Neuroprotection: Translation of Mechanism and Model into Therapy
Evaluating the Potential of Stem Cells: A Critical Assessment

The Therapeutic Potential of Stem Cells for Nervous System Diseases

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The mammalian adult brain is a regenerative system capable of incorporating embryonic stem (ES), progenitor, or fetal primary neurons into new circuitries. These implanted or regenerating neurons and glia grow to functionally repair damaged or degenerated neuronal connections. First, by transplanting immature neurons into various locations in the brain of animal models, we determined which connections and reparative interactions with the host are possible using fetal or ES cells. We found that implanted fetally derived or ES cell-derived dopamine neurons can survive in the long term, and gradually reduce signs of Parkinson disease in various animal-model systems. Second, the differentiation pathways and molecular switches necessary for specific dopamine cell identity and growth were evaluated. There are genetic modifications and trophic factor support involving Nurr1, PitX3, Shh, FGF8, and markers modifying growth-cone behaviors and cell type specification from ES to dopamine neurons. The presence of these factors can further enhance the restoration of normal neuronal dopamine function. The functional studies of neurodegenerative models and potential repair in Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis provide new opportunities for evaluating the therapeutic use of stem cells.

Translational Challenges: From Animal to Human Experimentation

Justin Zivin, MD, PhD

At present, only thrombolysis with tissue plasminogen activator has been approved by regulatory agencies (including the US Food and Drug Administration) in several countries for the treatment of acute stroke. Numerous neuroprotective agents have been tested in both poorly designed and well-designed clinical trials, but so far all have failed to provide convincing evidence of safety and efficacy. Many drugs, and some devices, have been shown to reduce neurological injury and histological damage to the brain in a variety of animal stroke models, but these encouraging experimental findings have not resulted in successful treatments for human stroke victims. Although it is commonly thought that the animal models do not predict the results of human clinical trials, I would contend that some animal models are actually reasonably accurate predictors of human responses to cerebral ischemia and the effects of some types of therapies. There are numerous possible reasons for the trial failures, and we have encountered obstacles at virtually every step in the process of translating theory into clinically practical therapies. I will discuss the reasons for many of the past difficulties and possible ways to achieve better results in the future.

What Has Fetal Transplantation Taught Us About Cellular Transplantation Into the CNS?

Olle Lindvall, MD, PhD

The clinical trials with transplantation of brain tissue from aborted human fetuses in patients with Parkinson disease (PD), and to some extent in patients with Huntington disease, provide proof-of-principle for the cell replacement strategy in the human brain. In PD, for which clinical cell therapy research has reached the furthest, intrastriatal grafts of mesencephalic tissue can reinnervate the striatum, restore dopamine release and movement-related frontal cortical activation, and give rise to significant clinical improvement. However, it is unlikely that transplantation of human fetal tissue can be developed into therapies for large numbers of patients owing to the poor availability of tissue for grafting and problems with standardization, purity, and viability. Stem cells from different sources could be useful to generate almost unlimited numbers of specific neuron types (e.g., dopamine neurons for PD). Most importantly, the clinical trials, as well as studies in animal models, have taught us which requirements have to be fulfilled for a graft to induce marked and clinically valuable improvement in patients.