse set of chronicneurological disordersthat is characterized by seizures[61]. Some definitions of epilepsy require that seizures be recurrent and unprovoked,but others require only a single seizure combined with brain alterations which increase the chance of future seizures[62].It was reported that epileptic seizures results from abnormal, excessive or hypersynchronous neuronal activity in the brain.Recently, fetal NSC and ESC-derived neural progenitors have been tested for their ability to integrate and restore function in rodent models of epilepsy. One of the therapeutic goals in epilepsy is to restore the normal balance between excitation and inhibition. So work on fetal neural precursor grafts has shown that they can enhance neuronal inhibition or cause hyperexcitability, depending upon the type of tissue that is used for transplantation and the location of the grafted cells [63].

Spinal cord lesions

It is believed that spinal cord injuries interrupt ascending and descending axonal pathways, and cause a loss of neurons and glia, inflammation and demyelination. These lesions lead to a loss of movement, sensation and autonomic control below the site of injury. To date, there is no cure, and the most common current treatment i.e., high-dose methyl-prednisolone, is of questionable value. Now it is evident that the transplantation of stem cells into injured spinal cord can lead to functional benefits[64, 65], mainly through trophic factor secretion or the remyelination of spared axons. Recently, a study showed that human NS cells implanted into damaged mouse spinal cord generated new neurons and oligodendrocytes, leading to locomotor recovery[66]. However, it was found that there are risks of side effects unless NS-cell differentiation after transplantation is controlled. For example, astrocytic differentiation and aberrant axonal sprouting after NS-cell implantation into injured rat spinal cord can cause hypersensitivity to stimuli that are not normally painful[67]. So the most realistic short-term clinical goal is to use stem cells for remyelination, which probably occurs to some degree after lesions from endogenous OPCs [68].In a recent study it was reported after NS-cell implantation into injured spinal cord in rats, there was a good correlation between the number of graft-derived oligodendrocytes, the amount of myelin, and the extent of functional recovery[67]. Similarly, another study reported that transplanted oligodendrocytes from human ES cells could myelinate the injured rodent spinal cord and improves motor function [69].

Conclusion and future aspects

Stem cells could soon be used to treat neurological disorders, but perhaps not in the way envisioned by most people. The precise mechanisms of stem cell therapy remain to be established, but are probably associated with release of growth factors and other trophic agents into the damaged brain. Future exploitation of stem cell biology, including enhanced release of therapeutic factors through genetic stem cell engineering, might thus constitute promising pharmaceutical approaches to treating diseases of the nervous system.

So firstly, the source of cellsmust be carefully considered, along with the surgicalapproach and patient selection. Even if theseprotective strategies were shown to be safe in patients,they could also pave the way toward improving hES or iPScell-based replacement strategies through increased motorneuron survival and subsequent fiber outgrowth. We can say that the challenges are great, but the rewards are even greaterin the continual fight against this devastating disease.

Now-a-days, the iPSC approach to studying braindisease remains one, overall, of tremendous promise.But these are clearly ‘early days’, and many challengeswill need to be overcome before mechanisticinsights for major brain diseases, such as Alzheimer’s disease, Parkinson’s disease, or stroke, are generated via iPSCapproaches. In this case perhaps the most critical challenge lies notwithin the derivation from a given patient and controlgroup of reasonably uniform lines of pluripotent cells in acost-effected manner, but developing the cell culture andxenograft approaches that will be required to use theselines for the study of brain disease.

In the case of Parkinson’s disease, the use of stem cells in conjunction with growth factor treatment, as well as ongoing development of techniques to introduce foreign genes into cellular substrates [31], holds great potential for PD but also warrants further investigation, similarly in the case of stroke the functional effects of transplants are still note established. In the case of Huntington’s’ diseases using stem cells for the delivery of trophic factors and neuroprotection to prevent disease progression seems a more achievable clinical goal as compared to neuronal replacement but still some mechanisms have to be fully understood.

So it would be premature to launch clinical trials to use stem cells to treatneurological disorders. However for each disease, it is now possibleto develop a road map that defines the necessary

scientific and clinicaladvances required for stem cells to reach the clinic. But before we applystem-cell therapies to patients, we must be able to control the proliferationand differentiation of stem cells into specific cellular phenotypes and toprevent tumour formation. Furthermore, the efficacy of stem cells andtheir mechanisms of action should be demonstrated in animal modelswith pathology and symptomatology resembling the human disease.

Update

Recently a new article has pushed further the idea of neuroprotectionby cells within the environment of dying neurons indiseases such as ALS. For example in an elegant study, Clement et al.,[70]have made chimeric mice that have both wild-typecells and cells expressing the superoxide dismutase-1mutation. When they studied at the pathology of bothcell types within the spinal cord, it was clear that wild typecells, probably astrocytes, were able to protect themotor neurons carrying the mutation. This is the majorobservation that supports the central tenant of the new upcoming ideathat the environment surrounding dying neurons isvital to their health and survival.

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