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Neural stem cell therapy for neurodegenerative disorders: The role of neurotrophic support

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ABSTRACT

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease currently affect tens of millions of people worldwide. Unfortunately, as the world's population ages, the incidence of many of these diseases will continue to rise and is expected to more than double by 2050. Despite significant research and a growing understanding of disease pathogenesis, only a handful of therapies are currently available and all of them provide only transient benefits. Thus, there is an urgent need to develop novel disease-modifying therapies to prevent the development or slow the progression of these debilitating disorders. A growing number of pre-clinical studies have suggested that transplantation of neural stem cells (NSCs) could offer a promising new therapeutic approach for neurodegeneration. While much of the initial excitement about this strategy focused on the use of NSCs to replace degenerating neurons, more recent studies have implicated NSC-mediated changes in neurotrophins as a major mechanism of therapeutic efficacy. In this mini-review we will discuss recent work that examines the ability of NSCs to provide trophic support to disease-effected neuronal populations and synapses in models of neurodegeneration. We will then also discuss some of key challenges that remain before NSC-based therapies for neurodegenerative diseases can be translated toward potential clinical testing.

Contents

1. Introduction

The potential of cell transplantation as a therapy for neurodegenerative disorders was first examined nearly three decades ago

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with landmark studies of fetal mesencephalic tissue transplantation in Parkinson's disease (PD) patients (Lindvall et al., 1988). Although these initial studies produced variable results, the field's interest in this approach continued to grow and increasingly focused on the regenerative potential of neural stem cells (NSCs) in the hope that they could provide a renewable and more precise source of cells for transplantation. Building upon preclinical findings from PD models, researchers began to also investigate NSC transplantation for other neurodegenerative conditions including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). As a result the field's understanding of NSC transplantation and the mechanisms by which they influence these disorders has grown immensely. Yet significant challenges remain regarding if and how these promising preclinical findings can be translated into successful clinical trials.

2. Are NSCs a viable therapeutic approach for neurodegenerative disorders?

Researchers initially hypothesized that NSCs could likely only be practically developed as a therapy for disorders that involve relatively focal neural degeneration. For example, PD that is characterized primarily by a loss of dopaminergic neurons within the Substantia Nigra Pars Compacta represented an excellent candidate disease in which to develop a neuronal replacement paradigm (Lotharius and Brundin, 2002; Martino and Pluchino, 2006). While the development of this approach continues to advance, the concept of neuronal replacement has proven to be far more complex that initially expected. For example, transplanted stem cells need to survive within the adult brain and migrate from a small initial injection site to populate the target region. They then need to differentiate with high fidelity into the appropriate neuronal subtype, such as dopaminergic neurons. Perhaps most challenging of all, these transplanted cells then need to project to the appropriate target neurons and form appropriate synaptic connections. In the PD field this has led most studies to instead pursue transplantation of cells into the striatum, the target of dopaminergic innervation, rather than the substantia nigra where the disease-affected neurons normally reside. In the case of other neurodegenerative disease that exhibit more widespread pathology and loss of varying neuronal subtypes in multiple brain regions, such as AD, this kind of neuronal replacement paradigm becomes even more challenging (Davies and Maloney, 1976; Davies et al., 1980; Hardy et al., 1987; Hyman et al., 1987; Lowe et al., 1990). How then can NSCs be a reasonable therapy for these more complex neurodegenerative disorders?

As we will discuss, recent studies have demonstrated that some of the most profound recovery following NSC transplantation in preclinical models is likely mediated via modulation of neurotrophic systems. Indeed a growing number of studies have found that differentiation of NSCs into supportive glial subtypes such as astrocytes that can produce key growth factors to influence synaptic plasticity and neuronal function and regulate brain vascularization and energetics may play an important role in functional recovery (Fig. 1).

3. Neurotrophic factors in CNS disorders & potential therapeutic approaches

Beginning with the discovery of the first neurotrophic factor, nerve growth factor (NGF), more than half a century ago

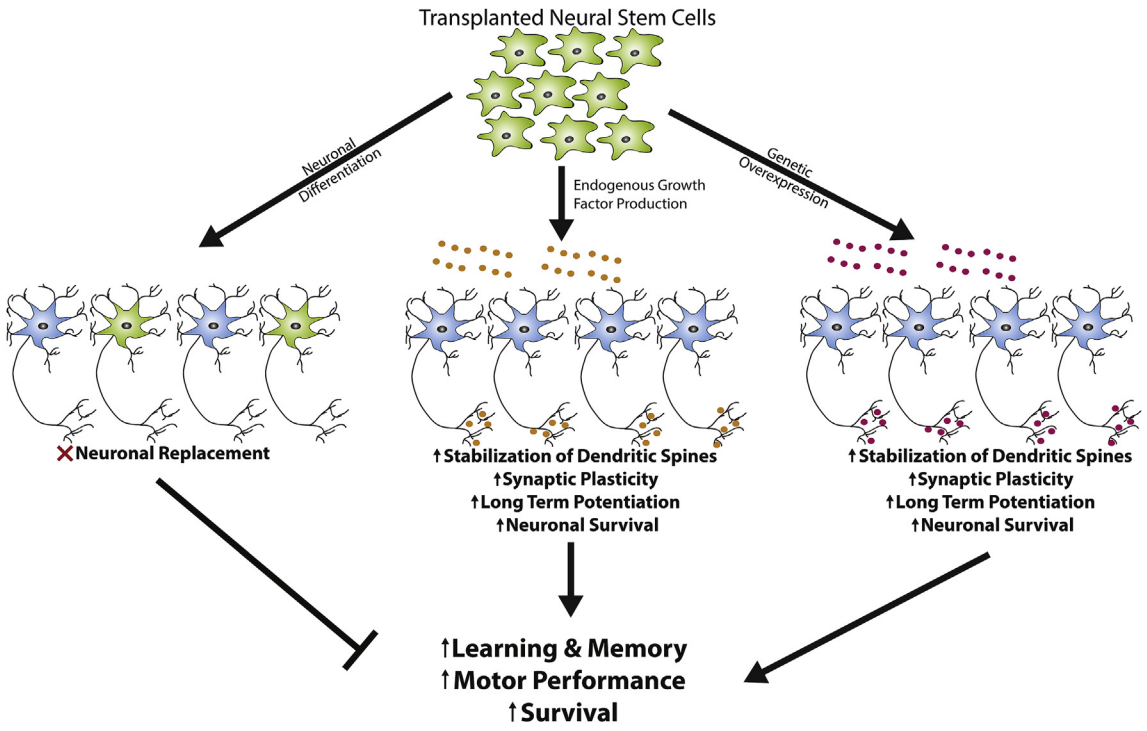

Fig. 1. Potential mechanisms of neurotrophic support provided by transplanted neural stem cells (NSCs). Initially many attempted to use NSCs for neuronal replacement, theorizing that following neuronal differentiation (neuron; green) cells would integrate with host neuronal circuitry (blue) to replace neurons that have died during the course of AD, PD, or other neurodegenerative disorders. However, work towards this goal has proven challenging and results are mixed. Recent research has instead demonstrated that endogenous secretion (center, orange) or genetic overexpression (right, purple) of neurotrophic factors (BDNF, GDNF, IGF-1, NGF) may provide an alternative and perhaps more promising approach for NSC-based therapy. Transplanted NSCs that secrete neurotrophins are capable of increasing synaptic plasticity, enhancing long-term potentiation, and promoting neuronal survival that together lead to improved cognitive and motor performance. (Figure adapted from Marsh and Blurton-Jones, 2015).