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STEM CELLS AND ITS APPLICATION IN THERAPEUTICS

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ABSTRACT

This review is detailed overview that deals with the stem cells and its application in therapeutics. As stem cells research has laid the foundation for cell based therapies of disease which cannot be cured by the conventional method & drugs. The review covers most contemporary development in transplantation and tissue engineering technologies of ESC's, MSC's, NSC's & DSC's in regenerative medicine. In the coming future, the stem cells therapies will bring considerable perk to the patients suffering from wide range of injuries, defects and disease. There is high optimism for use of ESCs, MSCs, NSC's & DSC's for treatment of various diseases to overcome the contradictions & confutation related with ESCs.

KEYWORDS: Stem cells, in-vitro fertilization, Chondrocytes, Myeloma, Transplantation, Neuroinflammation, Immunohistochemistry.

INTRODUCTION

Stem cells are having a unique ability to regenerate & develop into the specialized cell types in the body. Stem cells have the potential to carry out indefinite cell division & can transdifferentiate into other cell types that resulted as an regenerative medicinal source for repair of tissues & organs due to congenital defects, disease, and age associated factors (C. Mason and P. Dunnill 2008). Stem cells laid the basis for different tissue and organ system of the body and intercede diverse role in disease progression, development, and tissue repair processes in host. On the basis of transdifferentiation potential, stem cells are categorized into four types, that is, (1) unipotent (2) multipotent (3) pluripotent and (4) totipotent (L. A. Fortier 2005).

The National Institutes of Health created guidelines for human stem cell research in 2009. The guidelines state the importance of embryonic stem cells in research related fields & also have the recommendations relating to the donation of the embryonic stem cells (ESC's). As per the guidelines –embryonic stem cells from embryos generated through *in-vitro* fertilization can be used only when the embryo is no longer needed. The embryos that are used in ESC's research can be taken from eggs that were fertilized as *in-vitro* fertilization clinics. An adult stem cells can be promising but there is more likely the concern related to abnormalities due to environmental hazards or might be due to errors occurring during cells replication (K. Takahashi and S. Yamanaka 2006).

A stem cell line is a cluster of cells that all comes from a single indigenous stem cell that are produced in a lab. The stem cell therapy also called as regenerative medicine that aid in the repair response of diseased, deteriorated or defective worn out tissue using stem cells or it's derivatives. Researchers are still testing adult stem cells to cure the degenerative diseases such as heart failure (J. Yu et al., 2007). As stem cells replace the cells that are damaged by chemotherapy & even serve as means for donor's immune system to fight against the other such types of cancer causing & blood related disorders, such as leukemia, lymphoma, neuroblastoma and multiple myeloma in the stem cells transplant process.

STEM CELLS: APPLICATION IN REGENERATIVE MEDICINE AND DISEASE THERAPEUTICS

Stem cells have a huge application promises in disease therapeutics & as a regenerative medicine (Table:1).

Table: 1 Application of stem cells in regenerative medicine: stem cells have diverse applications in tissue regeneration and disease therapeutic.

Applications	References
In the study carried out by M. Thomson et al. 2011 stated that stem cells have diverse applications in the improvement of spinal cord injury, regeneration of retinal sheets, generation of retinal ganglion cells, healing of heart defects, hepatic cells formation, formation of insulin secreting beta-cells, cartilage lesion treatment, regeneration of pacemaker, in-vitro gametogenesis, treatment of diabetes and retinopathy, neurodental therapeutic application, restoration of cognitive function, brain and cancer treatment, ear acoustic function restoration, regeneration of intestinal mucosa, treatment of vision defects, muscle regeneration, regeneration of fallopian tube, regeneration of bladder tissue, regeneration of teeth tissue, healing of orthopedic injuries,	(M. Thomson et al. 2011)

recovery from muscle injury, hear scar repair after attack, SLE (autoimmune disease) treatment, application for HI treatment, Krabbe's disease treatment, hematopoiesis in neuroblastoma, treatment of anemia and blood cancer, retroviral therapy, correction of neuronal defects, generation of functional platelets, alveolar bone regeneration, regeneration of diaphragm tissue, regeneration of kidney tissue, vision restoration in AMD, treatment of placental defects, treatment of brain cortex defects, ASD and autism treatment, treatment of liver and lung disease, generation of serotonin neurons, regeneration of pacemaker, etc.,	
In the study done by E. W. Petersdorf et al. 2007 found that- For avoiding the outcomes of host-versus graft rejections, tissue typing of human leucocyte antigens (HLA) for tissue and organ transplant as well as use of immune suppressant is recommended.	(E. W. Petersdorf et al. 2007)
The study carried by A. M. Leferink et al., 2015 E. A. Gubareva et al., 2016 I.Garz'on et al., 2012 found different lineage commitment prospective constitute ESCs as ideal model for regenerative therapeutics of disease and tissue anomalies. Globally, especially in India, cardiovascular complication are a more common cause of human death, where biomedical therapeutics require immediate repair of heart functions for the very survival of the patient. Regeneration of cardiac tissue can be achieved by transplantation of cardiomyocytes, ESCs-derived cardiovascular progenitors, and bone marrow derived mononuclear cells (BMDMNCs); however healing by cardiomyocytes and progenitor cells is superior to BMDMNCs but mature cardiomyocytes have higher tissue healing possibility, suppress heart arrhythmias, couple electromagnetically into hearts functions, and furnish mechanical and electrical repair without any associated tumorigenic effects	(A. M. Leferink et al., 2015) (E. A. Gubareva et al., 2016) (I.Garz'on et al., 2012)
The study carried out by P. A. Thomson et al., 2016 found that -Under suitable culture conditions, ESCs have demonstrated a remarkable ability to self-renew continuously, that is, to produce more cells like themselves that are multipotent.	(P. A. Thomson et al., 2016)
As indicated at the workshop by Thomas Okarma and Ron McKay, ESC lines established from single cells have been demonstrated to proliferate through 300-400 population-doubling cycles. Human ESCs that have been propagated for more than 2 years also demonstrate a stable and normal complement of chromosomes, in contrast to the unstable and abnormal complement of embryonic cancer cell lines used in the past to study early stages of embryonic development.	(S. S. Nathamgari et al., 2015)
In the study done by Itskovitz-Eldor et al., 2000; Reubinoff et al., 2000; Schuldiner et al., 2000 they found that- When taken out from feeder cells and grown in suspension (in liquid), human ESCs form aggregated balls of cells called "embryonic bodies," which have been reported to give rise to a multiplicity of cell types representing all three layers of embryonic tissue development.	(Itskovitz-Eldor et al., 2000; Reubinoff et al., 2000; Schuldiner et al., 2000)
In the study done by Odorico et al., 2001 he found the evidence of the differentiation in culture includes detection of the products of genes associated with different cell types and in some cases by the characteristic shapes that are eccentric to different cell types & stated	(Odorico et al., 2001)

that the cells derived from human embryonic bodies include "rhythmically contracting cardiomyocytes, pigmented and non-pigmented epithelial cells, and neural cells displaying an buoyant outgrowth of axons and dendrites".	
In the study, B. Ning et al., 2015 Schuldiner et al., 2000 found that -In other experiments, cells arising from human ESCs have been reported to express genes associated with liver and pancreas function.	(B. Ning et al., 2015) (Schuldiner et al., 2000)
In the study carried out by A. Cheng et al., 2014 stated that- For young individuals and athletes replacement of joints is not practicable like old populations; in that case transplantation of stem cells represents an substitute for healing cartilage injuries.	(A. Cheng et al., 2014)
In the study done by V. Vedantham 2015 found that Chondrocytes, the cartilage forming cells derived from hESC, implant in fibrin gel effectively heal defective cartilage within 12 weeks, when transplanted to focal cartilage defects of knee joints in mice without any negative effect. Transplanted chondrocytes form cell aggregates, positive for SOX9 and collagen II, and defined chondrocytes are active for more than 12 weeks at transplantation site, recommending the clinical suitability of chondrocytes for treatment of cartilage lesions. The wholeness of ESCs to integrate and differentiate into electrophysiologically active cells supply a means for natural regulation of heart rhythm as biological pacemaker. Coaxing of ESCs into inert biomaterial as well as propagation in defined culture conditions leads to transdifferentiation of ESCs to become sinoatrial node (SAN) pacemaker cells (PCs).	(V. Vedantham 2015)

THERAPEUTIC APPLICATIONS OF MSCs IN BRAIN DAMAGE

The groundbreaking discovery of mesenchymal stem cells (MSCs) with their many benefits led to their widespread application in experimental medicine, including neurology. Here, Gierin Thomi et al., 2019 studied whether exosomes derived from hWJ-MSC have anti-inflammatory effects on microglia-mediated neuroinflammation in perinatal brain injury, and data suggest that the administration of hWJ-MSC-derived exosomes represents a promising therapy to prevent and treat perinatal brain injury (Gierin Thomi et al., 2019). In a study by Katherine A Ruppert et al., 2020, human adipose-derived mesenchymal stromal cells (MSCs) were administered at early (3 days) and delayed (14 days) time points after controlled cortical impact (CCI) injury in rats. Animals were routinely assessed for neurological and vestibulomotor deficits, and at 32 days post-injury, brain tissue was processed by flow cytometry and immunohistochemistry to analyze neuroinflammation. Treatment with HB-adMSC at either 3d or 14d after injury resulted in significant improvements in neurocognitive outcome and a change in neuroinflammation one month after injury (Katherine A Ruppert et al., 2020).

TBI could significantly increase the proliferation of adult neural stem cells in the hippocampus, but the survival and maturation of newborn cells is markedly low. Therefore, it is reasonable to hypothesize that the signaling molecules secreted in response to local tissue damage can further facilitate the therapeutic effect of the MSC secretome. To simulate the complex microenvironment in the injured brain well, Xiao-Yin Liu et. al., 2020, used traumatically injured brain tissue extracts to pretreat umbilical cord mesenchymal stem cells (UCMSCs) in vitro and stereotaxically injected the secretome from traumatic injury-preconditioned UCMSCs into the dentate gyrus of the hippocampus in a rat severe TBI model. The results revealed that compared with the normal secretome, the traumatic injury-preconditioned secretome could significantly further promote the differentiation, migration, and maturation of newborn cells in the dentate gyrus and ultimately improve cognitive function after TBI. Cytokine antibody array suggested that the increased benefits of secretome administration were attributable to the newly produced proteins and up-regulated molecules from the MSC secretome preconditioned by a traumatically injured microenvironment. This study utilized the traumatic injury-preconditioned secretome to amplify neurogenesis and improve cognitive recovery, suggesting this method may be a novel and safer candidate for nerve repair (Xiao-Yin Liu et al., 2020).

The secretome of mesenchymal stem cell (MSC) gives a series of immunoregulatory properties and is regarded as an effective method of mitigating secondary neuroinflammation induced by traumatic brain injury (TBI). Under hypoxia conditions the secretome of adipose-derived MSCs (ASC-ST) was collected. The neurological functional prognosis of TBI rats was significantly improved, and the vasogenic edema of brain tissues that was measured 14 days after TBI was relieved by ASC-ST. ASC-ST may be one of the most promising candidates for regulating the secondary inflammatory reactions of central nervous systems for clinical use (Chao Xu et al., 2020). Xiao Chen et al., 2020 found that transplantation of bone marrow MSCs (BM-MSCs) into the brains of mice could alleviate ICH-mediated injury and protect astrocytes from apoptosis by regulating mammalian sterile 20-like kinase (MST)1 and Yes-associated protein (YAP) and further demonstrated that astrocytes undergo astroglial-mesenchymal phenotype switching and become capable of proliferating after BM-MSC transplantation via the Hippo signaling pathway (Fangxia Guan et al., 2019).

THERAPEUTIC APPLICATIONS OF NEURAL STEM CELLS IN BRAIN DAMAGE

The Neural Stem Cells can be isolated from primary central nervous tissue (CNS), differentiation of Pluripotent Stem Cells or through transdifferentiation from somatic cells that can be used in the therapeutic once the cell transplantation is done. Neural Stem Cells can be differentiated on the injury site & it can also secrete paracrine factors that even carry out neurological repair.

Neural Stem Cells which are multipotent cells with immanent differentiation potentiality committed to the neuronal ancestry which are specially pertinent to advance & restore the damaged neuronal spinal tracts.

Adult hair follicle bulge-derived stem cells (HFBSCs) possess neuronal differentiation capability which makes them easy to harvest and are relatively immune-privileged, as well as potential candidates for autologous stem cell-based therapy. Luc2- and copGFP-expressing, ferumoxytol-loaded HFBSCs showed adequate neuronal differentiation potential *in-vitro*. Bioluminescence of the lesioned brain resulted in survival of HFBSCs and magnetic resonance imaging identified their localization in the area of transplantation, which supports their potential use for cell-based therapy for TBI (Timo Schomann et al., 2020).

HOMOGENEOUS DIFFERENTIATION OF HEPATOCYTE-LIKE CELLS FROM ESC's: APPLICATION FOR THE TREATMENT OF LIVER FAILURE

Almost 2% of the weight of an adult is accounted by the liver, which is the largest internal organ in the body. Loss of liver function causes 25,000 deaths a year and is one of the leading causes of death in the United States (Popovic et al., 2000). The only known treatment for liver failure is orthotopic liver transplantation. Unfortunately, this modality is limited by the shortage of available donor organs (Yarmush et al., 1992). Alternatively possible treatments to liver failure include hepatocyte transplantation (Fox et al., 1998) (Strom et al., 1997) transplanted tissue engineered liver (Demetriou et al., 1986) (Fontaine et al., 1995) and extracorporeal bioartificial liver (BAL) device (Chan et al., 2004) (Demetriou et al., 2004). However, the low availability of functional human hepatocytes severely limits these possible therapies. Hence, the generation of a hepatic progenitor cell, with the ability to rapidly increase *in vitro* while retaining liver-specific function, is a major goal of the field (Discussed in Table: 2).

Till date, the differentiation of ES cells toward the hepatic phenotype has resulted in mixed cell populations and low yields in the range of 10–50%. One alternative perspective for the differentiation of ES cells along the hepatic lineage is to expose them to cues from the liver. Final development of the hepatic progenitors happen when hepatic cords collaborate with the mesenchymal cells of the septum transversum, forming the liver sinusoids while expressing albumin and urea (Zaret et al., 2001). A similar path of differentiation happen during culture of embryoid bodies (EB), which is the most customary method of ES cell differentiation (Hamazaki et al., 2001). Conventionally the early cell populations that appear during inceptive ES cell differentiation comprise of neuroectoderm, mesoderm, definitive endoderm, and extraembryonic endoderm. In an effort to produce a homogeneous cell population, various groups have studied endoderm differentiation in monolayer culture thereby exposing the ES cells to uniform cues from their microenvironment Tada et al., 2005 have shown the existence of mesendodermal precursors in these cultures as well as the importance of collagen type IV to persuade endoderm with a yield of up to 50%.

The production of a hepatic progenitor cell population could lead to a variety of new products. In theory, a committed progenitor, such as a hepatic progenitor cell could be generated from the endoderm and used for cell therapies to treat acute or chronic liver failure as well as for further maturation and confinement within a tissue-engineered extracorporeal BAL device. Similarly, new generations of other cellular products and tissue-engineered products could be designed using an ESC-derived endodermal cell.

Table 2: Hepatocyte-like cells from ESC's: Application for the treatment of liver failure.

Applications	References
The study carried out by Keller et al., 1995 Odorico et al., 2001 Park et al., 2007 stated -Embryonic Stem (ES) cells are considered a potential source of cells for hepatic therapies due to their limitless capacity for self-renewal and proliferation, and their ability to differentiate into all major cell lineages.	(Keller et al., 1995) (Odorico et al., 2001) (Park et al., 2007)
The study carried out by Chinzei et al., 2002 Asahina et al., 2004 Jones et al., 2002 Miyashita et al., 2002 Novik et al., 2006 stated- that Embryonic Stem Cells cultured as Embryoid Bodies (EBs) differentiate spontaneously into hepatocyte-like cells.	(Chinzei et al., 2002) (Asahina et al., 2004) (Jones et al., 2002) (Miyashita et al., 2002) (Novik et al., 2006)
The study carried out by Shirahashi et al., 2004 Hamazaki et al., 2001 Rambhatla et al., 2003 Sharma et al., 2006 Maguire et al., 2006 Davidovich et al., 2006 had stated that- Efforts to induce a higher rate of differentiation toward the hepatic phenotype have shown limited success. These included various media and matrix combinations, essential growth factors, compounds such as sodium butyrate, or encapsulation-based systems.	(Shirahashi et al., 2004) (Hamazaki et al., 2001) (Rambhatla et al., 2003) (Sharma et al., 2006) (Maguire et al., 2006) (Davidovich et al., 2006).

STEM CELLS IN DENTISTRY: POTENTIAL APPLICATIONS AND PERSPECTIVES IN CLINICAL RESEARCH

Dental stem cells, one of the newest stem cells found in the MSC repertoire, appear to have enormous potential in terms of development, differentiation, regeneration, and immunoregulatory/immunomodulatory properties. Since their discovery, much development has been made in research and advancement towards clinical applications, highlighting the importance of this intriguing stem cell source. Using stem cells various clinical applications in dentistry can proceed to new heights by tapping on the conventional knowledge obtained on the origin of tooth development and bridging the missing gaps in biological understanding of dental stem cells. As such high throughput technologies at levels of genomics, transcriptomics, metabolomics, epigenetics, and proteomics can indisputably contribute to translational research and eventually lead to successful clinical applications. It is highly expected that deeper understanding of the regeneration potential of oral/dental tissues and stem cells would likely result in a paradigm shift in the therapeutic approaches in dentistry.

Dental Stem Cell Biology

The presence of stem cells in dental pulp tissues (DPSCs) first report was made by Yamamura in the year 1985 (Yamamura 1985). Although, the major setback in dental history was in 2000 when Gronthos (Gronthos S et al., 2002) and his team identified an isolated odontogenic progenitor population from adult dental pulp, which had the ability to regenerate a dentin-pulp-like complex (Gronthos et al., 2002; Karamzadeh and Eslaminejad 2013). However, frequent studies further isolated stem cell like populations from various other dental tissue sources, which include stem cells from human exfoliated deciduous teeth (SHED) (Miura et al., 2003); alveolar bone derived mesenchymal stem cells (Matsubara et al., 2005) (Kemoun et al., 2007); tooth germ progenitor cells (Ikeda et al., 2008), and stem cell from gingiva (GSCs) (Zhang et al., 2009). All these stem cell sources are easily accessible through no or minimally presumptuous procedure, and can be derived from both young and adult patients.

Dental Stem Cells as a Promising Source for Cell Therapy

Growing attentiveness in the field of stem cell applications originate from the potentiality to control their fate and consequently their functions during tissue repair and/or regeneration (Mitsiadis and Graf 2009). For any therapeutic implication surrounding cell based therapies, selecting a suitable cell source and knowledge on their microenvironment/niche is a pre-

requisite. Thus, any cells that can provide the systematic framework for new cellular differentiation and tissue growth might be considered as an ideal cell choice as long as they are guided by suitable signals and growth factors from their microenvironment (Srijaya et al., 2012). Further maneuver for facilitating tissue regeneration and growth can be made through formation of new vasculature and scaffolds made of biomaterials or matrix proteins to model and create three-dimensional structures (Srijaya et al., 2012).

The therapeutic approaches in dental-derived stem cell-based therapy under in-vivo & *in-vitro* models include ectopic dentin & associated pulp tissue, odontoblast, pancreatic cells, adipocytes, creation of root/periodontal complex, regeneration of peridontium, whole-pulp regeneration, improved muscular dystrophy, improvement of inflammation, acute myocardial infarction, etc.,

FUTURE PERSPECTIVE

The remarkable progress in the field of stem cells research constitute great opportunity of stem cells regenerative therapeutics. In the near future, there might be new pharmaceutical compounds; those can activate tissue specific stem cells, encourage stem cells to migrate to the side of tissue injury, and encourage their differentiation to tissue specific cells. Except few countries, the ongoing financial and ethical impediment on ESCs application in regenerative medicine have more chance for funding agencies to distribute funding for the least risky projects on UCSCs, BMSCs, and TSPSCs from biopsies. The existing stem cells therapeutics advancements are more experimental and high in cost; due to that application on extensive scale is not practicable in current scenario. In the coming future, the advancements of medical science expect using of stem cells to treat cancer, muscles damage, autoimmune disease, and spinal cord injuries among a number of impairments, injury, deficiency and diseases. It is assumed that stem cells therapies will bring considerable benefits to the patients suffering from wide range of injuries, defects and disease. There is high optimism for use of ESCs, MSCs, BMSCs, TSPSCs, and iPSCs for treatment of various diseases to overcome the contradictions & confutation related with ESCs. For development of translational application of stem cells, there is a need of clinical trials, which needs funding rejoinder from both public and private organizations. The crucial assessment of regulatory guidelines at each phase of clinical trial is needed to understand the success and efficacy in time frame. The prospective of Dental Stem Cells (DSCs) is mainly regarding the regeneration of damaged dentin and pulp or the repair of any perforations; in the coming future, it appears to be even possible to

generate the whole tooth. Such an enormous success would lead to the gradual replacement of implant treatments (Friedlander LT et al., 2009).

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