MOLECULE-TO-MALADY

Stem cells and neurodegenerative diseases

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The Promise of Stem Cell Research

A particularly exciting and novel development in the treatment of neurodegenerative diseases is the suggestion from both animal and human studies that cell transplantation offers the potential of effective future treatment for neurodegenerative disorders such as epilepsy, Parkinson's disease, Huntington's disease and Alzheimer's disease. In recent years, the transplantation of cells into the diseased human brain has emerged from the realm of the theoretical to that of the practical. Grafts of embryonic cells have been shown to partially restore some neurochemical deficits and to ameliorate behavioural and locomotor impairment in animal

models of these diseases.[1-6] In humans, patients with idiopathic and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease have shown remarkable improvements following human fetal neural transplants.[7-9] However, the use of human fetal embryonic tissue for cell transplantation therapy in neurodegenerative diseases is associated with major problems. The scarcity of this material is compounded by practical issues such as the age of the donor, viability, contamination and heterogeneity of tissue as well as overwhelming ethical and moral concerns.

Worldwide attention is presently focused on the potential use of 'stem cells' as an alternative source of tissue for cell transplantation and brain repair. The announcement that stem cells can be obtained from aborted human fetuses or from spare embryos from *in vitro* fertilization procedures has been met with both enthusiasm and opposition. Less controversial, and probably more notable, is the recent demonstration that stem cells can be obtained from adult brain tissue, raising the exciting possibility that these cells can be exploited to generate cells for autologous brain cell transplants. Furthermore, a recent report showing that human bone marrow stromal cells can differentiate into neurons[10] raises the possibility of obtaining an easily accessible renewable source of material for autologous transplantation.

The Use of Neural Stem Cells in Brain Repair

We are interested in the use of 'neural' stem cells for the treatment of neurodegenerative diseases.

What Exactly is a Neural Stem Cell? The term 'neural stem cell' is used loosely to describe cells that can generate brain cells or are derived from the central nervous system, have some capacity for self-renewal, and can give rise to cells other than themselves through asymmetric cell division.[11] Neural stem cells exist in both the developing mammalian central nervous system and the adult central nervous system of mammals, including man.[12,13] Neural stem cells can also be derived from more primitive cells that have the capacity to generate neural stem cells and stem cells of other tissues (Figure 1). Embryonic (pluripotent) stem cells are obtained from blastocytes (fertilized eggs) and this is currently the stem cell type being proposed for use in a wide variety of commercial and clinical applications. Most stem cells can be categorized as multipotential and only make cells that have a particular function. Usually between the stem cell and its final cell type is an intermediate population of committed progenitors with limited proliferative capacity and a restricted fate.

The Role of Neural Stem Cells in the Adult Brain. The use of adult stem cells in cell transplantation therapy could obviate the need to use stem cells derived from human embryos or human fetal tissue. At present, there are no legal or ethical concerns regarding research with adult stem cells. Furthermore, adult stem cells derived directly from the patient would reduce the likelihood that the transplanted cells will be rejected.

Stem cells have been identified and isolated from specific regions of the brain; (i) the subventricular zone (SVZ) lining the lateral ventricles and adjacent to the region of the basal ganglia affected in Huntington's and Parkinson's disease, and; (ii) the subgranular zone (SGZ) in the hippocampus, the region of the brain which is primarily affected in Alzheimer's disease and temporal lobe epilepsy. The stem cells located in these regions have been shown to multiply and form new replacement neurons for adjacent brain structures. In this regard it is especially exciting that stem cells located in these regions are found immediately adjacent to the basal ganglia and hippocampus that are respectively the areas of primary degeneration in Huntington's and Parkinson's disease, and in Alzheimer's disease and epilepsy. Indeed, there is increasing evidence that one function of stem cells in the adult brain may be to generate new cells in response to brain injury or disease. When the brain is injured, it may try to 'repair' itself with its own population of stem cells but, for most injuries that come to clinical attention, this repair process is restricted by the number of available stem cells and may even be counter-acted by a growth-inhibitory environment, especially in the adult brain. In order to investigate whether neurodegenerative conditions do stimulate stem cells in the adult brain to try and repair the area of injury, we are investigating the presence of stem cells in the human brain in Huntington's disease, Parkinson's disease, Alzheimer's disease and epilepsy. In several cases of advanced Huntington's disease, our preliminary studies have shown an increase in the number of putative stem cells in the SVZ compared to age-matched normal human brains suggesting that there is an injury-induced increase in the number of stem cells. However, this increase in stem cell proliferation is ultimately insufficient to compensate for the progressive cell loss observed in the Huntington's diseased brain. If this potential for cell replacement by the brain could be augmented pharmacologically then compensation may increase to a point where neuronal cell loss is slowed and even perhaps clinical improvement observed.

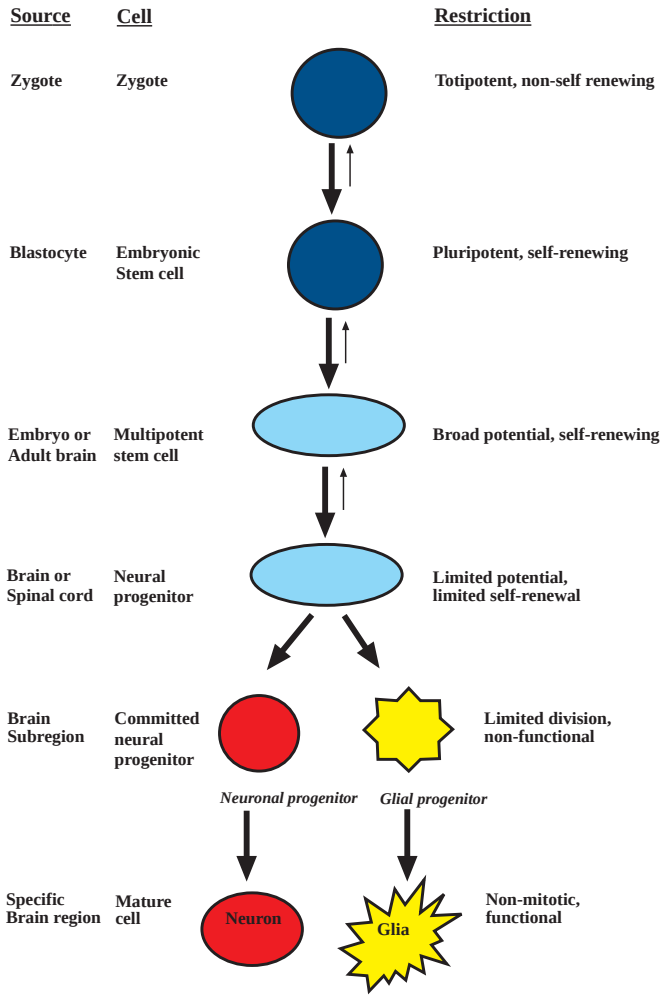

Figure 1. A schematic diagram demonstrating the different classes of mammalian stem cells.

Finally, recent studies suggest that neurogenesis is not merely a compensatory response to brain injury, but may play a

fundamental role in how our brains function. Shors et al[14] demonstrated that neurogenesis was involved in trace memory formation, and this may explain recent MRI studies showing that hippocampal volume in humans is associated with navigation experience.[15]

The Clinical Potential of Neural Stem Cells

Given that most neurodegenerative diseases affect specific cell populations, an ideal source of material for transplantation would be an expandable cell source that could be instructed to completely assume the desired cell type upon maturation. This would provide a valuable strategy for the repair of certain neurodegenerative disorders. Stem cells have the ability to achieve this.

Neural stem cells have been successfully transplanted into the normal adult mammalian brain where they form mature cells.[16-18] As with transplanted fetal neurons, neural stem cells transplanted into the lesioned rat brain have been observed to 'replace' lost brain cells and reduce lesion-induced behavioural impairment.[19-21] They appear to integrate into the brain after transplantation, possibly allowing for literal cell replacement; this makes them a potentially better source for cell transplantation therapy than human fetal embryonic neurons.

Whether stem cells take on the exact function of the cells they replace remains to be determined, but the answer will be the foundation on which therapeutic strategies are built. Transplanted stem cells may need to be genetically and/or pharmacologically engineered to direct them to the appropriate cell phenotype, or more likely, the cells that integrate into a particular region of the brain may need to be 'nurtured' by neighbouring cells in order to be functionally integrated into the neural circuitry. Alternatively, the delivery of factors that act to stimulate neural stem cells to repair the injured or diseased brain may have clinical potential in the treatment of neurodegenerative diseases. At present however, we do not know which soluble and intracellular factors will promote neural stem cells to grow and multiply to make mature, adult brain cells. We have some evidence to suggest that transcription factors are pivotal in this process.[22] In addition, growth factors, such as insulin-like growth factor-1,[23] brain-derived neurotrophic factor,[24] transforming growth factor-α,[25] fibroblast growth factor-2[26] and members of the Ephrin family[27] have been observed to promote the proliferation and differentiation of stem cells. Just as important are studies investigating the pathways controlling astrocytogenesis since much of the failure of cell transplantation in the brain may be due to the formation of astrocytes rather than new neurons.

Pharmaceuticals may also regulate neurogenesis in the adult brain. For example, recent studies suggest that lithium carbonate, commonly used to treat manic-depression, can promote neurogenesis in the brain[28] and increase grey matter volume after chronic (four weeks) use in humans with bipolar mood disorder.[29] Other antidepressants such as prozac also regulate neural stem cell production.[30]

In conclusion, the exciting possibility that the human brain has the potential, just like other organs of the human body, to repair itself is dramatically changing attitudes towards the treatment of neurodegenerative diseases. The era of the stem cell is upon us; hopefully we will no longer have to accept that the diagnosis of a neurodegenerative disease heralds an unremitting, inevitable clinical decline for the patient.

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