Stem cells

A clinical update

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BACKGROUND
Stem cells of adult origin have been used clinically for 40 years in the treatment of haematological neoplasms such as leukaemia. These cells were originally obtained from bone marrow, but are now also being derived from umbilical cord blood.

OBJECTIVE
With the increasing public awareness of stem cell use, general practitioners need to be aware for which disorders these cells can, and are, being used.

DISCUSSION
Recent clinical trials with stem cells have been for ischaemic heart disease and to assist nonunion of bone. Other adult stem cells used in clinical trials include olfactory cells for spinal cord lesions, and human fetal pancreatic cells for type 1 diabetes. Adult stem cells, however, have limited potential to differentiate into different cell types. Human embryonic stem cells can be converted into cells of all lineages. They first became available for research in 1998 but are yet to be used in clinical trials.

Stem cells are undeveloped cells capable of proliferation, self renewal, conversion to differentiated cells, and regenerating tissues. There are two main types of stem cells, embryonic and nonembryonic. Embryonic stem cells (ESC) are pluripotent because they can differentiate into all cell types; nonembryonic stem cells (non-ESC) are multipotent because their potential to differentiate into cell types is more limited. Embryonic stem cells are more prevalent than non-ESC and have a greater potential to spontaneously differentiate than non-ESC.

Embryonic stem cells

Embryonic stem cells are derived from the inner cell mass of a blastocyst, which forms several days after an egg is fertilised (*Figure 1*). If the blastocyst implants into the uterus, the inner cell mass will develop into a fetus, with the surrounding trophoblast developing into the placenta.

The first human ESC line was established in 1998 from the inner cell mass of an embryo.[1] Since then, at least 225 human ESC lines have been created; five of these being produced in Australia. An ESC line is created by taking the ESC and placing the cells on a feeder layer of fibroblasts. The feeder layer assists in maintaining the ESC in an undifferentiated state.

Human ESC lines can theoretically also be derived in a nonphysiological manner by a process called 'nuclear transfer' – also known as therapeutic cloning. This requires the transfer of the nucleus of a donor somatic cell, for example, a skin cell, into the cytoplasm of an enucleated egg. There are factors in the cytoplasm of this hybrid cell which then allow its differentiation into a blastocyst. The ESC line, which is then derived from the inner cell mass of the blastocyst, has the same nuclear DNA as the donor. Mature cells derived from this line should not be rejected if transplanted into the donor.

Nonembryonic stem cells

Nonembryonic cells are also known as adult stem cells, because the cells are obtained from adults, usually from the bone marrow. This source has two types of stem cells: haemopoietic, which are committed to differentiate into blood cells (and can be isolated by flow cytometric sorting as they are CD34 positive), and the less differentiated mesenchymal stem cells. Other adult tissue sources include the nose, muscle, liver, skin, brain, and the retina and limbus of the eye. The term 'nonembryonic stem cell' is also applied to less mature sources of tissue including umbilical cord blood obtained at birth, and placenta and fetal somatic tissues such as pancreas and liver. Fetal tissues can also provide stem cells of an embryonic nature,

however these can only be obtained from the gonads in the first trimester of development.

Benefits of stem cells

Therapeutic

Only non-ESC have been used clinically so far. Bone marrow cells were first used successfully 4 decades ago, and cord blood stem cells in the past 10–15 years. These cells have been of benefit for blood disorders such as leukaemia, multiple myeloma and lymphoma; and disorders with defective genes such as severe combined immune deficiency. An advantage of using cord blood cells over bone marrow cells from other donors is the relative lack of graft versus host disease. The Australian Bone Marrow Registry reports that there are approximately 900 transplants annually, with most being autologous cells.[2] It is probable that the establishment of cord blood banks will increase the use of allogeneic cells.

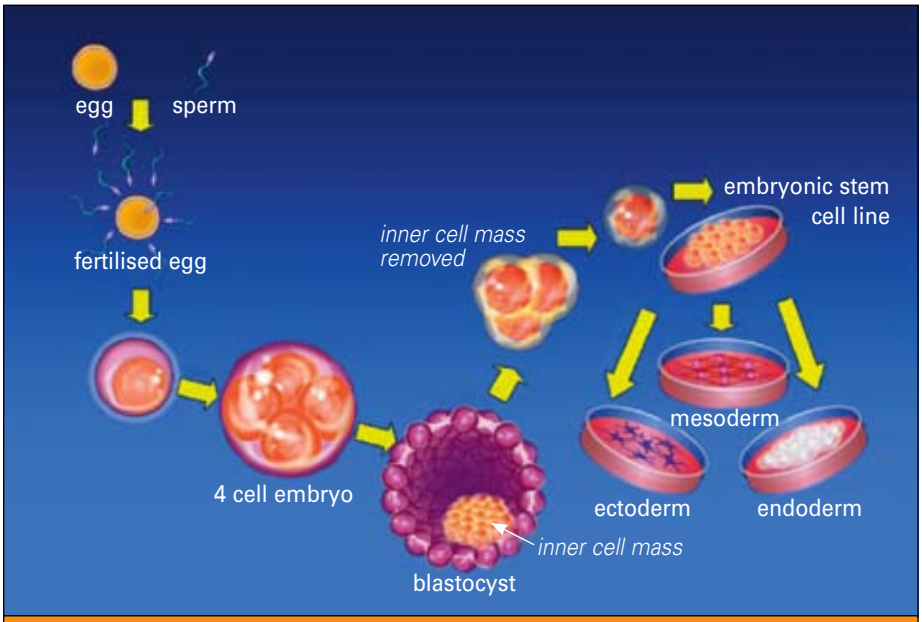

Figure 1. Fertilisation of the egg and sperm lead to the formation of a blastocyst, the inner cell mass of which is removed to create an embryonic stem cell line. The cells in this line are pluripotent and will differentiate under appropriate culture conditions into the three lineages of: ectoderm, endoderm and mesoderm, from which all mature cells will develop. Examples include nervous tissue, pancreas and heart respectively

Clinical trials – non-ESC

Ischaemic heart disease

In treating severe ischaemic heart disease using autologous stem cells from bone marrow and peripheral blood, cells are injected either into the coronary arteries or directly into the myocardium. Cells transplanted include mesenchymal stem cells from bone marrow, CD34+ cells from peripheral blood (collected by aphaeresis) enriched by pre-injection of donors with colony stimulating factor and skeletal myoblasts. Phase I trials indicate the relative safety of these studies and phase II/III studies are underway to determine if the benefits shown in some recipients are due to a direct result of the stem cells.[3] Recipients usually have severe coronary artery disease with an ejection fraction of less than 20%. When they occur, benefits are likely to be by increased vascularisation of myocardium, however, formation of new myocardial cells is a possibility.

Spinal cord lesions

Treatment of spinal cord lesions is with autologous olfactory ensheathing cells. Phase I trials in Australia with these cells indicate the procedure is safe,[4] with clinical improvement being reported overseas.

Nonunion of fractured bones

Treatment for nonunion of fractured bones is by way of using autologous mesenchymal stem cells from bone marrow which have been cultured to induce their differentiation toward an osteogenic lineage. It was only several months ago that the first Australian recipient was treated in this manner. Trials are underway overseas for treatment of osteogenesis imperfecta.[5]

Parkinson disease

Using human fetal dopaminergic cells, transient benefit was shown in some Parkinson disease recipients, but dyskinesia was exacerbated in a small number of recipients.[6]

Huntington disease

Using human fetal neural progenitor cells, some recipients improved clinically for 2 years, but subsequently relapsed.[7] Approval has recently been given in the USA to use similar cells for the treatment of lysosomal storage disease, which is lethal in neonates.

Type 1 diabetes

Treatment of type 1 diabetes is with human fetal pancreatic progenitor cells. Clinical trials in the 1980s with second trimester tissue showed some promise[8] with reduction of insulin requirements in some recipients.[9]

Other conditions

Other conditions for which therapies with non-ESC are being developed include corneal and retinal lesions, motor neuron disease, cerebrovascular disease, Alzheimer disease, and muscular dystrophy.

Clinical trials – ESC

As yet, ESC have not been used clinically, although an approach to regulatory authorities to seek approval for the first trial – perhaps for the treatment of spinal cord lesions – is likely within the next year. The first human ESC line was created only 8 years ago, too short a period to expect clinical outcomes, although these cells are being transplanted into animals. A more realistic time period to translate major new developments into humans is several decades. Indeed, it took 20 years after the commencement of in vitro fertilisation in humans to translate the technology into the formation of an ESC line.

It is imperative that ESC are fully differentiated before being transplanted, to avoid the formation of teratomas. To

differentiate ESC into ectodermal, mesodermal or endodermal cells and thence into more mature cells, requires an understanding of developmental biology which researchers throughout the world are trying to fully acquire. How endodermal cells, for example, can be induced to differentiate into insulin producing (ß) cells as a potential therapy for type 1 diabetes is complex. It requires the interaction of multiple genes, transcription factors and growth factors, each exerting its effect for a finite period of time, to achieve the formation of the ß cell. Attempts being trialled include alteration of culture conditions,[10] genetic manipulation[11] and co-culturing the cells with medium conditioned by fetal pancreatic progenitor cells.[12]

Ectodermal cells are the source of neuronal cells such as those containing dopamine, and are essential to treat Parkinson disease. Mesodermal cells are the source of haemopoietic and renal cells, which might be used for the treatment of blood disorders and renal dysfunction.

The list of human conditions that might eventually be treated by applying cells derived from ESC includes any disorder in which cells require replacing or regenerating. In addition to the above examples, they include Alzheimer disease, heart disease, burns, retinal and corneal disorders, liver disease, and infertility (using oocytes).

Other benefits

In addition to being of therapeutic benefit, ESC lines can assist in understanding the pathology of disease including the origin of cancers, testing the efficacy of drugs, and in monitoring the development of genetic disorders. For genetic disorders, human ESC lines could be created from affected blastocysts identified at pre-implantation genetic testing (eg. the genetic form of breast cancer, identified by the genes BRCA 1 and 2).

The future

It will take several decades of trials to determine the exact role that both ESC and non-ESC will play in regenerative medical therapies. At present, non-ESC, especially autologous cells, are being used in trials. Clinical trials with cells derived from ESC are likely to commence within the next few years. Preventing rejection of nonautologous cells will be an issue. Strategies include placing the cells inside immunoprotective microcapsules, inducing tolerance to the donor cells, and using compatible ESC derived by nuclear transfer. At present, the creation of such ESC lines is not permitted in Australia, although it is in Singapore, Japan, South Korea, England, six USA states, Israel, Sweden, and Belgium. The Australian Federal Government is currently reconsidering this possibility, with the Lockhart Report (which it commissioned in 2005) recommending that such technology be permitted.[13]

In surveys conducted by Biotechnology Australia, the majority of Australians have shown their support for the use of ESC in medical research.[14] Support comes from a range of backgrounds including scientific, political, religious, nonreligious, and women. However, there is strong objection from a section of the Christian community, which regards the use of blastocysts for anything other than the creation of a baby as being unacceptable.

Conclusion

At present, apart from the long standing use of stem cells for the treatment of haematological disorders, stem cell usage is at an experimental stage of development.

Summary of important points

- There are two main types of stem cells: embryonic and nonembryonic.
- Embryonic stem cells have more potential than non-ESC, as the ESC can form all three lineages: ectoderm, mesoderm and endoderm. Nonembryonic stem cells are generally committed to the one lineage.
- Stem cells from bone marrow and cord blood are used successfully for treatment of leukaemia, lymphoma and multiple myeloma.
- Clinical trials with autologous stem cells and fetal tissue have been or are being undertaken for treatment of ischaemic heart disease, spinal cord lesions, nonunion of bone, Parkinson disease, Huntington disease, and type 1 diabetes.

Conflict of interest: none declared.

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