

Stem Cell Therapy for Neurodegenerative Diseases

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Professor Rosser started her talk by explaining that there had been huge excitement regarding stem cells in the past 10-15 years. Stem cells have the potential to be used for many conditions (eg diabetes) but Professor Rosser was going to concentrate on their use in neurodegenerative disease.

Neurodegeneration:

Which diseases? – common diseases are Parkinson's Disease, Alzheimers Disease, Multiple sclerosis, Huntington's Disease.

What is the burden? – personal, society, care burden.

What is available?

Professor Rosser reminded us of what a stem cell actually is – it can self replicate and renew itself, can divide and culture, can differentiate into a diverse range of specialised cells.

Totipotent cells can differentiate into embryonic and extra embryonic cell types.

Pleuriotent cells can produce all cell types of an adult but not of a blastocyst.

Professor Rosser listed the potential uses of stem cells in neurodegenerative diseases:

1. Cell replacement therapy
2. Delivery of trophic support
3. Delivery of other molecules
4. Immune modulation – bone marrow replacement.

The remainder of the talk would concentrate on the first of these – cell replacement therapy and is it a viable strategy in neurodegeneration?

General principles in cell replacement:

Try and replace the cells but also try and restore function. For example in parkinson's disease the dopamine producing substantia nigra cells degenerate. The aim is to inject fetal dopamine cells into the denervated striatum.

Do functional neural transplants work? Professor Rosser stated how animal studies not only demonstrated that transplanted cells could survive, but in addition, when these animals were tested behaviourally the graft ameliorated many of the deficits. Therefore an anatomical and functional effect had been demonstrated in animals.

Can grafts alleviate Parkinson's Disease in the clinical setting? Studies have been done which have showed anatomical improvements (using PET scanning) but have also showed marked improvement in clinical symptoms. Professor Rosser summarised the results of the Parkinson's Disease Clinical Trials : 2 well designed open labelled trials have given excellent results, 4 other centres have shown optimistic results but these were not as well designed as the above 2 trials. There are 2 double blind placebo controlled trials that have shown a poor response but the graft technology in these were not optimal.

Huntington's Disease:

Inherited Autosomal Dominant condition, onset in mid life, progressive.

Professor Rosser explained how Huntington's Disease maybe a better model for cell replacement therapy than Parkinson's Disease:

- inherited condition
- genetic tests allow diagnostic certainty
- focal degeneration
- better test of circuit reconstruction than Parkinson's Disease
- availability of animal models

Principles of cell replacement in Huntington's Disease:

- developing Medium spiny neurons from embryonic striatum
- placing them back directly to the area of degeneration (different from Parkinson's Disease)

Requirement of donor cells:

- appropriate phenotype
- correct developmental stage

Does it work? Animal Models:

Anatomical and electrophysiological models suggest recovery and behavioural recovery has also been shown.

Does it work? Clinical trials:

The first 5 patients who had grafts – 2 had grafts that didn't survive, 3 grafts survived (they did not improve to normal and not all modalities improved but there was a clear sustained improvement).

Professor Rosser explained the need for alternative cell sources to replace human fetal tissue as donor - a renewable source that can be directed to the required phenotype, amenable to quality control and cryopreservable.

Stem cells are likely to satisfy many of the above criteria. Stem cell sources being considered are, for example, ES cells (from inner cell mass of trophoblast), EG cells (from gonadal ridge), non neural stem cells (bone marrow, umbilical cord), adult CNS stem cells.

What do we need stem cells to do?

- proliferate in vitro
- produce neuronal precursors
- produce specific neuronal phenotypes
- integrate and reconstruct circuits
- improve functions

With continued culture, neural stem cells lose positional information and stop producing medium spiny neurons. There is therefore a limited period of proliferation. There is also the need to “direct” cells towards a medium spiny neuron phenotype, with the use of exogenous factors.

In conclusion, Professor Rosser positively commented on the fact that there is accumulating evidence that neural transplantation can improve function in the clinical setting but there is a need for renewable source of donor cells. There is a need to link laboratory science/clinical research and preclinical/clinical trials. Professor Rosser acknowledged the work of the whole Stem Cell team and collaborators.