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EDITORIAL

Cultivating stem cells for treating amyotrophic lateral sclerosis

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Abstract

This editorial addresses the current challenges and future directions in the use of stem cells as an approach for treating amyotrophic lateral sclerosis. A wide variety of literature has been reviewed to enlighten the reader on the many facets of stem cell research that are important to consider before using them for a cell based therapy.

Key words: Stem cell therapy; Amyotrophic lateral sclerosis

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), also known as Lou Gerhing disease/motor neuron disease is defined as the neuronal and muscular atrophy, loss of motor neurons. In the United States alone, ALS affects 30 000 individuals and death occurs 2-5 years post-diagnosis. Modalities including pharmacological, enzyme or genetic therapies have proven to be ineffective. New therapy is desperately needed. Promising results derived from animal models[1], prompted the first Food and Drug Administration (FDA) approved phase I safety trial of direct intraspinal transplantation of neural stem cells (NSCs) into patients in 2009[2]. Currently the FDA approved 18 clinical trials treating ALS (http://clinicaltrial.gov). However, no beneficial impact is shown in three completed clinical studies and the treated patients developed persistent dyskinesias in two studies[3]. The disappointment and anxiety prompt us to rethink about stem cell therapies. Here, we review the literature and address the challenges (cell types, preparations, routes of administration, mechanisms) and potentials (cytokine regulation, cell replacement, functional integration).

Multiple lines of stem cell types have been proposed for treating ALS: mesenchymal stromal cells (MSCs)[4-7], human skeletal muscle-derived stem cells with MSCs-like characteristics[8], human NSCs[9-11], human embryonic stem cells (hESCs)[12,13], human cord blood mononuclear cells[9-11], and human induced pluripotent stem cells (hiPSCs)[14]. None of these cell types in their natural forms is ideal for ALS therapy because they do not naturally carry all the features suitable for therapeutic as described previously[15-17].

Different methods have been used in preparing stem cells with variation in efficacies[8]. Establishing standardized paradigms for culturing human stem cells may allow a more unified study with consistent efficacies, such as cultivating stem cells in the natural microenvironment[16,18].

It appears that there is an optimal point of time, named therapeutic window, in disease progression and such a therapeutic window, mirroring disease development, may exist in stem cell development, in which stem cells are most effective in targeting ALS[19]. Indeed, Hefferan *et al*[20] found that FK506 and mycophenolate can significantly improve survival of human spinal stem cells after intraspinal transplantation in SOD1 (G93A) rats by employing monotherapy or combined immunosuppressive regimens only in certain points in time of postoperation. The pre-symptomatic phase in Wobbler mice is the most effective therapeutic window for stem cell therapy[8]. These imply that a disease state may dictate the choice of certain stem cell types, for example the choice of NSCs for anti-inflammatory support or the choice of NSCs-generated motor neurons for cell replacement.

The route of administration of stem cells needs to be pre-determined: systemic[21], intracerberoventricular[22], and local injection[23-28]. Upon systemic injection, transplanted stem cells migrated to the damaged areas in SOD1G93A mice[22]. Neural precursor cells transplanted specifically into the cervical spinal cord ventral gray matter of both SOD1G93A rats survived[29].

Tracking administered stem cells is critical for stem cell therapies. We have proposed eight criteria for tracking stem cells[30]. Canzi's group tracked stem cells at various times after intracerebroventricular injection by magnetic resonance imaging[8] and the method needs to be optimized for clinical setting.

Mechanisms of action for stem cell therapies need to be defined for ALS. Human skeletal muscle-derived stem cell-treated Wobbler mice (ALS model) led to improve mouse behavior (forepaw adduction)[8]. This effect of stem cell transplantation proved to be through anti-inflammatory cytokines. Similar studies supported this notion[28,31,32]. Stem cell-derived motor neurons are ideal for cellular replacement in ALS. Using transcriptional coding for generating electrophysiologically-active motor neurons from hESCs and hiPSCs significantly reduces the time required to by approximately 30 d in comparison to conventional differentiation techniques[12]. However, these electrophysiologically-active motor neurons remain to be elucidated for the functional integration *in vivo*.

Addressing these issues could provide a successful framework for developing stem cell therapy of ALS. Advancing research on understanding ALS mechanisms (including genomic and epigenomic approach), developing new drugs, and conducting cell therapies may help herald a new era in managing the unmet medical need of other neurodegenerative diseases.

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