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Review on Stem Cells as Regenerative Therapy

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Abstract
Stem cells are a population of undifferentiated cells characterized by the ability to extensively proliferate (self-renewal), usually arise from a single cell (clonal), and differentiate into different types of cells and tissue (potent). There are several sources of stem cells with varying potencies. Pluripotent cells are embryonic stem cells derived from the inner cell mass of the embryo and induced pluripotent cells are formed following reprogramming of somatic cells. Pluripotent cells can differentiate into tissue from all 3 germ layers (endoderm, mesoderm, and ectoderm). Multipotent stem cells may differentiate into tissue derived from a single germ layer such as mesenchymal stem cells which form adipose tissue, bone, and cartilage. Tissue-resident stem cells are oligopotent since they can form terminally differentiated cells of a specific tissue. Stem cells can be used in cellular therapy to replace damaged cells or to regenerate organs. In addition, stem cells have expanded our understanding of development as well as the pathogenesis of disease. Disease-specific cell lines can also be propagated and used in drug development. Despite the significant advances in stem cell biology, issues such as ethical controversies with embryonic stem cells, tumor formation, and rejection limit their utility. However, many of these limitations are being bypassed and this could lead to major advances in the management of disease.

Keywords
Stem cells, regenerative medicine, cryopreservation, embryonic stem cells and cell banking.

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INTRODUCTION:
Stem cells are undifferentiated or partially differentiated cells that can differentiate into various types of cells and proliferate indefinitely to produce more of the same stem cell. They are the earliest type of cell in a cell lineage. [1, 2] They are found in both embryonic and adult organisms, but they have slightly different properties in each. They are usually distinguished from progenitor cells, which cannot divide indefinitely, and precursor or blast cells, which are usually committed to differentiating into one cell type. In mammals, roughly 50-150 cells make up the inner cell mass during the blastocyst stage of embryonic development, around days 5-14. These have stem-cell capability. In vivo, they eventually differentiate into all the body's cell types (making them pluripotent). This process starts with the differentiation into the three germ layers – the ectoderm, mesoderm, and endoderm – at the gastrulation stage. However, when they are isolated and cultured in vitro, they can be kept in the stem-cell stage and are known as embryonic stem cells (ESCs).[3]

Adult stem cells are found in a few select locations in the body, known as niches, such as those in the bone marrow or gonads. They exist to replenish rapidly lost cell types and are multipotent or unipotent, meaning they only differentiate into a few cell types or one type of cell.[4] In mammals, they include, among others, hematopoietic stem cells, which replenish blood and immune cells, basal cells, which maintain the skin epithelium, and mesenchymal stem cells, which maintain bone, cartilage, muscle and fat cells. Adult stem cells are a small minority of cells; they are vastly outnumbered by the progenitor cells and terminally differentiated cells that they differentiate into. [5]

Current state of newborn stem cell banking

In September of 2018, the umbilical cord blood transplant and new born stem cell banking communities celebrated the 30th anniversary of the first hematopoietic stem cell (HSC) transplant using cord blood as a graft for a patient with Fanconi's anaemia. The successful demonstration that cords blood is capable of reconstituting a patient's blood and immune system, coupled with the confirmation that cord blood can be cryopreserved for later use, led to the 15establishment of cord blood banks, and thus the newborn stem cell banking industry, in the early 1990s [6]. It is estimated that more than more than 800,000 cord blood units are cryopreserved in public banks and over 5 million more are stored in private cord blood banks [7]. Newborn stem cell banking encompasses public cord blood banks, which store cord blood units for use in an unrelated recipient; private banks, which store cord blood for future use by the donor or a first- or second-degree relative; and hybrid banks, which offer combined services [8]. Storage of an additional newborn tissue, such as umbilical cord tissue or placental tissue, costs an additional $800–1300. There is no charge to families donating newborn tissues, as public banks cover costs associated with collection, processing, and storage [9]. Certain maternal and neonatal parameters associated with cord blood quality, such as gestational age and birth weight, can be used by public banks to optimize donor selection in an effort to increase likelihood of utilization and as part of managing costs associated with tissue procurement [10]

Stem cell applications in regenerative medicine and disease therapeutics

Regenerative medicine, the most recent and emerging branch of medical science, deals with functional restoration of specific tissue and/or organ of the patients suffering with severe injuries or chronic disease conditions, in the state where bodies own regenerative responses do not suffice [11]. In the present scenario donated tissues and organs cannot meet the transplantation demands of aged and diseased populations that have driven the thrust for search for the alternatives. Stem cells are endorsed with indefinite cell division potential, can transdifferentiate into other types of cells, and have emerged as frontline regenerative medicine source in recent time, for reparation of tissues and organs anomalies occurring due to congenital defects, disease, and age associated effects [12]. Stem cells pave foundation for all tissue and organ system of the body and mediates diverse role in disease progression, development, and tissue repair processes in host. On the basis of trans differentiation potential, stem cells are of four types, that is, unipotent, multipotent, pluripotent and totipotent [13]. Zygote, the only totipotent stem cell in human body, can give rise to whole organism through the process of trans differentiation, while cells from inner cells mass (ICM) of embryo are pluripotent in their nature and can differentiate into cells representing three germ layers but do not differentiate into cells of extraembryonic tissue [14]. The ideal scaffolds support cell adhesion and ingrowths, mimic mechanics of target tissue, support angiogenesis and neovascularisation for appropriate tissue perfusion, and being non-immunogenic to host, do not require systemic immune suppressant [15]

Table: 1 Application of stem cells in regenerative medicine: stem cells (ESCs, TSPSCs, MSCs, UCSCs, BMSCs, and iPSCs) have diverse applications in tissue regeneration and disease therapeutics

SCs	Disease	Factors causing disease	Mode of stem cells application	Physiological and mechanistic aspects of stem cells therapeutics
ESC's	Spinal cord injuries	Infection, cancer, and accidents	ESCs transplantation to injury site	ESCs and secreted vasculogenic and neurogenic factor support tissue homing
	Diabetes	Lifestyle, heart defects, and genetics	Transplantation of ESCs-derived PPCs	Progenitors ($CD24^+$, $CD49^+$ & $CD133^+$) differentiate into β-cells, secrete insulin, and express PDX1, GCK, and GLUT2

	Corneal diseases	Burns, genetics, and inflammation	LPSCs transplantation to corneal tissue	LPSCs in transplant marked by ABCB5 differentiate into mature cornea
	Cardiovascular disease	Diabetes, drugs, genetic factor, and lifestyle	ESCs-derived CMs & biomaterial coaxed ESCs	Cardiomyocytes express GCaMP3, secreting vasculogenic factors, and Tbox3 differentiates ESCs into SANPCs
	Corneal diseases	Burns, genetics, and inflammation	LPSCs transplantation to corneal tissue	LPSCs in transplant marked by ABCB5 differentiate into mature cornea
TSPSCs	Eye disease & retinopathy	Toxins, burns, and genetic factors	AdSCs intravitreal transplantation	AdSCs from healthy donor produce higher vaso protective factors
	Corneal diseases	Burns, genetics, and inflammation	LPSCs transplantation to corneal tissue	LPSCs in transplant marked by ABCB5 differentiate into mature cornea
	Dental problems	Infection, cancer age, and accidents	Transplants of EMSCs + DSCs biopolymer tissue	EMSC-DSCs and vasculogenic factors in biopolymer give rise to mature teeth units
	Bone degeneration	Injuries and tumor autoimmunity	Coaxed MSCs transplant & MSCs infusion	Actin modelling by cytochalasin-D transforms MSCs into osteoblasts
MSCs	Muscle degeneration	Genetic factors and work stress	Coaxed MSCs transplant and MSCs infusion	Alginate gel protects MSCs from immune attack and controls GFs release
	Alopecia	Age, disease, and medicine use	Transplantation of GAG-coated DPCs	GAG coating mimics ECM microenvironment, promoting DPCs regeneration UCSCs
	LSD & neurodegenerative diseases	Genetics, tumor, age, and lifestyle	Allogenic UCSCs cells and biomaterial coaxed UCSCs organoids	Organoids consisted of neuroblasts ($GFAP^+$, $Nestin^+$, and $Ki67^+$) & SCs ($OCT4^+$, $SOC2^+$); UCSCs recover from MSE deficiency and improve cognition
	Cartilage and tendon injuries	Accident	Transplantation of UCB-SCs, UCB-SCs-HA gel	HA gel factors promote regeneration of hyaline cartilage & tendons in wks time
	Anaemia and blood cancer	Injury, genetics autoimmunity	Two-step infusion of lymphoid and myeloid	Haplo identical BMSCs can reconstruct immunity, which is major process for minority
BMSCs	AIDS	HIV1 infection	Transplantation of HIV1 resistant $CD4^+$ cells	Anti-HIV1 $CD4^+$ cells express HIV1 anti-RNA, which restrict HIV infection
iPSCs	Lung degeneration	Tuberculosis, cancer, and fibrosis	Biomaterial coaxed iPSCs transplantation	Miniature iPSCs lung resembles airways and alveoli, model drug testing
	Lung degeneration	Tuberculosis, cancer, and fibrosis	Biomaterial coaxed iPSCs transplantation	Miniature iPSCs lung resembles airways and alveoli, model drug testing

Benefits of stem cell treatment

- ✓ Stem cell treatments may lower symptoms of the disease or condition that is being treated. The lowering of symptoms may allow patients to reduce the drug intake of the disease or condition. Stem cell treatment may also provide knowledge for society to further stem cell understanding and future treatments. [16]
- ✓ Surgical processes by their character are harmful. Tissue has to be dropped as a way to reach a successful outcome. One may prevent the dangers of surgical interventions using stem cells. Additionally, there's a possibility of disease and whether the procedure fails, further surgery may be required.
- ✓ Risks associated with anaesthesia can also be eliminated with stem cells.[17]

Drawbacks of stem cell treatment

- ✓ Stem cell treatments may require immunosuppressant because of a requirement for radiation before the transplant to remove the person's previous cells, or because the patient's immune system may target the stem cells.
- ✓ One approach to avoid the second possibility is to use stem cells from the same patient who is being treated.
- ✓ Pluripotency in certain stem cells could also make it difficult to obtain a specific cell type.
- ✓ It is also difficult to obtain the exact cell type needed, because not all cells in a population differentiate uniformly. Undifferentiated cells can create tissues other than desired types.[18]
- ✓ Some stem cells form tumors after transplantation pluripotency is linked to tumor formation especially in embryonic stem cells, fetal proper stem cells, induced pluripotent stem cells.[19].
- ✓ Fetal proper stem cells form tumors despite multipotency. [20]
- ✓ Ethical concerns are also raised about the practice of using or researching embryonic stem cells.
- ✓ Harvesting cells from the blastocyst result in the death of the blastocyst. The concern is whether the blastocyst should be considered as a human life. [21]

Challenges concerning stem cell therapy.

Although stem cells appear to be an ideal solution for medicine, there are still many obstacles that need to be overcome in the future. One of the first problems is ethical concern. The most common pluripotent stem cells are ESCs. Therapies concerning their use at the beginning were, and still are, the source of ethical conflicts. The reason behind it started when, in 1998, scientists discovered the possibility of removing ESCs from human embryos. Stem cell therapy appeared to be very effective in treating many, even previously incurable, diseases. The problem was that when scientists isolated ESCs in the lab, the embryo, which had potential for becoming a human, was destroyed. Because of this, scientists, seeing a large potential in this treatment method, focused their efforts on making it possible to isolate stem cells without endangering their source—the embryo. For now, while hESCs still remain an ethically debatable source of cells, they are potentially powerful tools to be used for therapeutic applications of tissue regeneration. Because of the complexity of stem cell control systems, there is still much to be learned through observations in vitro. For stem cells to become a popular and widely accessible procedure, tumour risk must be assessed. The second problem is to achieve successful immunological tolerance between stem cells and the patient's body. For now, one of the best ideas is to use the patient's own cells and devolve them into their pluripotent stage of development.

New cells need to have the ability to fully replace lost or malfunctioning natural cells. Additionally, there is a concern about the possibility of obtaining stem cells without the risk of morbidity or pain for either the patient or the donor. Uncontrolled proliferation and differentiation of cells after implementation must also be assessed before its use in a wide variety of regenerative procedures on living patients [22]

Stem cell obstacles in the future

Pioneering scientific and medical advances always have to be carefully observed in order to make sure they are both ethical and safe. Because stem cell therapy already has a large impact on many aspects of life, it should not be treated differently. Currently, there are several challenges concerning stem cells. First, the most important one is about fully understanding the mechanism by which stem cells function first in animal models. This step cannot be avoided. For the widespread, global acceptance of the procedure, fear of the unknown is the greatest challenge to overcome. The efficiency of stem cell-directed differentiation must be improved to make stem cells more reliable and trustworthy for a regular patient. The scale of the procedure is another challenge. Future stem cell therapies may be a significant obstacle. Transplanting new, fully functional organs made by stem cell therapy would require the creation of millions of working and biologically accurate cooperating cells. Bringing such complicated procedures into general, widespread regenerative medicine will require interdisciplinary and international collaboration. The identification

and proper isolation of stem cells from a patient's tissues is another challenge. Immunological rejection is a major barrier to successful stem cell transplantation. With certain types of stem cells and procedures, the immune system may recognize transplanted cells as foreign bodies, triggering an immune reaction resulting in transplant or cell rejection.

Further development and versatility of stem cells may cause reduction of treatment costs for people suffering from currently incurable diseases. When facing certain organ failure, instead of undergoing extraordinarily expensive drug treatment, the patient would be able to utilize stem cell therapy. The effect of a successful operation would be immediate, and the patient would avoid chronic pharmacological treatment and its inevitable side effects. Although these challenges facing stem cell science can be overwhelming, the field is making great advances each day. Stem cell therapy is already available for treating several diseases and conditions. Their impact on future medicine appears to be significant.

Risk factors in developing of stem cell therapy.

For an adequate benefits, all important identified risks should be thoroughly evaluated [23]. Such an evaluation at the start and during the development of a stem cell-based therapy may help to determine the extent and focus of the product development and safety evaluation plans. Here we discuss several risks associated with stem cell based medicinal products, and the risk factors contributing to these risks in table: 2

S. No	Type of risk factor	Risk factors
1.	**Intrinsic factors**	✓ Origin of cells (e.g. autologous vs. allogenic, diseased vs. healthy donor/tissue) ✓ Differentiation status. ✓ Tumo urigenic potential
2.	**Cell characteristics**	✓ Proliferation capacity ✓ Life span ✓ Long term viability Excretion patterns (e.g. growth factors, cytokines, chemokines)
3.	**Extrinsic factors manufacturing and handling**	✓ Lack of donor history ✓ Starting and raw materials ✓ Plasma derived materials ✓ Contamination by adventitious agents (viral/bacterial/mycoplasma/fungi, prions, parasites) ✓ Cell handling procedures (e.g. pro curement) ✓ Culture duration ✓ Tumourigenic potential (e.g. culture induced transformation, incomplete removal of undifferentiated cells) ✓ Non cellular components ✓ Pooling of allogenic cell populations ✓ Conservation (e.g: cryopreservatives) ✓ Storage conditions (e.g. failure of traceability, human material labelling) ✓ Transport conditions
4.	**Clinical characteristics**	✓ Therapeutic use (i.e. homologous or non-homologous) ✓ Indication ✓ Administration route ✓ Initiation of immune responses ✓ Use of immune suppressive.

Table: 2 Factors contributing to these risks

Quality control during stem cell cryopreservation process

Storage temperature is a key factor for long-term storage of stem cells in a stable state. Lower temperatures can reduce metabolism of cells and efficiently reduce the rate of degradation [23]. In general, the lower the storage temperature, the more stable the cells remain and the longer they can be preserved [24, 25]. The traditional method for long-term cryopreservation of stem cell is storage in liquid nitrogen, which can reach a terminal temperature of −196 °C [26]. Quality control

methods should be applied to keep a stable temperature environment in long term storage vessels as stored cells may be subjected to temperature changes during the maintenance of storage vessels. For example, storage vessels are opened frequently to gain access to stored vials, intermittent warming may occur to cryovials. Furthermore, some storage racking material can act as good heat conductors and may promote warming cycles and temperature gradients within the storage vessel. Finally, there may be failures in the liquid nitrogen filling process [27]. Before putting the donated cell lines into storage, they are first proliferated and multiplied into a large number of identical cells before being stored in a number of cryovials. Along with the cells, cryoprotective agents are also added to the vials to protect the cells from rupturing from ice crystals during the freezing process. 10% DMSO solution is a common cryoprotective agent. [28]

A number of straight forward procedures can be taken to keep a stable temperature environment in stem cell storage vessels during the long-term storage process:

- ✓ Choose a suitable terminal temperature for the long-term storage of stem cells.
- ✓ Use appropriate facilities to cryopreserve samples and manual or automatic continuous temperature monitoring to detect and provide useful monitoring data of temperature.
- ✓ Set up an automatic liquid nitrogen filling system.
- ✓ Keep vessel vacuum checks, electrical testing, and other maintenance procedures regularly and periodically audited [29].

Contamination of stem cells during storage

It is crucial to prevent microbial/cross contamination during the long-term storage of stem cells. The risk of stem cell products is mainly associated with contaminated liquid nitrogen during long-term storage [30]. As microbial flora can easily accumulate within ice sludge debris [31]. Quality control methods should be taken to prevent contamination of cell samples in these long-term storage vessels [32]. It has been shown that vapour phase storage can largely overcome sample contamination as it can prevent the liquid nitrogen permeating into cryovials thereby avoiding contamination by contaminated liquid [33]. However, all long-term storage samples run the risk of cross contamination risk when they are stored in the same cryo tank, rewarmed in the same water bath, and because of other potential environmental sources.

Quality control methods can be taken as follows to reduce the contamination of stem cells during long-term storage:

- ✓ Choose a vapour phase liquid nitrogen containment vessel.
- ✓ Set security caps when sample have to be submersed in liquid nitrogen.
- ✓ Employ internal threads and double bagging to store cell samples.
- ✓ Maintain the storage container closure integrity and within the product shelf life.
- ✓ Set up a quarantined storage area to control the spread of pathogens and infectious agents.
- ✓ Keep storage containers in a clean and controllable environment to reduce the contamination risk from the surrounding area.
- ✓ Make sure the source of liquid nitrogen is clean [34]

Principles for the establishment, good governance, and regulation of stem cells.

With increasing acceptance of the research and clinical potential and promise of stem cell science, there has been a movement toward establishing repositories of stem cells. These repositories have adopted the name “banks,” following the lead of human tissue “biobanks.” The UK Stem Cell Bank, for example, was established with the aim of providing a repository of human embryonic, fetal and adult stem cell lines. Its role is to provide an international resource for stem cell research, supplying human stem cell lines, both for research and to those wishing to develop cell lines for clinical application *i.e.,* including an active programme of precompetitive research in collaboration with academia and industry [35]

In addition, stem cell banks have also been established in countries that are actively advancing the translation of stem cell science from the bench to the clinic, particularly in the USA, Japan, Australia, and Spain. In this respect, the work of the International Stem Cell Donald Chalmers et al. 103 Forum, International Stem Cell Banking Initiative (ISCBI) of the International Stem Cell Forum [36] aims to create a truly global network of stem cell banks to facilitate best practice in stem cell research and the eventual clinical application of these banked stem cells. In this respect, the aims of the ISCBI align closely with those of the International Society of Stem Cell Research (ISSCR). [37] Stem cell banks are being established with effective and proper organizational and governance structures. With the increasing prevalence of stem cell banks worldwide, it is timely to examine core ethical principles and best practice governance frameworks that should guide their establishment and use. Stem cell banks are

being established with effective and proper organizational and governance structures. With the increasing prevalence of stem cell banks worldwide, it is timely to examine core ethical principles and best practice governance frameworks that should guide their establishment and use. [38]

CONCLUSIONS:

Stem cells are acting as very important tool for understanding both the organogenesis and the continuous regenerative capacity of the body. They could be a model for the study of pathogenetic mechanisms and could assist researchers in understanding the pathophysiology of various diseases. They also offer the possibility of developing biological models for the study of new pharmacological agents. However, the most important potential of these cells is to replace damaged tissue and even regenerate organs. To date, a large number of research protocols, preclinical studies, and clinical trials have been published. Although, several clinical studies have already reported encouraging results for the development of new therapeutic strategies in cell-based medicine, there are a number of risks and obstacles. Despite this, there is ongoing research and development that gives us great optimism about regenerative medicine.

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