General Idea About the Reach of Stem Cell Regenerative Medicine: Evidence Based Review

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ABSTRACT

The use of Stem cells regenerative Medicine in the treatment of variety of disease is an innovation in the field of medicine. Therapeutic effect of MSCs can be clearly seen from wide range of studies. And this therapy can improve outcomes in case of damaged tissue or diseased tissue. The need of stem cell regenerative medicine increased because there is huge gap between demand of donated organs and needy patients who suffered from severe illness. This review outlines the, types of stem cells and their source, several innovative applications of SCRM for the treatment of disease, role of SCRM in orthopedics, role of micro - RNA, Glycans in the regulation of stem cells, Route of Administration &potential application of SCRM.

Key words: Stem cell regenerative medicine, Application of stem cells, Mesenchymal stem cells

INTRODUCTION

Stem cells are simply defined as cells following 2 basic criteria. First, stem cells have self-renewal property throughout their life i.e. the cells divide to produce identical daughter cells and so maintain stem cell population. Second, stem cells have potential to undergo differentiation to become specialised progeny cells [1]. Stem Cell Regenerative Medicine (SCRM) is the fastest growing, the most recent & emerging branch of medicine, which deals with restoration of organ function of the patient suffering from severe injuries or chronic disease, where body’s own regenerative capability is not sufficient for proper healing [2]. SCRM is regeneration of human cells, tissues, or organs to restore the normal health of patient by using growth factors to intensify the healing potential [2,3]. Additionally, in bones and joints disorders, even after arthroplasty, hardware implants can’t work as like our original joints. Simultaneously there is no method or approach ideal for fixation for all kind of pilon fractures or we can say that every method has its own complications like nerve injury, wound complications, hardware irritation, non-Union, malunion etc. In this case SCRM can provide a definitive treatment in wide variety of bone disorders [4-6].

In cervical disc degeneration disease (CDDD), spine surgeons commonly perform Anterior Cervical Discectomy and Fusion (ACDF), on the other hand, Artificial cervical disc Replacement (ACDR) Techniques is increasingly used by spine surgeons in order to decrease onset of Adjacent Segment Degeneration (ASD*). ACDR is a...
Double Edged Sword 'with potential drawbacks and motion sparing benefits [7].

In regenerative medicine, Mesenchymal stem cells have immunomodulatory functions and ability to differentiate into cartilage, hence are considered as potential and ideal source for Intervertebral Disc Regeneration [8].

In recent scenario, donated tissues and organs are on high demands for chronically ill and aged population and unfortunately this huge demand cannot meet the need, hence this demand is real driving for searching other options. Stem cells have for indefinite potential for cell division, can differentiate into other sort of cells, and have emerged as leading entity for treatment of age associated diseases, healing in non-Union case and reparation of congenital defects [1]. Onset of disease such as Paget’s disease, osteoarthritis, rheumatoid arthritis, osteogenesis imperfecti and osteoporosis happens only when there is an imbalance between bone and cartilage resorption and formation [9,10]. Osteoporosis is the most common type of musculoskeletal disorder which is also known as primary osteoporosis. Primary osteoporosis occurs mainly because of differentiation of a osteoblast or macrophage in to a osteoclast, it leads to deterioration of bone mass with advancing old age [11,12]. It is believed that osteoclastic bone resorption is regulated by RANK L/ osteoprotegerin (OPG)/RANK pathway, while osteoclastic activity controlled by canonical or Wnt/Beta-catenin signalling pathway (13-15). Vitamin D, calcium supplements, Teriparatide (recombinant human 1-34 amino acid sequence of parathyroid hormone), Hormone Replacement Therapy (HRT) Selective Estrogen Receptor Modulator(SERM), RANK legand inhibitors & strontium ranelate are the main therapeutic strategies used but at the same time the issue of side effects and safety need to be kept in mind [16]. Additionally, Gender, obesity, genetic predisposition, inflammation, stress, Tobacco smoking, nutritional status, lifestyle, and physical activity are multiple risk factors for osteoporosis [17].

Stem cell regenerative medicine for osteoporosis could potentially reduce the incidence of fracture and restore the lost mineral density by either increasing numbers or restoring the function of resident stem cell that can proliferate and differentiate into bone forming cells. This osteoporosis therapies can be administered by exogenous introduction of stem cells derived from adipose tissues, bind marrow, umbilical cord blood tissues. The main problem in the way of stem cell base osteoporosis therapy is the uncertainty of stem cell fate [18].

Stem cells can be manipulated in vitro for correction of genetic aberrations by using viral vector transduction. When such stem cells transplanted into the patients, might restore the normal function. A fundamental risk of neoplastic transformation of individual transduced clones is there because the sites of viral vector insertion varies in distribution [19]. However, these risks may be minimised/avoided by adopting safe design of viral vectors and second option is to pursue preclinical evaluation of these clones in animals [20].

**Micro RNAs and regulation of stem cells**

Hristo, et al. identified micro RNAs (mi RNAs) in differentiated and undifferentiated mouse embryonic stem (ES) cells, their results suggest that mi RNA may play a role in maintaining pluripotent cell state and in the regulation of early development [21]. The characteristic features of a stem cell are its self - renewal and to give origin to numerous differentiated cells. This unique virtue is controlled by a powerful and reciprocal interaction between extrinsic signalling, epigenetic, transcriptional & post-transcriptional regulations. Micro RNA (mi RNA) plays a key role in regulating stem cell renewal & differentiation [22].

Embryonic stem cells [ES] and Tissue stem cells (or Adult stem cells) mediate tissue development and homeostasis [23]. Inner cell mass blastocyst - stage embryo give rise to ES and fetus; in this process they generate progenitor cells &tissue stem cells, progenitor cells and ultimately each and every cell type of an organism. Both tissue stem cell and embryonic stem cells are capable of producing differentiated cells and replicating themselves. Self replication is hallmark feature of stem cells, this feature in tissue stem cell is achieved by a special pattern of asymmetric divisions. During this asymmetric division,two daughter cells are generated, out of which, one daughter cell retains self-renewal property while another daughter cell is committed to specialised function [24]. Self-renewal division of stem cell is controlled by both intercellular and intracellular mechanisms [25]. Inter cellular mechanisms
consist of signalling from neighbouring niche cells, whereas intracellular mechanisms consist of differential gene expressions that is controlled at epigenetic, transcription, translational & post-translational levels. Micro-RNAs have emerged as Key controller in translation regulation, stem cell fate and behaviour [26].

**Glycans in stem cell regulation**

There are various kinds of glycans regulate stem cell status, structure of many of them evolutionarily conserved from Drosophila to mammals. Cell surface glycans are tissue specific and regulated developmentally, play essential role as a modulators in ligand - receptor interactions, binding to many signal ligands including Wnt, Hedgehog, epidermal growth factor, fibroblast growth factor, bone morphogenetic proteins and in cell - cell interactions and cell-extra cellular interactions. These signals play essential role for stemness and differentiation of different kinds of stem cells. Additionally, the intercellular O-linked N-acetylglucosamine found only on cytoplasmic or nuclear proteins, regulates core transcription factors of stemness and phosphorylation of downstream signal components [27].

**Types of stem cells**

Based on trans differentiation potential, stem cells can be divided in to 4 types 1. Unipotent 2. Multipotent 3. Pluripotent 4. Totipotent [28].

**Sources of stem cell**

There are several methods for obtaining human embryonic stem cells [hES] and other Multipotent or pluripotent cells. These method are reprogramming somatic cells, arrested embryos, somatic cell nuclear transfer, single cell embryo biopsy, altered nuclear transfer [29].

**Amniotic fluid derived stem cells [AFS]**

Isolated amniotic fluid - derived [AFS] stem cell presents a tremendous possibility in the field of SCRM. AFS cells are Multipotent, showing ability to differentiate in to all three embryonic germinal layer cells. They express both embryonic and adult stem cell markers, expand massively without feeder cells, double in 36 hours and are without any tumorigenic potential. They differentiate easily into specific cell lineage and can be easily isolated without human embryo tissue, that is why avoiding the controversy concerned with use of human embryonic stem [ES] cells [30].

**Placenta- derived stem cells [p-SC]**

Placenta is a potential source if stem cells. Placenta- derived stem cells [p-SC] are having the characteristic of both embryonic and mesenchymal stem cells ie. they are non-carcinogenic, and characteristic of differentiating into all embryonic germ layers. Basically feral membranes are source of placenta derived stem cells, many preclinical have been done to assess the potential of p-SC worth in different streams of medicine, such as cardiology, neurology, orthopedics, gastroenterology, etc showing promising outcomes, but with some drawbacks [31].

**Retinal stem cells [RSC]**

Retinal stem cells are rare variety of pigmented cell stem cells have been identified in adult mouse eye. Tropept, et al. reported the identification of stem cell in the adult mouse eye, which shows the possibility of retinal regeneration, though mature mammalian retina is regarded lacking regeneration potential. Single pigmented ciliary margin cells can proliferate in vitro to produce sphere colonies of cells that can differentiate into retina specialised cells such as Müller glia, bipolar neurons, photoreceptors rods [32].

**Human Embryonic Stem Cells [HESC]**

Embryonic stem cells are pluripotent cells that are capable of differentiating in to about all type of cells, including glial and neuronal fate cells [33]. Hence these cells are differentiated oligodendrocytes and motor-neurons [34,35] and possibly used for the treatment of neurodisorders, trauma and spinal cord injury, lumbar disc degeneration disorder, cervical disc degeneration disorder, spinal cord injury [SCI] because of tumors, violence (war wounds, stab wound and gunshot wound), multiple sclerosis, SCI in fall from height. Human embryonic stem cells treatment showed significant improvement in sitting balance, control and sensation of bowel and bladder, coordination & power of lower and upper limb movements in five paraplegic or quadriplegic patients but without any adverse effect [36].

Sources of stem cells are bone marrow, periosteum, placenta, adipose tissue, umbilical cord, human amniotic fluid, synovial tissue, dental pulp, skin, adipose tissue and skeletal muscles. Among above sources mentioned, bone marrow, adipose tissue and muscle derived mesenchymal stem cells are most commonly used, because they can be obtained easily and available in ample quantity too [37].
Route of administration
Stem cells can be directly applicable to the lesion sites either via local injections or through surgical procedures with appropriate carriers. Mesenchymal cells [MSCs] may be taken via initial surgical procedures with appropriate carriers. These mesenchymal cells have capability to migrate to the desired tissue or organ, the same quality has been used to treat the disease like Osteogenesis Imperfecti [38] and several other diseases, details are mentioned in table 1. (Table 1).

Risks
There are several factors play role in long term outcomes of stem cell regenerative medicine. The epigenetic and genomic of cell lines that have been manipulated in vitro prior...
to transplantation play an important role in the clinical application of stem cell therapy. Additionally, the use of Embryonic stem cells [ESCs] raises ethical and social issues, because of which, many federal funding were stopped and that hampered the progress of stem cell therapy research [73]. Rest all the risk factors associated with stem cell regenerative medicine [SCRM] mentioned in [74].

**Future perspectives**

Implementation of Artificial Intelligence in several branches of medicine is well known, as it can change several important decisions in clinical settings. Innovative gene therapy and stem cell therapy in pediatric patient could also be optimized with integration of AI techniques. Hopefully, AI techniques may minimize the risk associated with Stem Cell Regenerative Medicine [75,76]. Several studies tried to contribute to the definitive treatment of Polycystic Ovarian Syndrome [PCOS], but there is no effective treatment as of now. PCOS is a multi-headed monster with increased risk of obesity, type II Diabetes mellitus, cancer, infertility, Obstructive Sleep Apnea [OSA], Hirsutism, Metabolic syndrome, and psychological disorders [77]. Qi Xie, et al. Concluded that Human umbilical cord - derived MSCs [HUC-MSCs] treatment significantly improved ovarian and uterine pathological changes of PCOS mice [78].

**CONCLUSION**

Stem cell regenerative medicine [SCRM] is a unique branch of medicine with huge therapeutic potential. Therapeutic potential of stem cells to regenerate the damaged tissue and enhance the body's natural healing power. But at the same time, SCRM has its own risks and drawbacks as mentioned above. More clinical studies over a longer time are needed to evaluate the benefits and drawbacks of SCRM.

**ABBREVIATIONS**

RANKL: Receptor Activator of Nuclear Factor Kappa-B-Ligand.
OPG: Osteoprotegerin.
SCRM: Stem Cell Regenerative Medicine.
SERM: Selective Estrogen Receptor Modulator.
ES: Embryonic Stem Cell.
mRNA: micro RNA
GVHD: Graft Versus Host Disease.
BMMSC: Bone Marrow Derived Mesenchymal Stem Cells.
ADSC: Adipose Derived Stem Cell.
e-CSC: Early Chorionic Stem Cell.
A1AD: Alpha-1 antitrypsin deficiency
COPD: Chronic Obstructive Pulmonary Disease.
IPSC: Induced Pluripotent Stem Cells.
CDDD: Cervical Disc Degenerative Disease.
ACDF: Anterior Cervical Discectomy and Fusion.
ASD*: Adjacent Segment Degeneration.
OPG: Osteoprotegerin.
SERM: Selective Estrogen Receptor Modulator.
ES: Embryonic Stem Cell.
P-SC: Placenta Derived Stem Cells.
RSC: Retinal Stem Cells.
HESC: Human Embryonic Stem Cells.
SCI: Spinal Cord Injury.
MSC: Mesenchymal Cells.
ADSC: Adipose Derived Stem Cells.
MI: Myocardial Infarction.
PEG: Polyethylene Glycol.
MABs: Monoclonal Antibodies.
IVDD: Intervertebral Disc Degeneration Disease
hES: Human Embryonic Stem Cells.
AFS: Amniotic Fluid Derived Stem Cells.
IPCs: Induced Pluripotent Cells.
IESCs: Induced Epithelial Stem Cells.
UCSCs: Umbilical Cord Stem Cells.
DPSCs: Dental Pulp Stem Cells.
PPCs: Pancreatic Progenitor Cells.
ESCs: Embryonic Stem Cells.
ARMD: Age Related Macular Degeneration.
BD- MSCs: Bone Marrow Derived Mesenchymal Stem Cells.
EMSCs: Early Mesenchymal Stem Cells.
AFSCs: Amniotic Fluid Stem Cells.
WJ-SCs: Wharton’s Jelly Mesenchymal Stem Cells.
SCRM: Stem Cell Regenerative Medicine.
T1DM: Type 1 Diabetes Mellitus.
T2DM: Type 2 Diabetes Mellitus.
AD: Alzheimer’s Disease.
ALD: Adrenoleukodystrophy.
MLD: Metachromatic Leukodystrophy.
ALS: Amyotrophic Lateral Sclerosis.
TBI: Traumatic Brain Injury.
ASD: Autism Spectrum Disorder.
MI: Myocardial Infarction.
AI: Artificial Intelligence.
PCOS: Polycystic Ovarian Syndrome.
HUC- MSCs: Human Umbilical Cord-Mesenchymal Stem Cells.

REFERENCES


