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STEM CELL THERAPY FOR NEUROLOGICAL DISORDERS

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Abstract

Stem cells have long been in focus as potential therapy or even cure for a whole myriad of diseases. Many neurodegenerative disorders, both acute and chronic, are characterized by irreversible neuronal damage and loss, and only a few efficient treatment options exist. In contrast to many other tissues, the potential of self-regeneration of the central nervous system is highly limited. There is hope that stem cells could replace the damaged neuronal and glial cells, and provide biological and functional restoration based on their properties of self renewal and the ability to give rise to different cells. In recent years, the promising results of research on animal models has led to the establishment of the first clinical trials; although no clear evidence of therapeutic benefit for any of the conditions have been ascertained. Here we give a review of the current strategies of stem-cell based therapy for some of the more common neurological disorders, discussing the progress and current challenges, and giving an overview of future perspectives.

Keywords

• Stem cells therapy • Neurological disorders

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1. Introduction

There are two basic types of stem cells: 1. embryonic stem cells which are isolated from the inner cell mass of blastocyst. Embryonic stem cells are pluripotent which means they can differentiate into all the specialized cells (i.e. cells derived from any of the three germ layers), and 2. adult (somatic) stem cells which are found in different tissues. Those stems cells are multipotent which means they can differentiate into a number of cells, but only those of a closely related family of cells. In recent years induced pluripotent stem cells have been derived from patients somatic cells by genetic manipulation. Those stem cells are also pluripotent. The major advantage of these cells is that they are not associated with ethical controversies and immune rejection as pluripotent embryonic cells and they can be used as patient-specific therapy.

There are several ways in which stem-cell therapy may be beneficial for the neurological patient. Stem cells may be differentiated, *in vitro* or *in vivo*, to neuronal or glial cells and be transplanted to replace the malfunctioning or missing cells in the nervous system. Stem cells can be transplanted into brain directly or can be delivered by blood infusion or bone marrow transplantation. Stem cells can also be engineered to repair certain genetic defects or can be genetically modified to produce molecules that can promote neuroprotection such as cytokines, trophic or growth factors. It has been proven that„traditional" stem cells, such as neural, embryonic, bone marrow mesenchymal, and human umbilical cord blood-derived stem cells can successfully yield neurons, oligodendrocytes and astrocytes [1,2]. A novel approach in the field has been the introduction of induced-pluripotent stem cells, reprogrammed from patients' somatic cells [3], providing both an excellent source for human disease modeling [4-6], and a potential for patient-specific transplantational therapy, all the while without the ethical controversies and immune rejection associated with pluripotent embryonic stem cells [7].

Another way to achieve cell replacement is to induce the activity of endogenous neural stem cells located in the central nervous system. These are found in the subventricular zone of the lateral ventricles [8,9] and the dentate gyrus of the hippocampus [10], and are responsible for neurogenesis throughout the lifetime [11-14]. A pathological process such as stroke [15], traumatic brain injury [16] or inflammatory demyelination [17] stimulates this formation of new neurons. However, this process is stimulated only to a certain degree which is insufficient for regeneration and functional recovery. It is believed that neurogenesis can also be induced by stem cell transplantation [18,19]. It has been noted that transplanted stem cells which have not differentiated into neural or glial cells or have not survived in the brain, have still provided beneficial functional improvements [20] The proposed mechanism of action is the secretion of trophic factors which may have neuroprotective activity,reduce local inflammation or promote remyelination [21,22].

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease with progressive loss of dopaminergic neurons in substantia nigra. Among the therapeutic options, replacing degenerated neurons with other cells capable of producing dopamine seems to be the most hopeful. This was tried as early as 1987 by transplanting human fetal mesencephalic tissue, and has since been the subject of research ever since with

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varying results [23]. Stem cells could provide a more reliable and available alternative as a source of dopaminergic neurons [24] Although studies have so far been limited to only a small number of patients, the results are promising. In autologous stem cell transplantation, significant clinical improvement may be expected [25,26], albeit the effect seems to diminish after a few years [27]. No significant adverse effects have been reported; and apart from the adverse-effects associated with all stem-cell therapy, there is the possibility of developing dyskinesias, as observed with embryonic mesencephalic grafts [28]. Finally, Parkinson's disease is a complex degenerative process and to focus treatment solely on the restoration of the nigrostriatal dopaminergic system may be an oversimplification [29] and methods which also provide neuroprotection should be sought. One possibility is the transplantation of stem cells engineered to express neuroprotective molecules like glial-cell-line-derived neurotrophic factor [30].

Huntington's disease

Unlike other neurological disorders, Huntington's disease (HD) is the result of a single gene mutation, and is therefore an ideal candidate for gene or cell therapy. The main pathological changes occur in the medium-sized spiny neurons in the striatum, and cell therapy aims to replace them. As with PD, first attempts have been made with fetal neural grafts, which resulted in clinical improvement; athough a permanent cure cannot be expected [31]. Since transplantation of fetal tissue is associated with significant ethical concern, future investigations will likely use adult/autologous stem cells. Stem cell use has not yet reached the clinical setting in HD, but animal model studies show that functional recovery is achievable [32,33]. A possible mechanism is the protection of endogenous neurons by cytokine production, while further possibility includes modifying the stem cells before transplantation in order to overproduce neurotrophic factors [34].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive upper and lower motor neuron disease which is often rapid in progression with most cases resulting in death a few years after its onset. As there is no effective treatment, stem cell therapy gives great hope to scientists, clinicians and patients [35]. Recent focus has shifted from replacing the damaged motor neuron to providing a „healthy" glial environment which appears to be more important for slowing disease progression [36], as shown in mutant rodent studies [37,38]. Several clinical trials are currently being conducted. Phase I of intrathoracic transplantation of mesenchymal stem cells proved to cause no serious adverse effects, although there was no significant clinical benefit [39], possibly explained by a lack of crucial motoric functions of this cord segment. Changing the graft location to the motor cortex [40] or cervical cord [41] seems to yield better clinical results. Intrathecal administration of mesenchymal stem cells also had an acceptable safety profile and possibly provided clinical stabilization by immunomodulatory effects [42]. Future trials to prove treatment efficacy should focus on patients in the early stage of disease since the aim of stem cell treatment is to provide support and enrichment for still existing motor neurons [43]. Genetically modified stem cells capable of secreting substances that promote the survival of motor neurons are expected to improve the efficacy of stem cell treatment.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune, inflammatory disease of the nervous system leading to demyelination and axonal loss, causing a broad spectrum of neurological symptoms. Anti-inflammatory and immunosuppressive therapy provides benefit, but only to a certain extent. Stem cell therapy in MS is based either on transplantation of stem cells/oligodendrocytes which are capable of remyelinating axons, or inducing remyelination by endogenous neural stem cells. Due to the inflammatory process in the central nervous system, the possibility exists for the destruction of transplanted cells. Additionally, because of the multiple locations of demyelinating lesions it may be difficult for the grafted cells to migrate to all those areas [21]. This explains the current focus on establishing a microenvironment which supports endogenous remyelination [44,45].

Another approach is to target the auto-immune mechanism of MS by "resetting" the immune system. This may be performed by autologous haemopoietic stem cell transplantation preceded by immunoablation, [46]. It has mainly been reserved for late, secondary progressive forms, not responsive to standard therapy, mostly because of the dangerous adverse effects associated with this type of aggressive treatment. Results indicate that clinical stabilization, defined by disease progression-free survival, is feasible, by as much as 74% at 3 years after intervention [47] and 25% at 15 years [48]. It has recently been argued that choosing patients still in the early, relapse-remitting phase with active inflammation may not only results in disease stabilization , but also in the reversal of neurological deficit [49].

Spinal cord injury

Traumatic spinal cord injury results in inflammation, demyelination damage and subsequent loss of neurons and glia. This all leads to various degrees of sensory and motor loss, and loss of autonomic function below the segment involved. Stem cell grafts could aid by limiting tissue damage and scarring, promoting remyelination, differentiating into neural and glial cells and integrating into the neuronal circuitry, and thus improving functional recovery as shown in animal models [50-53]. Safety has been assessed by a few studies with a small number of patients using bone marrow derived cells, and reporting no serious adverse effects [54,55]. The main concerns though are possible tumor formation and increased chance of allodynic pain after transplantation, explained by aberrant axonal regeneration [56,57].

In 2009, the FDA approved phase I on the first ever clinical trial of embryonic stem cells performed by the US company Geron. The Phase 1 multi-center trial was designed to assess the safety and tolerability of oligodendrocyte progenitor cells, derived from human embryonic stem cells, in patients with complete subacute thoracic spinal cord injuries (http://clinicaltrials.gov/ct2/show/NCT01217008). Aware of the increased frequency of cysts when applied in animal models, the trial was temporarily put on hold until additional animal studies were made; and the first patient was enrolled in October

2010. In the following year three more patients received the cell therapy, and the company reported no serious side-effects (http://www.geron.com/media/releases.aspx). It was then a surprise when in November 2011 the company announced the closure of the trial for further enrollment, citing financial reasons (http://www.geron.com/media/releases.aspx).

Stroke

Ischemic stroke is caused by a disturbance in the blood supply which causes death of neural and glial cells. Brain plasticity enables recovery of lost neurological function, but only to a certain extent. Although current treatment may be effective with thrombolysis, its use is limited with the short time frame for application. As regeneration of brain tissue continues for days or weeks after the initial damage [58], this allows the possibility for the therapeutic benefit of stem cells. In animal models, transplanted stem cells have been shown to migrate towards ischemic lesions, differentiate into neuronal and glial phenotypes and integrate into neuronal circuitry, and thus provide a behavioral benefit [59] Replacing lost neurons likely is not the main mechanism responsible for the therapeutic benefit of transplantation, as the degree of differentiation and integration of the transplanted cells do not correlate with the functional outcome [60]. Furthermore, it has been shown that transplanted cells do not have to cross the blood brain barrier in order to provide neuroprotection [61]. Other proposed mechanisms of improving outcome by transplantation are by reducing the death of host cells, inducing brain plasticity, increasing neovascularization, attenuating inflammation and by recruiting endogenous stem and progenitor cells [62]. Clinical trials are currently underway, with the first few involving stem cells derived from human teratocarcinoma [63], or xenogeneic grafts [64]; however, these have not provided clear evidence of major clinical improvement. Intravenous infusion of autologous mesenchymal stem cells seems to be safe and may improve recovery [65-67].

An alternative approach is to modulate endogenous neurogenesis. In responding to damage, neuronal stem cells proliferate, migrate to the area involved, differentiate into neuronal and glial cells and integrate into existing circuitry. Although stroke itself promotes this process, the extent is not enough for functional recovery [68]. Delivering growth factors or other molecules able to mobilize endogenous stem cells, either alone or in combination with stem cell grafts, is promising [59,60].

2. Discussion and conclusions

As certain neurological diseases currently have no effective treatment, stem cell therapy is an attractive and promising new approach for the treatment of neurological patients. Different strategies of stem cell treatment including cell replacement, promotion of neuroprotective mechanisms and endogenous stem cell recruitment can be used alone or in combination for each disease depending on the underlying pathological mechanism in that particular disease. Tailored treatment that targets the unique dysfunction of each disease is the goal for successful therapy with stem cells in the future. Variables still to be determined include the type/stage of the disease which is optimal for stem cell therapy, the ideal stem cell type, its preferable *in vitro* conditioning and finally, route of administration. This should first be done on animal models with the pathology and symptomatology resembling human neurological diseases. After proven efficacy in animal models, safety issues must be addressed and resolved before the use of stem cells therapy in humans. This involves prevention of possible tumor formation which is a major safety concern of stem cell therapy. The risk of serious adverse effects may be partially justified in a rapidly progressive, incurable disease such as ALS when compared to a non-life threatening condition which can be managed relatively well with standard therapy, like PD. Also, mechanisms of proliferation, migration, differentiation, survival, and different functions of stem cells should be investigated so they can be effectively controlled. Finally, all ethical and regulatory issues need to be addressed before stem cell therapy can be used in patients. In addition to the well-known properties of self renewal, other interesting properties like neuroprotection, immunomodulation, trophic actions and stimulation of angiogenesis require extensive studies in order to be able to ensure treatment optimization.

Stem cells can act both as immune suppressors or enhancers. It has been demonstrated that mesenchymal stem cells show high density expression of MHC-II at low levels of IFN γ, and decreased density at high IFN γ levels [70]. This leads to the conclusion that levels of IFN γ and possibly other cytokines involved in the regulation of MHC-II may be important in determining whether the mesenchymal stem cells will act as immune suppressors or enhancers. The immunosuppressive function may be useful in preventing immune rejection. Further investigation of the effects of cytokines on genes associated with pluripotency is also necessary since most of these genes are linked to oncogenesis and tumor suppression.

In contrast to *in vitro* investigations, injured or damaged tissue represents a complex microenvironment with various factors influencing implanted stem cells, therefore, future investigations should focus on cytokines and other inflammatory and anti-inflammatory mediators and the microenvironment interactions with stem cells.

Unfortunately Geron has stopped the enrollment of new patients in its clinical trial but has stated that they will continue to follow currently participating patients. We hope that their results will be encouraging and will provide a basis for new clinical trials. Although much work still has to be done prior to safe application of stem cell therapy in humans, stem cell–derived dopaminergic neurons are likely to be implanted in patients with Parkinson's disease within the next few years. In contrast with cell replacement therapy for Parkinson's disease, clinical attempts at neuronal replacement for stroke, ALS, spinal cord injury and Alzheimer's disease seem to be more distant. Besides cell replacement, the use of stem cells for treatment of these disorders may lead to improvements that could also be of clinical value through neuro- and immunomodulation, trophic actions, neuroprotection, and stimulation of angiogenesis [22].

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