Cell Stem Cell
Forum

Why Is It Taking So Long to Develop Clinically Competitive Stem Cell Therapies for CNS Disorders?

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The remarkable advancements in basic stem cell research with implications for several central nervous system disorders have so far not been translated into clinically effective therapies. Here I discuss some of the underlying problems and how they could be overcome.

Introduction

The first attempt to treat a central nervous system (CNS) disorder with cell transplantation took place three decades ago (Backlund et al., 1985). In this study, autologous adrenal medulla cells were implanted into the striatum of Parkinson's disease (PD) patients to provide a local catecholamine source, but the beneficial effects were minimal. A few years later, human fetal mesencephalic tissue rich in dopaminergic neuroblasts was transplanted to the striatum in PD patients. These clinical trials established some important basic principles of cell therapy for CNS disorders: grafted neurons can replace dead host neurons in the diseased, 50- to 60-year-old human brain, reinnervate denervated areas, release transmitter, and, in some patients, give rise to therapeutically valuable effects (Lindvall and Kokaia, 2010). Based on these findings, stem-cell-based therapy for PD has been regarded as a low-hanging fruit, with the requirement for successful treatment being seemingly simple, namely to generate large numbers of standardized dopaminergic neurons for transplantation from stem cells. However, despite major efforts in basic and clinical research, there is still no clinically competitive cell therapy for PD or any other CNS disorder. Clinical trials with stem cells, often of bone marrow origin, are ongoing in, e.g., stroke, amyotrophic lateral sclerosis (ALS), and spinal cord injury (http://www.clinicaltrials.gov), but whether they will show efficacy is unclear. From my perspective, there are several major problems that explain why the clinical translation of stem cells for neurological disease is so difficult, as outlined below.

The Problem of Generating the Right Cells and Understanding Their Mechanisms of Action

Stem cells can act in brain diseases by replacing those cells that have died, but they can also restore function through other mechanisms (Lindvall and Kokaia, 2010). In the case of cell replacement, disease pathology determines which cells have to be generated from the stem cells. Different cells will be needed for different diseases. Substantial improvement in PD and ALS will require cells with the properties of dopaminergic and motor neurons, respectively. The situation for cell replacement in Alzheimer's disease (AD) is much more complex because the stem cells would have to be predifferentiated in vitro into many different types of neuroblasts for subsequent implantation into a large number of brain areas. Similarly, in stroke there is a loss of several different types of neuron, glial cells, endothelial cells, and parenchyma. These broad defects raise the question of whether it is realistic to expect that clinically valuable improvement in disorders like AD or stroke could be achieved through cell replacement.

Importantly, efficacious cell replacement will require the generation of the correct neuronal phenotype. For example, in PD it is not sufficient to generate just any type of dopaminergic neuron. Rather, to induce substantial clinical benefit, the human stem-cell-derived dopaminergic neurons must exhibit the specific properties of the neurons that have died, i.e., the substantia nigra neurons (Lindvall et al., 2012). A recent study did succeed in showing efficient conversion of human embryonic stem cells into bona fide substantia nigra dopaminergic neurons using a differentiation protocol guided by developmental principles (Kriks et al., 2011). These cells ameliorated PD symptoms after transplantation in animal models without forming tumors.

For optimum recovery in many CNS diseases, neuronal replacement and at least partial reconstruction of circuitry should probably be the long-term goal. However, a large number of experimental studies in animal models of these disorders have demonstrated that stem cell delivery gives rise to functional improvements that cannot be explained by neuronal replacement. These beneficial effects may also be relevant in clinical settings. For example, systemic or intracerebral delivery of neural and other stem cells in stroke models has been reported to lead to improvements by trophic actions, modulation of inflammation, promotion of angiogenesis, remyelination and axonal plasticity, and neuroprotection (Lindvall and Kokaia, 2010). The functional effects can be enhanced if the stem cells have been genetically modified to secrete various factors such as trophic molecules. For clinical competitiveness, it is necessary, though, that the efficacy and safety of the stem-cell-based approach is superior to that of available treatments (e.g., drugs) acting on the same targets. Clinical trials are ongoing in stroke and ALS with delivery of stem cells, which are intended to act not by neuronal replacement but instead through one or more of the other presumed mechanisms. However, it is conceivable that effective therapies will not be developed until the mechanisms of action of the

stem cells are much better understood and can therefore be optimized.

The Problem of Using the Right Animal Model and Behavioral Tests

Available animal models of CNS diseases do not mimic all aspects of the pathology of the human condition, which may explain lack of efficacy of cell therapy when it is translated to the clinical setting (Lindvall et al., 2012). For example, animal models of PD are mostly based on lesions of the nigrostriatal dopaminergic pathway, induced by toxins, and studies of sensorimotor functions. These models do not imitate the clinical disorder, which has many nonmotor and motor features with nondopaminergic pathology outside the substantia nigra. Attempts to develop transgenic models of PD have been pursued in recent years, but these represent only partial models of the core pathologies. For efficient clinical translation, better animal models that reflect the complex pathology and pathogenesis of CNS disorders accurately have to be developed through collaboration between basic scientists and clinicians. Many current models use otherwise healthy, young animals, which again is distinct from the clinical situation in many neurodegenerative diseases, where patients are often older, with concurrent diseases and chronic medication. For example, stroke patients frequently also suffer from hypertension and diabetes.

The animal models may not be able to fully predict the adverse events, toxicity of the cell product, immune and other biological responses, and risk for tumor formation that would occur after implantation of cells into patients. A lesson can be learned from the clinical trials with fetal dopaminergic cell therapy in PD. When troublesome graft-induced involuntary movements (so-called dyskinesias) were observed in patients (Freed et al., 2001), this side effect came as a surprise because none of the preclinical studies in rodent and primate models of PD had observed any adverse responses of this type. The risk of tumor formation from cells derived from pluripotent cells also makes clinical translation difficult. For example, life expectancy is virtually normal in PD patients, and therefore even a minor risk of tumor formation associated with stem cell therapy would be unacceptable. It is difficult to assess the clinical tumor risk with human embryonic stem cell derivates using preclinical xenograft studies (Erdö et al., 2003). Thus, for clinical translation, there will need to be rigorous mechanisms for determining the tumorigenicity of stem cells and their derivatives.

A prerequisite for application in patients must be a demonstration in an animal model that a given cell-based approach induces substantial improvement of clinically relevant functional deficits (Lindvall et al., 2012). For example, in rodent models of PD, behavioral improvement after stem cell therapy is often reported as a reversal of rotational asymmetry in animals with unilateral lesions of the nigrostriatal dopaminergic system. While this test gives a good measure of the dopamine-releasing capacity of the grafts, the deficit does not reflect any symptom seen in PD patients. Other behavioral tests are available but have only been used in few studies. Basic scientists and clinicians together have to develop functional and behavioral tests that assess deficits in animals resembling the impairments in patients with CNS disorders.

The Problem of Distribution and Progression of Pathology

Even if stem cells improve function in a specific area by neuronal replacement or other mechanisms, effective therapy is hindered if there is concurrent degeneration in other brain regions or if such changes develop after transplantation. For example, dopaminergic denervation in areas not reached by the intraputaminal grafts, such as the ventral striatum, in PD patients with fetal dopaminergic grafts counteracts the symptomatic relief following transplantation (Piccini et al., 2005). Similarly, even if replacement of motor neurons in the spinal cord of ALS patients did work, central motor neurons such as corticospinal neurons, which also degenerate in ALS, would most likely have to be replaced for effective, life-saving restoration of function. For successful, long-term clinical efficacy of stem cells in chronic neurodegenerative disorders, patient selection will be crucial, and neuronal replacement probably has to be combined with a neuroprotective therapy to hinder disease progression.

In chronic neurodegenerative disorders, host pathology may also affect the cells derived from the transplanted stem cells, as has been observed in fetal grafts after implantation in PD and Huntington's disease patients (Kordower et al., 2008; Cicchetti et al., 2009). This consideration may be particularly relevant when patient-specific cells for transplantation are produced by therapeutic cloning, from induced pluripotent stem cells, or by direct conversion of somatic cells. Such cells could exhibit increased susceptibility to the neurodegenerative disease process. In the case of PD, this problem may not be a serious one, because with fetal grafts the propagation of disease pathology is slow, the majority of grafted neurons are unaffected after a decade, and the patients can experience long-term improvement.

The Problem of Translating Basic Research Findings to Patients

A major problem hindering effective translation is, in my view, insufficient communication between basic scientists and clinicians. My own experience as a clinical neurologist is that the clinic and the basic research laboratory are often completely different worlds. For basic stem cell research to have more impact on the clinical challenges, clinicians have to be involved from an early stage and not just immediately before application in patients. Basic scientists should be educated in the clinical features of CNS disease and the problems related to diagnosis and therapy. The critical scientific steps from basic research to patient application should be defined through cooperation between basic scientists and clinicians. This partnership must function throughout all stages of clinical translation if basic research findings are to be efficiently converted to novel treatments for CNS disorders. The new imaging techniques for monitoring brain and spinal cord in vivo in animals and humans will create golden opportunities for fruitful interaction between basic scientists and clinicians. It is important to emphasize that successful clinical application of stem cells will depend not just on the generation of the right type of cell but also on several other factors, such as appropriate site of delivery of the cells and selecting the suitable patient.

The Problem of Competing Therapeutic Approaches

There is considerable variation in terms of the availability of existing therapeutic options for different CNS disorders, and these differences will influence how quickly stem cells can be translated to the clinic. For example, to be clinically competitive in PD, grafts must give rise to major recovery (at least 70%) of motor function. Motor symptoms in PD patients can already be treated quite well with L-dopa, DA agonists, enzyme inhibitors, and deep brain stimulation. Thus, the efficacy of stem cell grafts in relieving disease symptoms would need to be high. If transplantation of stem-cell-derived dopaminergic neurons in a PD patient gave only a 30% reduction in motor symptoms, it would be regarded as scientifically exciting but clinically useless. The efficacy of currently available human stem-cell-derived dopaminergic neurons and predictions for the clinical setting are unclear, presenting a problem for clinical translation. As a first step toward patient application, a cell-potency assay should be used to compare the efficacy of the stem-cell-derived neurons versus equivalent fetal dopaminergic neurons (which can be regarded as the gold standard) in appropriate animal models of PD.

Many brain diseases, however, lack effective current treatments. Several such diseases are progressive and ultimately fatal, such as ALS or Huntington's disease. In these conditions, even a minor improvement induced by stem cells would be clinically useful. If efficacious therapy is lacking, the severity of a disease such as ALS or Huntington's disease might justify the risks of a stem-cell-based experimental intervention in patients. It should be emphasized, however, that even when there is no effective alternative therapy, no application in patients can be justified if it does not have proven efficacy in the laboratory and scientific understanding of the mechanism of action. For these CNS disorders, careful, laborious, and time-consuming preclinical studies are also required. Clinical trials showing safety alone, without any scientific grounding for their use, are unethical.

The Problem of Costs

Stem-cell-based treatments for CNS disorders should not only relieve human suffering but also be cost-effective compared to other therapies. To promote clinical translation, scientists should perform health economics studies at an early stage to estimate the potential value of further research in stem cell therapy for various disorders in order to ensure that society makes the best use of research investments. Using health economics modeling and a range of assumptions, it is possible to determine which patients should be targeted with stem cell therapy. Moreover, such modeling will give a price at which the intervention would be cost neutral, i.e., the stem cell therapy would bear its own cost from a societal perspective. This estimated price for stem cell therapy will be important for companies manufacturing the stem-cell-based product to be delivered to the patient. Translation of discoveries in basic stem cell research into safe and effective clinical products for CNS disorders will be very expensive. The European Court of Justice recently decided that no patents can be granted for inventions based on human embryonic stem cells, even if the cell lines were established in the laboratory many years ago and the invention itself does not involve obtaining new embryonic stem cells. This decision may well cause companies in Europe to be reluctant to invest in translational stem cell research because they would be unable to protect their procedures via the patent system. The end result will unfortunately be further delay in the development of clinically effective stem cell therapies for CNS disorders.

Conclusions

Many CNS disorders in humans currently lack effective treatments, but there is now reason to be optimistic. Experimental studies have clearly indicated that stem cells have the potential to give rise to radical new therapies for these diseases. However, there is no fast track for stem cells to the clinic. Strong investigative basic research remains fundamental for clinical advancement of stem-cell-based approaches. For efficient clinical translation, a road map to the clinic, taking into account the critical scientific, clinical, regulatory, and ethical issues, should be defined and continuously revised by basic scientists and clinicians together. The commitment must be long term, and the aims must be realistic. The biological problems that will be encountered along the way are complex and should not be underestimated.

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