Stem cell therapies: a tale of caution

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ABSTRACT

- One of the most exciting possibilities in human therapeutics is that stem cells (embryonic or adult) may compensate for cell loss in disease, with functional recovery.
- This has received considerable publicity in the lay press.
- Much work remains to be done to turn stem cell therapy into a practical reality for major degenerative diseases, especially those affecting the nervous system.
- Medical scientists and journalists should work together in ensuring that the general public has a realistic understanding of the likely time frame in which benefits from stem cell therapies will be realised.

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ONE OF THE CHALLENGES facing modern medical science is to develop the means to regenerate failing organs in incurable illness. This applies especially to the central nervous system (CNS); many of the major CNS illnesses have either no treatment or relatively ineffective treatments.

In recent years in Australia, advances in stem cell technologies have claimed a higher public profile than any other medical advance. This has fostered a public perception that new treatments for disorders such as stroke, Parkinson's disease, Alzheimer's dementia and motor neurone disease, are not only highly likely, but imminent. Australia has outstanding groups working in both the adult and embryonic stem cell technologies. As a result, scientific advances often receive a high media profile for work which is still some distance from clinical trials, let alone translation into proven remedies. Indeed, the correspondence columns of major newspapers and the current embryonic stem cell debate reveal a high expectation by some members of the public that stem cell therapy will soon provide successful treatments for progressive neurodegenerative disease. Further, anecdotal information suggests that the potential benefits of stem cell therapy are now commonly discussed in clinical practice.

The topicality of stem cell research is indicated by 93 articles which mention stem cells in one newspaper, *The Melbourne Age*, over the past 12 months. Topics covered include an article indicating that stem cell therapies may be expensive and only available to the wealthy, and articles linking stem cell research to treatments in AIDS, renal disease and cardiac failure. One recent report in the electronic media mentions stem cells as a possible future treatment for multiple sclerosis. It is clear that the non-scientific or non-medical reader could justifiably conclude from much of this information that practical stem cell therapies for many human conditions will be available in the not-too-distant future.

Types of stem cells

There are many different types of stem cells. Cells from fertilised ova form embryonic stem cells, which can develop into any tissue or tissues. Stem cells found in most adult tissues still have the potential to generate several different types of tissue. Other stem cells are already advanced on a particular lineage and are committed to one cell type (unipotent).[1]

One of the keys to most approaches to stem cell therapy is to generate a stable pool of cells. These are usually unipotent. However, in some cases, such as the CNS, several cell lines (ie, neuronal, glial) might be required at the same time for clinical applications. Skeletal muscle is, in many ways, an ideal tissue for stem cell therapy, in that it has been shown that the muscle architecture can be restored even after severe disruptions.[2] Endogenous muscle cells are known to be exhausted in degenerative muscle disease such as Duchenne dystrophy.[3]

Work with muscle cells

Attempts to reconstitute skeletal muscle in human muscle disease through myoblast transfer therapy (a form of unipotent stem cell therapy) have now been under way for more than a decade, and provide many lessons about the hurdles that have to be overcome in stem cell therapy. Although early experiments in animal models of Duchenne dystrophy showed that transplantation infusion of committed muscle stem cells from normal muscle resulted in partial restoration of the deficient protein, a high percentage of introduced stem cells died within a short time of transplant, and clinical trials in boyhood Duchenne dystrophy showed no significant clinical improvement.[4]

Ten years of work with a fairly simple stem cell model in a non-complex tissue that can regenerate effectively has been frustratingly slow. Major problems of immunorejection, both of foreign cells and dystrophin, have not been adequately overcome with readily available immunosuppressive therapies. Difficulties in delivering stem cells to a wide range of muscle tissues remain formidable, and, in spite of enor-

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mous hope and enthusiasm for this strategy by investigators and the muscular dystrophy community when it was introduced, little practical progress has been made.

Problems with stem cell therapy for the central nervous system

The complexity of issues and the range of problems to be overcome in achieving stem cell therapy for the CNS dwarf those in skeletal muscle.[5] These problems include:

- isolation, enrichment and propagation of stable CNS neural stem cell lines are not yet reliable, although this field is advancing rapidly;
- processes which allow introduced stem cells to help restore injured neuronal networks in the damaged adult brain are not yet adequately understood;
- disease processes in progressive neurological disorders which may adversely affect introduced stem cells need to be understood and alleviated;
- factors that drive introduced stem cells preferentially to glial lines in most parts of the CNS need to be better understood and able to be manipulated;
- there are delivery problems in generalised CNS disorders because of a need to deliver stem cells to many different parts of the brain or spinal cord (this applies to Alzheimer's dementia and motor neurone disease);
- introduced stem cells must have a useful physiological role, and neurones must be integrated into effective neuronal networks — those that are not could theoretically impair function (similar considerations apply to other tissues, such as heart, where stem cell therapy is only likely to be useful if generated cardiomyocytes are effectively incorporated into the contracting myocardium);
- uncontrolled proliferation of stem cells can result in benign tumours (teratomas), which may be of great significance in the CNS (and the myocardium).[5]

Other developments

Exciting developments in bone-marrow-derived stem cell technology have the potential to overcome some of these difficulties. The identification of pluripotent cells in the two major bone marrow fractions (the mesenchymal and haemopoietic cell fractions), which can differentiate into a number of cell lines, offers a potential for the development of treatments that can be delivered systemically and manipulated to avoid rejection.[6] Treating three children who had osteogenesis imperfecta with allogenic bone marrow transplantation allowed mesenchymal progenitor cells to differentiate into osteoblast lineages, resulting in new bone formation and clinical improvement.[7] This approach has potential in a number of tissues, but currently the ability of mesenchymal stem cells to repopulate tissues such as muscle is low.

In stroke studies in which millions of cells were implanted into animals, as few as 330 of the implanted cells took on any role, and implantation did not reduce infarct volumes.[8] Thus it seems likely that these stem cell implants stimulate endogenous host repair mechanisms[8] or provide a degree of neuroprotection which limits the effects of ongoing damage rather than replace lost neurones and repair the damaged neural architecture.

Ongoing work is also necessary to further define the growth potential of stem cell subtypes, and to identify the factors that drive differentiation in a particular direction. In the neurological sphere, most work has been done on Parkinson's disease. This condition lends itself to stem cell therapy in that the targeted area is small and accessible neurosurgically in a part of the brain that neurosurgeons are familiar with through a long history of stereotaxic surgery.

When fetal dopaminergic tissue (not stem cells) is implanted into the striatum of patients with Parkinson's disease, it normalises dopamine turnover and has produced a moderate clinical benefit which develops gradually over 6–24 months.[9-12] However, in a double-blind trial of fetal dopaminergic cell transplantation, which included a sham surgery arm, the results fell short of those expected from previous case reports and short series.[13] Although postmortem examination of two patients showed marked improvements on ^{18}F-fluorodopa positron emission tomography scans and dopaminergic re-innervation of the putamen,[13] only modest clinical improvements were seen in younger patients (aged < 60 years), and older patients showed no overall improvement. Importantly, 15% of these patients developed severe dystonia and dyskinesias that persisted even when levodopa therapy was ceased. While they may provide a more convenient source of tissue, there is no conceptual framework to suggest that survival, differentiation and integration of stem cells will lead to a better outcome than survival and integration of predifferentiated fetal mesencephalic dopaminergic neurones. It should also be noted that when embryonic stem cells were implanted into the denervated striatum of hemiparkinsonian rats, 20% of animals developed teratomas.[14]

The road ahead

Stem cell therapy holds huge promise, not only for brain disease, but also for many other illnesses that are currently incurable. The science in this area is currently in the early stages of development, and a huge amount of work and new discovery is a prerequisite to realising these hopes. It is not known which degenerative disorders will be treatable by stem cell therapies, or how long the work will take. Information about scientific achievements needs to be communicated to the public properly, and in a rigorous and cautious way, so that it does not raise excessive expectations.[5] Further, confining the hopes of a cure for neurological disease to stem cells is reductive and possibly even risky. Stem cell therapy will be important, but probably not sufficient in itself to treat neurodegenerative disease.[5]

The great majority of neuroscientists, including those working in the stem cell area, would probably agree with these views. The current explosion in new knowledge in neurobiology offers real hope in many areas. However, it is crucial that the medical–scientific and medical–media communities work together to keep the general public not only well informed, but also realistically appraised as to the

significance of scientific breakthroughs in the development of new treatments.

Competing interests

None identified.

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