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Research report

Regenerative cellular therapies for neurologic diseases

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ABSTRACT

The promise of stem cell regeneration has been the hope of many neurologic patients with permanent damage to the central nervous system. There are hundreds of stem cell trials worldwide intending to test the regenerative capacity of stem cells in various neurological conditions from Parkinson's disease to multiple sclerosis. Although no stem cell therapy is clinically approved for use in any human disease indication, patients are seeking out trials and asking clinicians for guidance. This review summarizes the current state of regenerative stem cell transplantation divided into seven conditions for which trials are currently active: demyelinating diseases/spinal cord injury, amyotrophic lateral sclerosis, stroke, Parkinson's disease, Huntington's disease, macular degeneration and peripheral nerve diseases.

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1. Introduction

Unlike other organs, the central nervous system (CNS) has a limited intrinsic capacity to regenerate following most types of injury, often leading to permanent disability. Stem cell trials for a variety of neurologic diseases provide patients and physicians with regenerative stem cell treatments that can potentially restore neurologic function previously lost due to disease, maldevelopment or trauma. In this review, we provide the current state of clinical stem cell research for several neurologic diseases in which stem cell trials are promising.

1.1. Goals of stem cell trials

The goal of regenerative stem cell trials in neurological diseases is to restore function that was lost due to the disease. Stem cells could achieve this goal in multiple ways. The most obvious way stem cells could restore function is to replace lost cells. In this model, the stem cells would be injected into the area of damage, differentiate into the lost cell type based on environmental cues, and reconnect with local circuits. Although several stem cell trials have shown a clinical benefit, many of them did not demonstrate a mechanism of cell replacement. Rather, the stem cells provided some other benefits. Some stem cells provided a

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local "neuroprotective" effect by secreting growth factors and stimulating anti-oxidants. Other stem cells appeared to provide trophic support while some stem cells only impacted the immune system, which indirectly benefited the nervous system.

In the area of regenerative neurological trials, we are still in the stage of first identifying potential benefits of stem cells, and then figuring out how the stem cells helped.

1.2. Stem cell types

We refer to "stem cells" as undifferentiated cells that can be cultured and expanded for transplantation into the CNS (Tai and Svendsen, 2004). Human pluripotent stem cells isolated from the inner cell mass of blastocysts (embryonic stem cells, ESCs) or derived from adult somatic cells using reprogramming factors (induced pluripotent stem cells, iPSCs) have the potential to become any cell type, for instance neural lineages, by using specific culture conditions. Multipotent neural stem cells isolated from fetal brain tissue are further along the developmental axis, and hence more limited in their cell fate potential. These progenitor cells are committed to becoming neural tissue but can still proliferate in culture. Stem cells from all along this spectrum have been investigated in animal models and human trials of neurologic disease.

In addition to embryonic and fetal stem cells there have been many clinical trials in neurology using mesenchymal stem cells (MSCs). These are non-hematopoietic stromal cells that originate in the bone marrow and other adult tissues. MSCs can produce a limited number of tissue types *in vivo* including cartilage, bone and fat. However, when infused into the circulation they have a unique ability to avoid the host immune system, release growth factors and modulate inflammation and dampen the immune response. These global properties, perhaps related to regenerating an aging immune system, explain some of the early benefits of MSC transplantation seen in a range of conditions from myocardial infarction to multiple sclerosis (Lalu et al., 2012). MSCs are also under extensive investigation for spinal cord and peripheral nerve injury and trials are underway or being established for stroke, amyotrophic lateral sclerosis (ALS) and other conditions (Supplementary Table 1). There are a range of sources of mesenchymal or mesenchymal-like stem cells being developed for use in neurological conditions including umbilical cord blood and adult adipose tissue.

Two other cell types have been studied as potential candidates for neural regeneration that can be isolated from adult humans – Schwann cells and olfactory ensheathing glial cells (OEGs). These are non-CNS supportive cells and are responsible for axonal growth and targeting of peripheral and olfactory nerves, respectively. They are mature cells but similar to stem cells, they can proliferate, migrate and respond to their local environment. The advantage of these cells is a potential autologous supply of tissue with defined differentiation capacity to overcome safety and immunological barriers.

Most agree that other than in the hippocampus there is little stem cell regeneration in the adult human brain that involves long axonal connections. Current regenerative neurology efforts are therefore primarily based on promoting a supportive local environment for the function of remaining neuronal circuits.

2. Current state of regenerative stem cell therapies

2.1. Demyelinating diseases and spinal cord injury

Most demyelinating diseases are relapsing–remitting autoimmune conditions such as multiple sclerosis that cause inflammatory-mediated damage, especially to myelin. Spinal cord injury, though not considered a demyelinating disease, is included in this section because of the important contribution of demyelination to neurologic dysfunction after trauma (Waxman, 1989). The primary goal for regeneration in demyelinating conditions and trauma is to remyelinate otherwise healthy, intact axons. To that end, several companies and academic groups have developed stem cells designed for transplantation into the area of the demyelinated lesion, intended to differentiate in response to the local environment and produce functional myelin. While animal studies have suggested this may be possible, no human study has yet definitively demonstrated this objective (Walczak et al., 2011).

Currently, there are over 20 ongoing stem cell trials for demyelinating diseases and traumatic spinal cord injury worldwide (Supplementary Table 1). The majority of these trials offer MSC infusions (intravenous and/or intrathecal) or surgical transplantation into the lesion. Four published studies of autologous MSC infusions for multiple sclerosis suggested some improvement in neurologic function, but the mechanism of action could not be conclusively based only on remyelination (Mohyeddin Bonab et al., 2007; Karussis et al., 2010; Yamout et al., 2010; Connick et al., 2012). One of these studies found that mesenchymal cell infusions led to an increase in regulatory T cells and a decrease in lymphocyte proliferation, suggesting a beneficial immunomodulatory effect (Karussis et al., 2010). In addition, neuroprotection or trophic factor production by MSCs could provide a favorable local environment for healing and regrowth (Chiu and Rao, 2011). A fifth completed phase I study at the Cleveland Clinic reported they had reached their safety endpoints (Bar-Or et al., 2014). All of the studies demonstrated the relative ease and safety of this approach, contributing to the large number of MSC trials taking place worldwide.

Although it has been suggested that MSCs can migrate to the brain and differentiate into neurons, in most studies, the vast majority of these transplanted stem cells do not appear to survive nor remyelinate (Mezey et al., 2003). Thus several groups have focused on transplantation of neural stem cells derived from embryonic, fetal and adult stem cells for the treatment of demyelinating conditions. The Geron Corporation performed the only neurologic trial employing embryonic stem cells. Oligodendrocyte precursors derived from this stem cell line, originally created by Dr. James Thomson at the University of Wisconsin-Madison in 1998 (Thomson et al., 1998) and approved by the Food and Drug Administration (FDA) in 2010, were tested for safety and efficacy in five patients with acute spinal cord injury. The study ended prematurely in 2012 due to financial constraints (Scott and Magnus, 2014) but the five subjects continue to be followed for safety. None of the five suffered any adverse effect but, unfortunately, none of them have made any significant recovery from their traumas.