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Review Article

Stem cells and their applications: A review

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ABSTRACT

Stem cells have the capacity to build every tissue in the human body as well as they have the ability to differentiate into specific cell types. There are two major classes of stem cells: Pluripotent that can become any cell in the adult body, and Multipotent that are restricted to becoming a more limited population of cell. Stem cells research is beginning to address many important diseases, and some new therapies will move from pre-clinical to clinical trials. Many diseases such as diabetes, atherosclerosis and leukemia treatment are likely to benefit from stem cell research. Embryonic stem cell show great potential in treating degenerative diseases and as pharmaceutical testing platforms. Cell although stem cells are potentially used for treatment for different diseases, their application is controversial. Due to these ethical concerns scientists are trying to find new ways of obtaining stem cells that behave like embryonic stem cells without harming a blastocyst. Moreover, there is a growing body of evidence showing that administration of stem cells leads to the successful regeneration of tissues or organ. Stem cell research in the field of skeletal diseases opens important new perspectives in multiple areas of medicine and orthopedic surgery.

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1. Introduction

Stem cells are autologous cells having a long-term self-renewal ability that regenerates and differentiates into various cells, tissues, organs, and systems in the human body (Shrihari, 2011). Stem cell therapy is an amazing modern medical advancement that goes straight to the source of the problem and treats various disorders like muscular dystrophy, Alzheimer's disease, Atherosclerosis, Diabetes, Inflammatory Bowel Disease, Parkinson's disease, Rheumatoid Arthritis, acute lung injury and many others (Meregalli et al.,2011). Adult stem cells can rapidly proliferate to regenerate the specialized tissues. Mesenchymal stem cell (MSC) is a type of stem cell has entered the scene as a developing therapy. Recently, mesenchymal stem cells have been found in skin, liver and other tissues (Silvani et al.,2011). MSCs have the capacity to differentiate into several cell types and it can be isolated from embryonic or adult tissues such as bone marrow and adipose tissue (Ghodsizad et al.,2010). MSCs found to have anti-inflammatory effects and treat various painful states such as degenerative disc disease, osteoarthritis, cartilage regeneration, multiple sclerosis (Waterman & Betancourt, 2011). Stem cells are unique from other cell types by two important characteristics. First, they are undifferentiated cells capable of renewing themselves through cell division, even after long periods of inactivity. Second, under certain experimental and physiologic conditions, they can be induced to become tissue- or organ-specific cells with special functions. Researchers primarily worked with two kinds of stem cells from animals and humans embryonic stem cells and adult stem cells (somatic stem cells).

Embryonic stem cells: Embryonic stem cells (ES cells) are unique biological entities that have the ability both to reproduce themselves endlessly and to give rise to all specialized cell types of the body. The capacity to form all cell types is called "pluripotency". This property is normally restricted to cells that only exist for a few days in the early embryo before formation of the initial body plan. ES cells, however, preserve pluripotency even after massive expansion in the laboratory. Therefore, they can in principle provide a continuous supply of specialized cells for basic research, disease modeling, drug testing, and possibly future cell replacement therapies. ES cells are produced from early embryos called blastocysts. Blastocysts are the stage before implantation into the uterus or formation of specialized tissues. They contain up to 100 unspecialized cells that are pluripotent and will act as founders for the entire body if the embryo implants. Pluripotent cells in the embryo do not maintain themselves after implantation but turn into specialized cells, a process called differentiation. In the laboratory, however, it is possible to induce a state called self-renewal in which the cells multiply without differentiation. ES cell self-renewal depends on specific signals called growth factors.

Mesenchymal stem cells (MSCS): The mesenchymal stem cells (MSCs) in the adult bone marrow are necessary for the body to generate tissues such as bone, cartilage, muscle, ligament, tendon, adipose, and bone marrow.. Reproducible differentiation of human embryonic stem cells (hESCs) into MSCs does not require the use of any feeder layer. MSC stem cells can be grown for many generations in the laboratory and still retain a stable morphology and normal chromosome complement. MSCs, are contact inhibited, can be grown in culture for about 20 to 25 passages, have an immunophenotype same to bone marrow MSCs positive (CD34, CD45, CD44, CD13, CD73, CD90, CD105) human leukocyte antigen [HLA]-ABC, and stage-specific embryonic antigen [SSEA]-4), can differentiate into osteocytes and adipocytes, and can be used as fibroblast is a type of cell to support the growth of undifferentiated hESCs. The able to developed MSCs from hESCs should prove useful to produce large amounts of genetically identical and genetically modifiable MSCs that can be used to study the biology of MSCs and for therapeutic applications.

Cancer stem cells: Cancer stem cells (CSCs), also known as tumor-initiating cells (TICs), are cancer cells that possess capability of proliferation, differentiation, and self-renewal. It is widely believed that CSCs play critical role in the initiation, metastasis, and relapse of cancers, but the origin of CSCs remains unclear. Up to date, several hypotheses have been described, and cell fusion and horizontal gene transfer, which may occur during development and tissue repair process, are considered as important origins of CSCs. In addition, critical gene mutations in stem cells, progenitor cells or even differentiated cells may also contribute to the formation of CSCs, and cell microenvironment is critical to CSC self-renewal and differentiation. The ongoing efforts to identify the CSCs origins may shed more light on understanding of cancer initiation and progression, as well as the development of novel cancer therapies.

The uses of adult stem cells are morally ethical, but it is unethical to use embryonic stem cells since it involves the destruction of the embryos. The embryonic stem cells can be taken for research with the informed consent from the donor (Jamil et al., 2009). The donor will be fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate. All the ethical problems related to this field of research should be reviewed by the institutional review board (IRB) (Smalheiser, 2011). Organ regeneration is also possible through organ-specific and tissue-specific stem cells. Hematopoietic stem cells were believed to restore blood cells. It has been discovered recently that using cell lineage tracking, stem cells from one organ can be used to form cells of another organ. MSCs shown to have the ability to form neural cells both in vitro and in vivo, although the exact molecular mechanisms underlying these apparent trans diferentiation events are not known (Jackson et al., 2007). Stem cell therapy has been shown successful for the treatment of leukemia. One way is to get rid of all the abnormal leukocytes in the patient, allowing healthy ones to grow in their place it can be done by chemotherapy the other way is to carry out the bone marrow transplant. In bone marrow transplantion, the patient's bone marrow stem cells are replaced with those from a healthy, matching donor. To do this, first of all patient's existing bone marrow cells and abnormal leukocytes are first killed using a combination of chemotherapy and radiation. Next, donor bone marrow containing healthy stem cells should be introduced into the patient's bloodstream. If the transplantation is successful, the stem cells will migrate into the patient's bone marrow and begin producing healthy leukocytes to replace the abnormal cells (Ziai et al., 2010).

2. Stem cell biology

Most of the 300 trillion cells of the body have completely specialized functions. Blood, lung, brain, skin or liver cells are all specialized for what they do. They cannot do anything other than what they were designed for. Stem cells, on the other hand, do not have a specialized function; they are an immature kind of cell that still has the potential to develop into many different kinds of cell (Schwartz et al., 2012).

2.1. Properties of stem cells

In addition to being unspecialized, all stem cells have two additional properties: self renewal, and potency (Robinton and Daley, 2012)

Self renewal: Self-renewal is the ability of cells to proliferate without the loss of differentiation potential and without undergoing senescence (biologic aging). Stem cells are hypothesized to be able to divide symmetrically (in which both daughter cells are either stem cells or differentiated cells) or asymmetrically (yielding one stem cell and one more differentiated cell).

Potency: specifies the potential to differentiate into different cell types of the stem cell. Stem cells can be either totipotent, pluripotent, multipotent, or unipotent.

- Totipotent cells have the capability to produce all cell types of the developing organism, including both embryonic and extra embryonic (ex. placenta) tissues.

- Pluripotent cells can only make cells of the embryo proper, but make all cells of the embryo including germ cells and cells from any of the germ layers. Therefore, they can make any cell of the body.
- Multipotent cells can only make cells within a given germ layer. For example, multipotent stem cells from a mesodermal tissue like the blood can make all the cells of the blood, but cannot make cells of a different germ layer such as neural cells (ectoderm) or liver cells (endoderm).
- Unipotent cells make cells of a single cell type. An example is a germ cell stem cell that makes the cells that mature to become egg or sperm, but not other cell types.

The potency of cells is tied to the time of embryonic development of the organism. Cells that have totipotency arise from the first few cell divisions following fertilization of the egg. Pluripotent cells were thought to be limited to cells derived from either the inner cell mass of the blastocyst or nascent germ cells in the embryo. It is now known that pluripotent cells can arise from other cells types as well. In day 10 to 14 post-fertilization in the human, most stem cells are restricted to be either multipotent or unipotent.

3. Skin Stem Cells

Skin stem cells as well fall into the classification as somatic stem cells, however, due to the cellular heterogeneity of skin, various types of skin stem cells were found in past decades (Shi et al., 2006). Recently, significant advances have been made in identifying different types of skin stem cells with the aid of molecular tools. Subgroups of skin stem cells are listed as below.

3.1. Epidermal stem cells

Most resided in the basal layer of epidermis, can derive into transient amplifying cells and terminal-differentiated epidermal cells (Suzuki and Senoo, 2012).

3.2. Follicular stem cell

Located at the follicle bulge region, can derive into hair follicle epithelium, including outer root sheath, inner root sheath, and hair shaft. Specified cell markers are K15, CD34, Lgr5, Sox9, Lhx2, NFATC1, NFIB, K15, PHLDA1, CD200, K19, etc. (Liu et al., 2003)

3.3. Melanocyte stem cells

Located at the follicle bulge region and hair germ. Specified cell markers are Dct, Sox, and Pax3 (Harries et al., 2013).

3.4. Sebaceous gland stem cells

Resided around sebaceous glands and infundibulum. The unique cell marker is Blimp1 (Horsley et al., 2006).

3.5. Mesenchymal stem –cell- like cell

Located at dermis, might divide into Mesodermal derivatives and some neural cell types. Specified cell markers are CD70, CD90, and CD105 whereas negative for CD34 (Garzon et al., 2013).

3.6. Neural progenitor cells

Located at the follicle dermal papillae, might divide into neural and glial lineages, shared similar cell markers as counterparts in other organs or tissues.

3.7. Hematopoietic stem cells

Located at the follicle dermal papillae, might divide into erythroid and myeloid lineages, shared similar cell markers as counterparts in other organs or tissues.

Among all these distinct skin stem cell subgroups, epidermal stem cells are the most deeply correlated to tissue repair and skin regeneration. Scientific reports supported that stem cells of epidermis are rare, infrequently dividing, and generate short-lived, rapidly dividing cells that carry out the regeneration of the epidermis. The same infrequently dividing stem cells of epidermis are assumed to be the major epidermal cell population responsible for repairing skin injury. Most epidermal stem cells reside in the basal layer of epidermis, some might also be found in the bulge region of the hair follicle and the base of the sebaceous glands (Watt et al., 2006). With the major advances of molecular biology, the role of small molecules involved in skin repairing has been well documented, examples the miRNAs. miRNAs are central regulators of gene expressions and are capable of tuning genes with either up regulation or down regulations. Therefore, miRNAs play key roles in various biological processes including cell survival, homeostasis, and differentiation. Several miRNAs were identified to be expressed exclusively in epidermal stem cells in animal models compared with other skin cells, including miR-200, miR-141, miR-429, miR-19 and miR-20 (Andl et al., 2006).

4. Stem cell as implications for regenerative medicine

For the purposes of regenerative medicine, the ideal stem cells would be pluripotent stem cells (PSCs) or multipotent stem cells (MultSCs), which, ac cording to their definition, have a broad potential to differentiate into cells from all 3 germ layers (meso , ecto , and endoderm) in the case of PSCs or from 2 germ layers in the case of MultSCs (Ratajczak et al., 2012). Based on encouraging data in experimental animals, several types of stem cells isolated from embryonic and adult tissues hold a more or less justified promise for treating patients. Regenerative medicine is searching for stem cells that can be safely and efficiently employed for regenera tion of damaged solid organs (e.g., the heart, brain, or liver). Ideal for this purpose would be pluripotent stem cells, which, according to their definition, have broad potential to differentiate into all types of adult cells. Induced pluripotent stem cells (iPSCs), generated by genetic modification of adult somatic cells, are a more promising source. However, both iPSC and ESCs are associated with a risk of teratoma formation. At the same time, various types of more differentiated adult stem and progenitor cells derived from the bone marrow, umbilical cord blood, mobilized peripheral blood, or fat tissue are being employed in clinical trials to regenerate damaged solid organs. Researchers suggest that adult stem cells are crucial for all physiological tissue renewal and regeneration after injury or disease. Another theory says that the bone marrow cell injected secretes cytokines that

promote angiogenesis and consequently, osteogenesis is induced on the necrotic area by increasing angiogenesis, suggesting that stem cells can heal necrotic tissue. Some study suggests that MSC showed a fibroblast-like morphology and can be differentiated in vitro into osteogenic lineages. Adult human stem cells have also been isolated or identified from human kidney, breast, pancreas, mesenchyme, liver and prostate. These stem cells can be used for regeneration treatment.

5. Nanotechnology in stem cell research

Nanotechnology is manifested in efficacious nanobiomaterials, drug delivery systems, gene therapies, robotic-based diagnostics and surgical aids, nano biomedical devices, biological micro electromechanical systems (BioMEMS), among others. Stem cells research, also started drawing interest of biologists from the 1960's. Stem cells are distinguished from other cell types by their ability of indefinite proliferation and multilineage differentiation. Recent state of the art is driving biologists to translate their findings into clinical therapeutics. Efforts are made to prompt stem cells to grow into all body tissues under defined and reproducible conditions and assume characteristic 3-D morphologies. Stem cells breed optimism to find cures for degenerative disorders, cancer, and congenital abnormalities and radically transform management of these disorders.

5.1 Nanotechnology for stem cells imaging and visualization

Some mammalian tissues can be restored to their original state after injury; however, most adult tissues can be repaired but not completely restored, as a natural process. For tissue regeneration to occur correctly (usually a lineage progenitor) sufficient number of cells needs to be produced and delivered to the right location at the right time. The potential for long lasting regeneration of the tissues remain within the stem cells and their ability to divide symmetrically and asymmetrically, determining cell fate. The existing imaging techniques can be divided into two major categories: electron microscopy imaging techniques and continuous imaging techniques.

5.2 Nanotechnology for genetic engineering and stem cell therapies

To completely understand stem cell biology, and make them suitable for tissue engineering and organ regeneration, it is necessary to genetically engineer (or manipulate or reprogram) them. This may be done with a view to generate patient-specific stem cells, make them pluripotent, for differentiation, proliferation, trans differentiation or dedifferentiation, induce expression of signaling factors, produce transgenic animals as models of diseases, upregulate or downregulate receptor molecules on surface, amongst others. For genetic manipulation, somatic cell nuclear transfer, cell fusion, and forced expression of genes are some of the techniques available. With the mapping of the human genome project, considerable amount of information on the genetic basis of disorders has become available (Kharlamov et al., 2010). Vectors are required since genetic elements like (DNA peptide nucleic acid or more importantly the siRNA) have to overcome many barriers before they can be integrated into gene expression machinery of the cell.

5.3 Nanotechnology for creating stem cell niches

Stem-cell populations are established in 'niches' specific anatomic locations that regulate how they participate in tissue generation, maintenance and repair. The niche saves stem cells from depletion, while protecting the host from over exuberant stem-cell proliferation. It constitutes a basic unit of tissue physiology, integrating signals that mediate the balanced response of stem cells to the needs of organisms.

6. Application of stem cells

*6.1. In clinical cardiology***:** Cardiovascular disease continues to be one of the main causes of death worldwide, and despite improved outcomes of patients with acute myocardial infarction (AMI), the incidence of heart failure (HF) increases. Because AMI leads to a substantial and irreversible loss of cardiomyocytes, there is clearly a need for new therapies, which could restore the myocardial structure and function (Coulombe et al., 2014). Cell therapies have been used in patients with AMI, HF, refractory angina, as well as critical limb ischemia and claudication. In the past 13 years, numerous clinical studies have been performed, in particular in patients with AMI. Several types of cells were used, isolated either from the BM or adipose tissue. In the majority of trials, a heterogeneous population of mononuclear cells isolated by centrifugation was used, which consists of differentiated cells as well as HSCs and endothelial progenitor cells. Subsequently, some other populations of more purified BM stem cells have been employed in the clinic, such as $CD34^{+}CXCR4^{+}$ and $CD133^{+}$ cells.

*6.2. In neurology***:** Brain damage (e.g., stroke) and spinal cord injury as well as several neurodegenerative disorders, including Parkinson disease, amyotrophic lateral sclerosis, and Alzheimer disease, are potential targets for stem cell therapies(Trounson et al.,2011) Several preclinical animal models indicate the feasibility of such treatments. Stroke is the third leading cause of death and disability in developed countries. Several clinical trials are currently registered to ameliorate the side effects of stroke using autologous HSCs, BM derived MSCs, and adipose tissue derived MSCs. Cells are injected into patients intracerebrally, intra-arterially, or intravenously.

6.3. In ophthalmology: Stem cell therapies for retinal disease are underway, and several clinical trials are recruiting patients to treat diseases such as age related macular degeneration, Stargardt disease, and retinitis pigmentosa, for which there are currently no curative treatments. In most of these trials, autologous BM derived HSCs are being employed, and a clinical trial has been initiated recently using patient derived VSELs. Age related macular degeneration and Stargardt disease are also potential targets for ESC derived retinal pigment epithelium cell lines, and stem cell based treatments have already been performed on patients (Ramsden et al.,2013).

6.4. As a therapy for diabetes: Stem cell provides the compelling need to develop novel therapies for diabetes mellitus. Human embryonic stem cells induced to form pancreatic β-cells could provide a replenishable supply of

tissue. Early studies on the spontaneous differentiation of mouse embryonic stem cells have laid the foundation for a more directed approach based on recapitulating the events that occur during the development of the pancreas in the mouse. A high yield of definitive endoderm has been achieved, and although β-like cells can be generated in a step-wise manner, the efficiency is still low and the final product is not fully differentiated. Future challenges include generating fully functional islet cells under Xeno-free and chemically defined conditions and circumventing the need for immunosuppressant. (Docherty et al.,2007)

6.5. Embryonic and adult stem cells in immunomodulatory aspects:

Now a day the immunomodulatory properties of mesenchymal stem cells have attracted interest. Mesenchymal stem cells have been shown to inhibit the proliferation of activated T-cells both in vitro and in vivo but to stimulate T-regulatory cell proliferation. Mesenchymal stem cells are also known to be weakly immunogenic and to exert immunosuppressive effects on B-cells, natural killer cells, dendritic cells and neutrophils through various mechanisms. Furthermore, intravenous administration of allogeneic mesenchymal stem cells has shown a marked suppression of host immune reactions in preclinical animal models of large-organ transplant rejection and in various autoimmune- and inflammatory-based diseases.

6.6. Embryonic stem cells as a model to study human genetics

Human embryogenesis is one of the most exciting fields in biology and medicine. However, apart from the very early stages of pre implantation development, human embryos are in accessible for research and are limited to section studies of diseased aborted fetuses. One approach to overcome this obstacle is to use animal models usually mice, taking advantage of their well-defined genetics and reproductive characteristics. The use of mice as a model for human development has been justified by the observation that there is strong conservation throughout evolution of developmental processes and control genes. Moreover, the relative ease by which their genome can be genetically manipulated and used for the introduction of specific mutations by homologous recombination has made them extremely important for studying specific genes and pathways that are involved in embryonic development.

6.7. Applications of human embryonic stem cells in drug discovery

The isolation of human embryonic stem cells about a decade ago marked the birth of a new era in biomedical research. These pluripotent stem cells possess unique properties that make them exceptionally useful in a range of applications. Discussions about human stem cells are most often focused around the area of regenerative medicine and indeed, the possibility to apply these cells in cell replacement therapies is highly attractive. More imminent, however, is the employment of stem cell technologies for drug discovery and development. Novel improved in vitro models based on physiologically relevant human cells will result in better precision and more cost-effective assays ultimately leading to lower attrition rates and safe new drugs (Sartipy et al., 2007).

6.8. Mesenchymal stem cells and their therapeutic applications in neurodegenerative diseases

The contribution of stem cells to cure neurodegenerative diseases has been unraveled and explored extensively over the past few years. Beyond substitution of the lost neurons, stem cells act as immunomodulators and neuroprotectors. A large number of preclinical and a small number of clinical studies have shown beneficial outcomes in this context.

7. Ethical consideration on stem cell research

Most of the ethical issues surrounding stem cell research involve embryonic stem cells because they are derived from fertilized embryos, which are subsequently destroyed in the research process. The embryos used for research, however, are not derived from eggs fertilized in a woman's body; rather they are fertilized *in vitro* in a fertilization clinic and donated for research purposes with informed consent of the donor or human fetal tissue following elective abortion (Triolo et al., 2010). NIH guidelines for stem cell therapy say that, embryonic stem cells can be derived from stem cells of an embryo only when the embryo is no longer needed for reproductive purposes. A written informed consent should be obtained from the donor, indicating the willingness of the donor to allow use of the embryo for human embryonic stem cell related research and therapy. No commercialization will be allowed. Guidelines have included even medical benefit of donation that in the future such cells might be used for the medical benefit of the person donating them. National Academy of Sciences (NAS) has given specific guidelines for the conduct of research on Human embryonic stem cells (hESC) (Gallagher and Holmes, 2011).

8. Conclusion

In conclusion, the controversy over human embryonic stem cell research still remains unsolved, but the potential of stem cell to treat the disease is most exciting. Unlocking stem cell potential still require much more continued research and one day it is going to be a common treatment for degenerative diseases. The future of stem cell research is indeed promising, yet scientific challenges must be overcome one-by one. In future, stem cells may be able to treat and possibly cure diseases for which there is no adequate therapy today. Clearly, the pace of research needs to be accelerated, and the funding for high quality projects assessing therapeutic benefit of stem cells increased. Furthermore, translational medicine approaches need to be incorporated more fully into stem cell research. Many human trials remain to be completed and it is hoped that the results of these will be as promising as the early studies. Early success in small, often poorly controlled studies makes the large placebo-controlled, fully blinded, multicentre studies all the more important. There are many reasons to be optimistic about stem cell therapy in the future, but a lot more research and investigation will be needed for success to be achieved in the clinic.

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