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Development of Disease Specific Stem Cell-Lines for Therapeutic Applications: Advantages and Progress in Translational Stem Cell Research

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Abstract

One of the most significant developments in cell and developmental biology in recent years has been the incredible interest in the potential of stem cells in regenerative medicine. In spite of the ongoing political, ethical and scientific challenges interest in the potential clinical utility of stem continues to increase. Extraordinary developments in the field of stem cell research continued in developing disease-specific stem cell lines; advances were made in creating induced pluripotent stem (iPS) cell lines using technologies compatible with clinical use; and the US Food and Drug Administration (FDA) gave approval for the first clinical trial using cells derived from human embryonic stem cells (hESC) for the treatment of spinal cord injury. Both regenerative medicine and tissue engineering rely on the success of stem cell technology. Advances in the embryonic and adult stem cell research, particularly over the past two decades, have enabled cell-based therapies. Now it is also possible to genetically reprogram the somatic cells and induce pluripotency in them to function in a manner similar to embryonic stem cells. However, further studies on teratogenic or tumorigenic properties, cellular dose, cell proliferation, senescence, karyotyping, and immunosuppressive activity are essential to translate the technology into clinical application.

Keywords: Human Embryonic Stem Cells (hESC) • Regenerative medicine • Pluripotent stem (iPS) Cell Lines

Introduction

The year 2006 marked the major milestone in the progress made for stem cell therapy when scientists Shinya Yamanaka, and Kazutoshi Takahashi reported that it is possible to reprogram the multipotent adult stem cell into a pluripotent state. This method can avoid endangering the foetus development. In the study, the retrovirus-mediated transduction of mouse fibroblasts with four transcription factors (Oct-3/4, Sox2, KLF4, and c-Myc) factors that are originally expressed in embryonic stem cells could successfully induce the fibroblasts to transform into pluripotent cells. About a year later the experiment was also successful with human cells. Another most significant discovery was by John Gurdon who successfully cloned frogs by transferring the nucleus isolated from the somatic cells into an oocyte transforming the somatic cell into pluripotent. Prior to this it was thought that the cell differentiation was essentially a one way process. Takahashi and Yamanaka and Loh et al. discovered that octamer-binding transcription factor 3 and 4 (Oct3/4), sex determining region Y (SRY)-box 2 and Nanog genes function as core transcription factors in maintaining pluripotency of the cells. Among them, Oct3/4 and Sox2 are essential for the generation of induced pluripotent stem cells. The reprogrammed somatic cells using retroviral or lentiviral vectors for expression of genes related to embryonic transcription factors (NANOG, OCT4, and KFL4) in addition to c-Myc. These cells have multipotent ability like ESCs but nevertheless have the potential for teratoma formation [1-10].

Literature Review

For many years, the ethical discussion surrounding human embryonic stem cell research has focused on the moral status of the embryo. This report takes a wider moral berth and focuses on numerous ethical, legal and social aspects involved in translating the results of stem cell research into diagnostic and therapeutic applications.

What are stem cells?

Stem cells have distinct morphology with high nucleus to cytoplasm ratio and a prominent nucleolus. Stem cell lines have characteristic physical properties with regard to their shape and the cell border. The differentiation and specialization of the stem cells depend on external physical contact between the cells or chemical secretion and internal signals controlled by the genes. The organ in which the stem cell exists determines the stem cell activity. For example in bone marrow, the cellular division is a constant phenomenon while in pancreas; the division takes place under defined physiological conditions [11-15].

Stem cells are cells found in most, if not all, multi-cellular organisms. They are characterized by the ability to renew themselves through mitotic cell division and differentiate into a diverse specialized cell types. Research in the stem cell field grew out of findings by Canadian scientists Emest A. McCulloch and James E. Till in the 1960s [4,5]. (Stem cells (centre ones) can develop into any cell type. They are valuable as research tools and might, in the future, be used to treat a wide range of diseases [16-20].

Embryonic stem cells that are isolated from the inner cell mass of blastocysts

Embryonic stem cells divide much faster while the somatic stem cells take longer time for proliferation. Zygotic cells are totipotent and are formed from the fertilization of egg with the sperm. These cells can develop into any of the three germ layers or can even form the placenta. After four days the blastocytes inner cell mass becomes pluripotent. These pluripotent stem cells can develop into all germ layers but not the embryonic structures or placenta. The inner cell layer develops into epiblast inducing development of foetus and trophectoderm. Trophectoderm gives rise to placenta.

Adult stem cells that are found in adult tissues

Adult stem cells are of several types. The unipotent stem cells form only one cell type, for example the dermatocytes. Oligopotent stem cells

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can differentiate into several cell types. For example a myeloid stem cell differentiates into white blood cells but not red blood cells. Among the adult stem cells, hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are the most studied cell types. Transplantation of adult stem cells can also result in the formation of tumors even though they are derived from chromosomally normal foetuses. HSCs isolated from bone marrow can proliferate and differentiate only into cells of myeloid and lymphoid lineages and may result in graft versus host disease due differences in the histocompatibility antigens of donor and host. MSCs isolated from bone marrow, adipose tissue, umbilical cord and dental pulp are multipotent differentiating into osteocytes, adipocytes and chondrocytes *in vitro*. Autologoues MSCs are applied for cell based therapy of osteogenesis imperfect and intracoronary transplantation. However carcinogenic potential needs to be further studied. Mesenchymal stem cells in bone marrow differentiate into bone, cartilage and fat cells. Neural cells give rise to nerve cells and their supporting cell such as oligodendrocytes and astrocytes. Haematopoietic stem cells form all kinds of blood cells such as red, white and platelets. Keratonocytes form protective layer of skin. Adult stem cells can be reprogrammed to pluripotent state by transferring the adult nucleus into the cytoplasm of an oocyte or by simple fusion with the pluripotent cell [21-23].

In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues. Stem cells can now be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells from a variety of sources, including umbilical cord blood and bone marrow, are routinely used in medical therapies.

Stem cell properties

The classical definition of a stem cell requires that it possess two properties:

1. **Self-renewal:** The ability to go through numerous cycles of cell division while maintaining the undifferentiated state.
2. **Potency:** The capacity to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either totipotent or pluripotent to be able to give rise to any specialized mature cell type.

Although multipotent or unipotent progenitor cells are sometimes referred to as stem cells.

What are embryonic stem cells?

Embryonic stem cell lines (ES cell lines) are cultures of cells derived from the epiblast tissue of the inner cell mass (ICM) of a blastocyst or earlier morula stage embryos. A blastocyst is an early stage embryo-approximately four to five days old in humans and consisting of 50-150 cells. ES cells are pluripotent and give rise during development to all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. They do not contribute to the extra-embryonic membranes or the placenta.

Nearly all research to date has taken place using mouse embryonic stem cells (mES) or human embryonic stem cells (hES). Both have the essential stem cell characteristics, yet they require very different environments in order to maintain an undifferentiated state. Mouse ES cells are grown on a layer of gelatin and require the presence of Leukemia Inhibitory Factor (LIF).

Human ES cells are grown on a feeder layer of mouse embryonic fibroblasts (MEFs) and require the presence of basic Fibroblast Growth Factor (bFGF or FGF-2). Without optimal culture conditions or genetic manipulation, embryonic stem cells will rapidly differentiate. A human embryonic stem cell is also defined by the presence of several transcription factors and cell surface proteins. The transcription factors Oct-4, Nanog and Sox2 form the core regulatory network that ensures the suppression of genes that lead to differentiation and the maintenance of pluripotency. The cell surface antigens most commonly used to identify hES cells are the glycolipids SSEA3 and SSEA4 and the keratan sulfate antigens Tra-1-60 and Tra-1-81. ES cells, being pluripotent cells, require specific signals for correct differentiation -if injected directly into another body; ES cells will differentiate into many different types of cells, causing a teratoma. After nearly ten years of research, there are no approved treatments using embryonic stem cells. The first human trial was approved by the US Food & Drug Administration in January 2009 [22].

Differentiating ES cells into usable cells while avoiding transplant rejection are just a few of the hurdles that embryonic stem cell researchers still face. Many nations currently have moratoria on either ES cell research or the production of new ES cell lines. Because of their combined abilities of unlimited expansion and pluripotency, embryonic stem cells remain a theoretically potential source for regenerative medicine and tissue replacement after injury or disease.

Stem cell types

1. **Foetal stem cells:** Foetal stem cells are primitive cell types found in the organs of foetuses. The classification of foetal stem cells remains unclear and this type of stem cell is currently often grouped into an adult stem cell. However, a more clear distinction between the two cell types appears necessary.
2. **Adult stem cells:** The term adult stem cell refers to any cell which is found in a developed organism that has two properties: the ability to divide and create another cell like itself and also divide and create a body stem cells and germline (giving rise to gametes) stem cells, they can be found in children, as well as adults.

Pluripotent adult stem cells are rare and generally small in number but can be found in a number of tissues including umbilical cord blood. Most adult stem cells are lineage-restricted (multipotent) and are generally referred to by their tissue origin (mesenchymal stem cell, adipose-derived stem cell, endothelial stem cell, etc.).

1. **Amniotic stem cells:** Multipotent stem cells are also found in amniotic fluid. These stem cells are very active, expand extensively without feeders and are not tumorogenic. Amniotic stem cells are multipotent and can differentiate in cells of adipogenic, osteogenic, myogenic, endothelial, hepatic and also neuronal lines.
2. **Induced pluripotent stem cells:** These are not adult stem cells, but rather reprogrammed cells (e.g. epithelial cells) given pluripotent capabilities. Using genetic reprogramming with protein transcription factors, pluripotent stem cells equivalent to embryonic stem cells have been derived from human adult skin tissue.

Stem cell lineage

To ensure self-renewal, stem cells undergo two types of cell division.

1. Symmetric division gives rise to two identical daughter cells both endowed with stem cell properties
2. Asymmetric division, on the other hand, produces only one stem cell and a progenitor cell with limited self-renewal potential

Progenitors can go through several rounds of cell division before terminally differentiating into a mature cell. An alternative theory is that stem cells remain undifferentiated due to environmental cues in their particular niche. Stem cells differentiate when they leave that niche or no longer receive those signals.

Studies in "*Drosophila*" *germarium* have identified the signals dpp and adherens junctions that prevent germarium stem cells from differentiating. The signals that lead to reprogramming of cells to an embryonic-like state are also being investigated. These signal pathways include several transcription factors including the oncogene c-Myc. Initial studies indicate that transformation of mice cells with a combination of these anti-differentiation signals can reverse differentiation and may allow adult cells to become pluripotent. However, the need to transform these cells with an oncogene may prevent the use of this approach in therapy (Figure 1).

The stem cell controversy

Opponents of the stem cell research argue that embryonic stem cell technologies are a slippery slope to reproductive cloning and can fundamentally

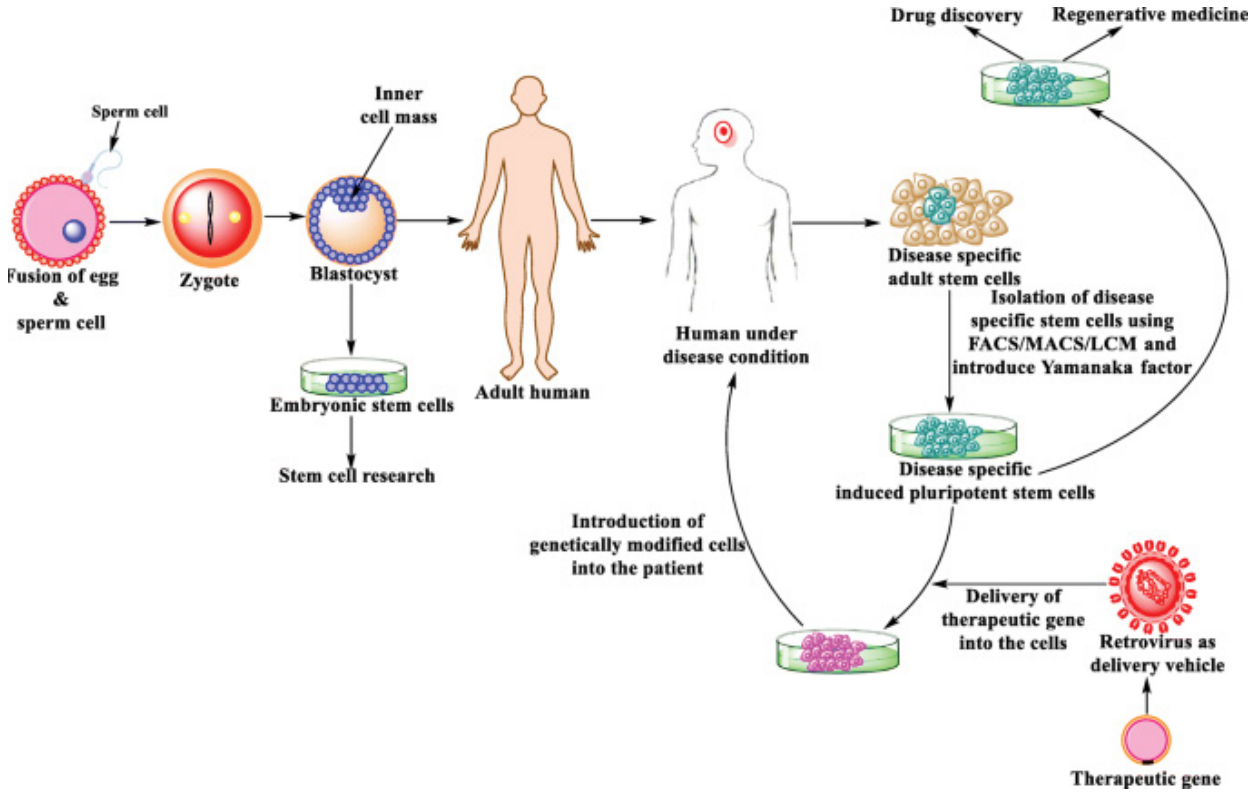

Figure 1. Recent technological advancements in stem cell research for targeted therapeutics.

devalue human life. Some in the pro-life movement argue that a human embryo is already a human life that is entitled to protection.

Contrarily, supporters of embryonic stem cell research argue that such research should be pursued because the resultant treatments could have significant medical potential. It is also noted that excess embryos created for *in vitro* fertilization could be donated with consent and used for the research.

The ensuing debate has prompted authorities around the world to seek regulatory frameworks and highlighted the fact that stem cell research represents a social and ethical challenge.

Research methodologies involving stem cells

1. A methodology called stem cell selection, in which a selectable marker under the control of related genes to its application and interpretation has been developed.
2. This has led to a significant body of research whose progeny provides the strongest evidence to date that the NSA represents a bonafide methodology for isolating and propagating neural stem cells.
3. The present invention relates to undifferentiated human embryonic stem cells, methods of cultivation and propagation and production of differentiated cells.
4. In particular it relates to the production of human ES cells capable of yielding somatic differentiated cells *in vitro*.

Recent stem cell news - A brief survey of research done by scientists

1. Transplantation of tissue-engineered vein is a success and offers hope for patients who lack suitable veins for dialysis or bypass surgery. The first biologically tissue-engineered vein grown from a patient's own stem cells has been successfully transplanted into a 10 year old girl with portal vein obstruction, dramatically enhancing her quality of life.
2. Study reveals molecular Link between ageing and cancer.
3. MRF announces achievement of myelin repair Phase 1 trial for MS

The Myelin Repair Foundation (MRF) announced the achievement of a myelin repair Phase 1 clinical trial for multiple sclerosis earlier than the foundation's goal set for 2014.

1. Minimally invasive procedure to treat high blood pressure
2. A controversial stem cell treatment for stroke is showing promising signs in the early results of a small safety trial:

The hope is that the treatment, by repairing damaged brain tissue, will one day help stroke patients regain some movement and ability to speak. US scientists have found a way to grow new bone using fresh purified stem cells from fat tissue that produces better quality bone faster than conventional methods:

They suggest this may one day eliminate the need for painful bone grafts that use material taken from patients with invasive surgery. Findings suggest a potentially favorable time to harvest stem cells for therapy and may reveal genes crucial to tissue production. With their potential to treat a wide range of diseases and uncover fundamental processes that lead to those diseases, embryonic stem (ES) cells hold great promise for biomedical science.

Assumptions

1. The transplantation of adult human neural stem cells into prenatal nonhumans offers an avenue for studying human neural cell development without direct use of human embryos.
2. Experiments involving the transplantation of human stem cells and their derivatives into early, foetal or embryonic nonhuman animals raise novel ethical issues due to their possible implications for enhancing the moral status of the chimeric individual.
3. Human/nonhuman stem cell chimeras will be increasingly applied to study human cells in developing nonhuman animals. Such experiments raise a number of issues that may create further controversy in the stem cell field.
4. However it critically examines the biology of species identity and the morality of crossing species boundaries in the context of emerging research that involves combining human and nonhuman animals at the genetic or cellular level.

5. On the creation of interspecies chimeras using human cellular material is that the creation of these chimeras would, or could, offend human dignity. However if we frame our possible objection to chimeras to human dignity rather than boundary crossing we might see that it perhaps is not the muddling of species so much, as the possible nature of the resultant part-human chimera that causes some of the concern.

The stem cell hypothesis

Much of the discussion surrounding stem cells today is focused on the promise of using these powerful cells to treat such diseases as diabetes and Parkinson's, or to repair damaged tissue-say, after a heart attack. But stem cell biology is also making inroads in another important area: breast cancer research.

Although the hypothesis is still somewhat controversial among oncologists, the real culprit in the disease may be a small subpopulation of cells called cancer stem cells, according to a growing body of evidence over the last decade.

Stem cells are unique cells in the body that have the ability to self- renew and to give rise to a range of specialized cell types, such as heart cells, immune cells and neurons. These potent cells are critical during development and in helping the body heal itself after an injury, for instance.

Researchers believe cancer stem cells are one of two things: normal stem cells that have gone awry, or more specialized cells that have somehow acquired stem cell-like properties, including an uncontrolled capacity to self-renew.

Many researchers believe that only cancer stem cells, which represent a tiny fraction of an entire tumor, have the intrinsic capacity to initiate cancer and fuel tumor growth. They may also underlie resistance to standard therapies. If the theory holds true, it could fundamentally change the way doctors diagnose and treat breast cancer.

The first study to show that cancer stem cells can initiate cancer was published in 1994. John Dick, a molecular biologist at the University of Toronto, succeeded in isolating cancer stem cells from patients with human acute myeloid leukaemia.

When he and his colleagues transplanted the cells into mice, the animals developed the disease. In contrast, mice that received other leukemia cells did not. In 2003, another group of researchers found cancer stem cells in breast cancer-the first evidence of the cells in a solid tumor. Led by cancer biologists Michael Clarke and Max Wicha at the University of Michigan in Ann Arbor, the researchers transplanted cancer stem cells from human breast tumors into mice. Once again, the malignant stem cells reconstituted tumors in animals but the other cancer cells did not. Since then, cancer stem cells have been found in a variety of cancers, including brain, prostate and pancreatic cancer. Many hypotheses have been proposed in which the stem cell is seen in association with other cells which determine its behavior. It becomes essentially a fixed tissue cell.

Its maturation is prevented and, as a result, its continued proliferation as a stem cell is assured. Its progeny, unless they can occupy a similar stem cell 'niche', are first generation colony-forming cells, which proliferate and mature to acquire a high probability of differentiation of many more tissue-specific stem cells has kept this field of study at the forefront of biological research.

Why are researchers interested in developing disease-specific or patient-specific pluripotent stem cells?

The development of patient-specific or disease-specific pluripotent stem cells has great therapeutic promise for two reasons. Firstly, these cells could provide a powerful new tool for studying the basis of human disease and for discovering new drugs. Secondly, the resulting embryonic stem cells could be developed into a needed cell type, and if transplanted into the original donor, would be recognized as 'self', thereby avoiding the problems of rejection and immunosuppression that occur with transplants from unrelated donors.

What are the obstacles that must be overcome before the potential uses of stem cells in cell therapy will be realized?

First, an appropriate source of stem cells must be found. The process of identifying, isolating and growing the right kind of stem cell, for example a rare cell in the adult tissue, is painstaking. In general, embryonic and fetal stem cells are believed to be more versatile than tissue-specific stem cells. Secondly, once stem cells are identified and isolated, the right conditions must be developed so that the cells differentiate into the specialized cells required for a particular therapy. This too will require a great deal of experimentation. Thirdly, a system that delivers the cells to the right part of the body must be developed and the cells once there must be encouraged to integrate and function in concert with the body's natural cells. Furthermore, just as in organ transplants, the body's immune system may need to be suppressed to minimize the immune reaction set off by the transplanted cells.

While results from animal models are promising, the research on stem cells and their applications to treat various human diseases is still at a preliminary stage. As with any medical treatment, a rigorous research and testing process must be followed to ensure long-term efficacy and safety.

Limitations of using stem cell technology

Some for the major challenges of these cell lines is the genomic instability during *in vitro* culture, miRNA and chromatic changes, immunosuppression and inflammation.

Clinical application of embryonic stem cells is limited by the ethical issues associated with the manipulation and destruction of embryos. Animal based experiments on embryonic stem cells transplantation resulted in teratomas in the receipient organisms. This also poses limitation to the cell based therapies.

Transplantation of the differentiated cell types from mouse and human embryonic stem cells ion target organs of animals resulted in restoration of function to some degree along with cancerous growth in the grafts. Studies have shown that selection and sorting of embryonic stem cells presenting SSEA1- SSEA3- EpCAM+ can avoid tumorigenic potential from differentiated ESCs.

Creating a favorable microenvironment or niche for the endogenous or autologous or allogenic transplanted stem cells enables better integration and proliferation and controlled differentiation. However, the *in vivo* niche is highly complex and dynamic and their physical and biological interactive effects need to be studied in great detail for microscale engineering. Several preclinical and clinical researches are underway for treatment of cancers, heart failure, neural degenerative diseases, autoimmune diseases and chronic degenerative disease. Conducing niches are developed by using grapheme scaffolds and extracellular vesicles based therapies.

Ethical issues of using embryonic stem cells

Stem cell therapy appeared to be highly effective in treating several diseases. However the contention arises when scientists isolate the embryonic stem cells from the embryo that has the potential to develop into a full-fledged human being was destroyed. This has led to the ethical conflict. Therefore there is greater emphasis on isolating the stem cells while preserving the embryo source.

The risk of tumor development is also poses a hurdle in stem cell based therapy. The immunological compatibility also poses limitations. Therefore the focus is on using the patient's own cells and evolve them into pluripotent stage of development. It is important to understand how the stem cells behave in animal models. This is very essential and unavoidable. This also created fear of the unknown or the development of chimeric tissues.

Conclusion

The pursuit and production of knowledge through scientific research is an undertaking that offers enormous intellectual rewards for researchers while

also performing an important social function. The advancement of science has transformed our lives in ways that would have been unpredictable just a half-century ago. Whether stem cell research will have a similar effect remains to be determined, but the promise is so great that it seems wise to consider seriously how best to further such research in a manner that is sensitive to public sensibilities.

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