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Stem cell therapies: hype or reality?

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ABSTRACT Advances in stem cell research provide great hope that these cells can be used to help tissue repair and avoid the need for complex surgery or organ transplantation. Despite extensive media coverage and enthusiasm for their therapeutic potential in patients, it may be years before such therapies reach their full potential. In this article, Dr Julie Crawford and Professor Marc Turner from the MRC Centre for Regenerative Medicine give a balanced view to help us decide whether stem cell therapy is 'hype or reality'.

KEYWORDS Regenerative medicine, stem cells

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INTRODUCTION

Stems cells are defined by their unique ability to self-renew, their high proliferative potential and their capacity for multi-lineage differentiation into specialised cells.

Totipotent stem cells can generate all cells constituting the body as well as the extra-embryonic tissue that gives rise to the placenta. Pluripotent stem cells are capable of generating all cells found within an individual but cannot form an embryo, as they are incapable of producing extra-embryonic tissue. Multipotent stem cells give rise to cells of one germ layer, while tissue-specific oligopotent stem cells are capable of differentiating into lineage-restricted tissue-specific cell types.

As the population ages, there is an increasing need to be able to repair damaged tissue and restore organ function. Transplantation of tissues (blood, heart valves) or organs (liver, kidney, heart) is limited by donor organ shortages, human leukocyte antigen incompatibility, the requirement for immunosuppression and the inability to transplant some organs and tissues. This has led to exploration of the use of stem cells or cell-based therapies derived therefrom for tissue regeneration.

EMBRYONIC STEM CELLS

Embryonic development reaches the blastocyst stage 3–5 days post fertilisation. The blastocyst consists of a hollow ball of 100–200 cells, the outer layer of which develops into the trophoblast/placenta, while the inner cell mass develops into the embryo. The inner cell mass can be extracted from the blastocyst and grown on a fibroblast (feeder) cell line to yield human embryonic stem cells (hESC), which display long-term self-renewal potential and retain pluripotency. Embryonic stem cells therefore potentially offer a route to develop human cells and tissues for transplantation. Since the first reports of successful isolation of hESC in 1989, ethical concerns have surrounded the procurement of cell lines from blastocysts derived from in vitro fertilisation programmes, usually using embryos excess to requirements. The clinical application of hESC or their products is currently limited by a number of issues. It is unclear, for example, how hESC proliferation can be reliably controlled and how cell differentiation to specific cell types may be directed. The transplantation of hESC also raises immunological concerns with the potential for tissue incompatibility, resulting in the need for long-term immunosuppression.[1,2]

SOMATIC CELL NUCLEAR TRANSFER

Somatic cell nuclear transfer (SCNT) (or 'cloning') involves the introduction of the nucleus of an adult donor cell into an enucleated oocyte. Cell stimulation gives rise to the fusion of the donor nucleus with the oocyte, which can then be cultured in vitro to form a blastocyst. If the blastocyst is successfully transferred into the uterus of a female recipient, the resulting animal will be genetically identical to the donor (reproductive cloning). This is the process that led to the birth of Dolly the sheep.

Therapeutic cloning describes the process in which a cloned blastocyst derived as above is explanted in culture to give rise to embryonic stem cells. Human embryonic stem cells derived in this way could in principle be differentiated in vitro into a homogenous population of syngeneic immune-compatible cells to regenerate tissue. In humans, nuclear transplantation therapy remains limited by the availability of ova and the inefficiency of the process, with the potential for errors. It remains unclear whether epigenetic modifications affect cell phenotype or the functions of these cloned cell lines.[1]

ADULT STEM CELLS

Adult stem cells are found within differentiated tissue. They were traditionally considered to be oligopotential cells with restricted proliferation and differentiation potential. Adult stem cells may remain quiescent for many years before becoming activated by inflammation or injury,[3,4] with cells being directed to differentiate into specific cell types in order to replenish damaged tissue. Adult stem cells have been identified within many organs, including the bone marrow, skin, muscle and liver, but are thought to be present in most, if not all, tissues.[3]

Haematopoietic stem cells (HSC) are the best-characterised adult stem cell. These are rare, comprising one in 10^5–10^6 of bone marrow cells. Haematopoietic stem cell transplantation, in the form of bone marrow and now peripheral blood stem cell transplantation, has been a clinical treatment for patients with haematological disease for more than 30 years and is a paradigm for stem cell therapies. Over this period, understanding of stem cell biology has improved and transplant techniques have been refined. Accurate and reliable monitoring of stem cell collections can predict subsequent transplant success.

New discoveries have recently challenged long-held views on adult stem cells. Research has shown that adult stem cells are found in many more tissues than originally thought, and there is evidence that these cells under some circumstances appear to display the ability to differentiate into cells of other germ lines (plasticity or transdifferentiation), rather than being restricted to tissue types present in a specific organ. Questions remain as to whether plasticity is due to inherent cell properties or a reflection of culture conditions, contamination or cell fusion. This potential plasticity of adult stem cells has increased interest in using bone marrow-derived cells as sources of material for a wide range of cellular therapies.[5,3]

Non-haematopoietic stems cells found in the bone marrow compartment include mesenchymal stem cells (MSCs), which can give rise to bone marrow stromal cells, and endothelial progenitor cells, which give rise to vascular structures. Differentiation of MSCs into fibroblasts, bone, cartilage, neural tissue and fat has been demonstrated in an experimental context. An exception to the restricted differentiation capacity of the adult stem cell appears to be the bone marrow-derived multipotential adult progenitor cell (MAPC) population, reported to have the ability to differentiate into cells of all three germ lines. The therapeutic potential of these cells has yet to be demonstrated.

Additionally, there is evidence that rather than being locally restricted, adult (tissue) stem cells can contribute to tissue repair in sites remote to their origin by entering the circulation and migrating to other sites in the body. The factors that stimulate stem cells, promote stem cell circulation or direct homing of these cells to remote sites are not yet understood. They offer the hope of being useful in the treatment of many disease processes, including neurodegenerative disease, diabetes and myocardial ischaemia.

Isolation and characterisation of the adult stem cell populations remain difficult. Basic science questions remain unanswered, stem cell phenotypes are not well defined, the best source of material is undetermined and optimal culture methods are unknown.

ROUTE TO CLINIC

Stem cell advances provide great hope that cell therapies can be used to alleviate organ shortages and repair tissues that are not able to be transplanted, without the need for surgical procedures. However, there are many hurdles that need to be overcome before these can be taken forward to in vivo patient testing and clinical care.

There are issues surrounding cell procurement. For example, the use of ova and embryos to generate cells for therapy remains ethically challenging. Donor consent must be thorough. Donor selection may be based on personal or family history, the results of screening infectious agents or genetic testing. This may lead to discoveries that may have medical implications for the donor.

During culture, stem cells may need to be purified, maintain pluripotential lineage capacity, be capable of directed differentiation, be accessible to genetic modification, expandable in culture and non-tumorigenic.[4] The latter is of specific concern since cancer stem cells have been isolated from breast and brain cancers and there is strong evidence supporting stem cell transformation in haematological malignancies. This suggests that the stem cell is a potential target for neoplastic transformation and that stem cell therapies may be accompanied by the risk of tumourigenesis. Transferring stem cell advances from the laboratory to the clinic requires stringent and defined protocols, quality management systems, rigorous testing and the long-term follow-up of patients.

We should not let our enthusiasm for the potential advances that these new technologies and stem cell therapies offer lead to them being rushed into the clinical setting. It may be many years yet before this field reaches its full potential.

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FURTHER READING

Institute for Stem Cell Research: www.iscr.ed.ac.uk
Scottish Stem Cell Network: www.sscn.co.uk/home.aspx

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