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A Review of Stem Cells in Regenerative Medicine

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ABSTRACT

Regenerative Medicine encompasses many fields of science and medicine. The efficiency of regenerative medicine can be ameliorated by improving the biological performances of stem cells before their transplantation. Stem cells have a capacity for self-renewal and capability of proliferation and differentiation to various cell lineages. They can be classified into embryonic stem cells (ESC) and non-embryonic stem cells (non-ESC). Mesenchymal stem cells (MSC) show great promise in several animal studies and clinical trials. ESCs have a great potential but their use is still limited due to ethical and scientific considerations. The use of amniotic fluid derived cells, umbilical cord cells, fat and skin tissues and monocytes might be an adequate "ethically pure" alternative in future. Stem cells can improve healthcare by using and augmenting the body's own regenerative potential. This article reviews focused on stem cells, properties of stem cells, Stem cell sources, stem cells in therapeutic strategies for tissue repair.
Keywords: Regenerative Medicine, Stem cell, Totipotency, Retinal regeneration, Umbilical cord.

I. INTRODUCTION

Regenerative Medicine is a comprehensive term used to describe the current methods and research employed to revive or replace dead or damaged tissue. Regenerative medicine aims at helping the body to form new functional tissue to replace lost or defective ones. Human body has an endogenous system of regeneration through stem cells, where stem cells are found almost in every type of tissue. The idea is that restoration of function is best accomplished by these cells. Regenerative medicine comprises the use of tissue engineering and stem cell technology [1]. The most interest to patients and scientists is the role stem cells will play in Cell-Based Therapy. These therapies will apply the understanding of stem cell development, differentiation, and maintenance to generate new, healthy tissue for diseases needing transplant or replacement of damaged tissue, such as arthritis, Parkinson's disease, type 1 diabetes, and coronary disease [2]. This review is not meant to be exhaustive, but aims to highlight present and future applications of stem cells in this exciting new discipline.

II. STEM CELL

Stem cells are biological cells found in all multicellular organisms, that can divide and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. Stem cell biology has become an important topic in regenerative tissue engineering, specifically the use of multipotent mesenchymal stem cells (MSCs) [3]. Although embryonic stem cells are considered the gold standard in stem cell research, bone-marrow derived mesenchymal stem cells (BM-MSCs) are the most researched postnatal stem cells. Multipotent postnatal stem cells have been isolated from numerous tissues throughout the body such as bone marrow, adipose tissue, muscle, dental tissue, umbilical cord, etc. These stem cells are capable of differentiating into a variety of cell lineages, including bone. Therefore, transplanting a patient's own stem cells may be a potential treatment for repairing bone defects [1].

History of Stem Cells:
In early 1960s, Ernest A. McCulloch and James E. Till started several experiments leading to the discovery of stem cells. They injected bone marrow cells into irradiated mice, nodules developed in the spleens in proportion to the number of bone marrow cells injected. They concluded that each nodule arose from a single marrow cell. Later on, they obtained evidence that these cells were capable of infinite self-renewal, a central characteristic of stem cells [4]. Thus, stem cells by definition have two defining properties the capacity of self-renewal giving rise to more stem cells and to

differentiate into different lineages under appropriate conditions. There are two main types of stem cells, embryonic and non-embryonic. Embryonic stem cells (ESC) are pluripotent and they can differentiate into all germ layers. Non-embryonic stem cells (non-ESC) are multipotent. Their potential to differentiate into different cell types seems to be more limited [5]. The capability for potency and the relative ease to isolate and expand these cells are invaluable properties for regenerative medicine.

Stem Cell Niche:

A niche consists of signalling molecules, inter-cellular contact, and the interaction between stem cells and their neighbouring extracellular matrix (ECM). This three-dimensional (3D) microenvironment is thought to control genes and properties that define "stemness". Its self-renewal and development to committed cells [6]. Stem cells might be appropriately differentiated cells with the potential to display diverse cell types depending on the host niche. Stem cells implanted into a totally different niche can potentially differentiate into cell types of the new environment. For example, human neuronal stem cells produced muscle cells when they were implanted in skeletal muscle. Bone marrow cells differentiated into neuronal cells when they were transplanted into a neural environment [7]. These finding show possible niche influence and ASC plasticity, which is the ability to dedifferentiate into cells from other lineages. This can have clinical implications for example since both liver and pancreas develop from the same embryological line, specific growth factors and culture techniques achieved the "transdifferentiation" of liver cells to islet cells.

Properties of Stem Cell:

The classical definition of a stem cell requires that it possess two properties: Self renewal and Potency [8].

Self-Renewal:

Self-renewal is the ability to go through numerous cycles of cell division while maintaining the undifferentiated state. Two mechanisms exist to ensure that a stem cell population is maintained: Obligatory asymmetric replication: a stem cell divides into one father cell that is identical to the original stem cell, and another daughter cell that is differentiated. Stochastic differentiation: when one stem cell develops into two differentiated daughter cells, another stem cell undergoes mitosis and produces two stem cells identical to the original [9].

Potency:

Potency is the capacity to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either totipotent or pluripotent to be able to give rise to any mature cell type, although multipotent or unipotent progenitor cells are sometimes referred to as stem cells. Apart from this it is said that stem cell function is regulated in a feedback mechanism. Potency specifies the differentiation potential of the stem cell [10].

Totipotent **Stem Cells** can differentiate into embryonic and extra embryonic cell types. Such cells can construct a complete, viable organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent [11].

Pluripotent **stem cells** are the descendants of totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers [12].

Multipotent **Stem Cells** can differentiate into a number of cells, but only those of a closely related family of cells [10].

Oligopotent **Stem Cells** can differentiate into only a few cells, such as lymphoid or myeloid stem cells [10].

Unipotent **cells** can produce only one cell type, their own, but have the property of self-renewal, which distinguishes them from non-stem cells (e.g., muscle stem cells)[10].

Stem Cells are Unspecialized:

One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. A stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell). It cannot carry molecules of oxygen through the bloodstream (like a red blood cell) and it cannot fire electrochemical signals to other cells that allow the body to move or speak (like a nerve cell).

However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells [8].

III. STEM CELLS USED IN REGENERATIVE MEDICINE

Embryonic stem cells:

Embryonic stem (ES) cell lines are cultures of cells derived from the epiblast tissue of the inner cell mass (ICM) of a blastocyst or earlier morula stage embryos. At fertilization, a zygote is formed that contains totipotent cells which are cells with the ability to form any of the 200+ cell types in the body and the cells of the placenta. After four days (about 40-150 cells), the blastocyst develops. The blastocyst is identifiable by the development of the outer trophoblastic layer and inner cell mass (ICM). The outer layer of cells becomes the placenta and other tissues necessary for fetal development and survival. The inner cell mass forms the fetus and contains pluripotent cells that go on to form all the tissues in the human body [13].

The use of pluripotent embryonic stem cells in regenerative therapies is an attractive option with the ability to give rise to tissues from the three germ layers, including the mesodermal lineages such as bone. Both totipotent and pluripotent (blastocyst) embryonic stem cells (ESCs) are considered the gold standard in stem cells. Because of their combined abilities of unlimited expansion and pluripotency, embryonic stem cells remain a theoretically potential source for regenerative medicine and tissue replacement after injury or disease [14].

Non-Embryonic Stem Cells:
Non-ESCs are probably lower in the stem cell hierarchy. They are thought to have lost the pluripotent capability. However, throughout the organism's life, they maintain a multipotent differentiation potential. Non-ESCs can be derived from several sources including amniotic fluid, umbilical cord tissue and bone marrow.

Fetal stem cells:
The primitive stem cells located in the organs of fetuses are referred to as fetal stem cells. Fetal stem cells are cells obtained from an unborn fetus when the fetus has developed enough that cellular extraction does not cause fetal death. These cells are pluripotent and responsible for the development of all tissues before birth. Unlike ESCs, fetal stem cells can be obtained without completely destroying the embryo, allowing the fetus to develop into a full-term baby. However, the effect of removing cells during fetal development is unknown, and fetal stem cells have many of the same ethical considerations as ESCs. These pluripotent cells can undergo osteogenic differentiation, making them a valid source for regenerative bone tissue engineering [15].

Bone marrow-derived mesenchymal stem cells (BM-MSCs):

BM-MSCs are a heterogeneous population of multipotent cells. BM-MSCs are capable of differentiating into multiple lineages in vitro including the osteogenic lineage. BM-MSCs are a popular source of autologous adult stem cells, because they are readily available. However, the extraction procedure is extremely painful and invasive. In addition to their differentiation potential, BM-MSCs can be used directly to positively influence the repair mechanism and healing of cardiac tissue following a myocardial infarction [16]. Impressively, this is accomplished with BM-MSCs from living donor tissue, and the BM-MSCs inherent immunogenic characteristics limit the recipient's immune response to the foreign cells. This makes BM-MSCs a great source for regenerative tissue engineering applications, because they can be extracted, expanded, and banked, making them readily available when they are needed[17].

Umbilical cord blood stem cells:

Umbilical cord blood (UCB) stem cells are cells found in the umbilical cord blood of a newborn baby, and they share the newborn's genetic material. UCB cells can be obtained with higher cell yields and without the pain and morbidity associated with BM-MSC acquisition. These cells are multipotent, hematopoietic stem cells and can differentiate into various cell lines including the osteogenic lineage. In addition to their differentiation potential, UCB cells can be used directly to successfully treat leukemia, lymphoma, myelodysplasia, apalstic anemia, hemoglobinpathies, metabolic diseases, and immunodeficiencies [18].

Stem cells from dental tissues:

Physiological similarities between dental-tissue and bone make dental-derived progenitor cells a logical source of stem cells for osteogenic differentiation. Cells from dental tissues are called ectomesenchyme cells, because they are remnant tissues derived from the cranial neural crest. Cranial neural crest cells are capable of differentiating into bone, cartilage, and ligament during embryonic development; therefore, cells derived from them possess similar abilities [19].

Stem cells from human exfoliated deciduous teeth:

SHED (stem cells from human exfoliated deciduous teeth) are multipotent stem cells isolated from the remnant pulp of deciduous (baby) teeth. Similar to the umbilical cord, deciduous teeth offer the opportunity for painlessly obtaining primordial cells that would otherwise have been thrown away. SHED proliferate faster than BM-MSCs, can undergo osteogenic differentiation, and express ESC markers. Furthermore, SHED appears to have osteoinductive properties, meaning they induce new bone formation by recruiting osteogenic host cells into an osteoinductive template [20].

Periodontal ligament stem cells:

Heterogeneous populations of multipotent stem cells (PDLSCs) have also been extracted from the periodontal ligament, a descendant of the cranial neural crest. PDLs express several ESC markers and have an upregulated telomerase activity, suggesting similar differentiation abilities to ESCs. Similar to other dental tissues, PDLSCs are capable of undergoing osteogenic differentiation and express osteogenic characteristics. Furthermore, PDLSCs that are implanted in periodontal injuries regenerated a periodontal ligament-like tissue while aiding in the bone regeneration itself. This suggests that they would be a viable source for regenerative bone tissue engineering [21].

Adipose tissue-derived stem cells:

Adipose tissue-derived stem cells (ASCs) are multipotent cells located in fat that can differentiate into various cell lines including the osteogenic lineage. ASCs can be isolated from the lipoaspirate usually discarded from liposuction treatments. ASCs have been shown to not only undergo osteogenesis, but have actually been used to heal critical-size defects in mice. Furthermore, ASCs promote angiogenesis (new blood vessel formation), which can be crucial for engineered scaffolds to properlyintegrate with native tissue [22].

Induced pluripotent:

There are many ethical issues surrounding ESCs, most notably their source and the debate of whether or not the method used for the isolation of ESCs is murder. These ethical dilemmas and political restrictions on ESC use led researchers to investigate methods of reverting differentiated somatic cells back into their primordial pluripotent state. These reverted cells are called induced pluripotent stem (iPS) cells. Frozen blood samples can be used as a source of induced pluripotent stem cells, opening a new avenue for obtaining the valued cells. iPS cells represent a unique source for pluripotent adult stem cells which can serve as a source for generating patient-specific tissue for regenerative tissue engineering applications, such as repairing bone defects [23].

Fat tissue derived stem cells:

Human adipose “fat” tissue can be a source of multipotent stem cells. These cells can be differentiated in vitro into various cell lines including osteogenic, chondrogenic and neurogenic lineages. Myocytes and cardiomyocytes were also successfully obtained from fat tissue derived stem cells [24]. Haematopoietic cells were derived using mouse adipose tissue derived stroma vascular fraction. These experiments showed a possible alternative source for cellular transplants and gave evidence of adipocyte cellular plasticity.

Fat tissue derived stem cells can be maintained in vitro for extended periods of time with stable population doublings and low senescence levels. Fat tissue is abundant, contains a large number of cells, and can easily be obtained with low morbidity at the harvest site [25]. However, further work needs to be done to elucidate all the potential differences between marrow and fat derived stem cells. Still, the use of fat cells opens numerous and promising perspectives in regenerative medicine – “fat is beautiful once again”.

Monocytes:

Blood monocytes have been shown to de-differentiate under specific culture conditions, into cells which can proliferate and then differentiate into different cells including endothelial, epithelial, neuronal, liver like cells producing albumin, islet like cells producing insulin and fat cells or return back to monocytes. It might be that a "side population" of stem cells exists within a monocyte population. The ability to obtain and differentiate these pluripotent cells from autologous peripheral blood makes them valuable candidates for regenerative medicine [26].

IV. REGENERATIVE MEDICINE APPLICATIONS

Researchers are exploring the use of cord blood stem cells in the following regenerative medicine applications:

BONE:

Bone defects due to congenital and acquired causes such as trauma, surgery and tumors may lead to extensive bone loss and defects which require transplantation of bone tissue or substitutes to restore structural integrity and function. The treatment of post-traumatic skeletal complications such as delayed unions, non-unions and malunions are challenging. The current "gold standard" is the use of autologous cancellous bone grafting. However, the supply of suitable bone is limited especially in osteoporotic, paediatric and oncological patients and its harvest results in additional morbidity to the donor site, leading to pain, haematoma, or infection [27]. Allogenic bone has been used but this has minimal osteoinductive capacity, is possibly immunogenic, has a potential for disease transmission and is minimally replaced by new bone. Bone grafting is not effective in all cases. These patients are the ones who urgently need an improved alternative therapy. Most of the experimental and clinical evidence to date is supportive of the efficacy of MSCs in enhancing bone formation and healing of bone defects. This was proven by subcutaneous implantation in small animal models in mice and in small experimental osseous defects. Large animal models showed that the treatment of large bone defects with the application of MSCs on an osteoconductive carrier can be used successfully [28]. Thus, experimental data in the field are strong enough to envisage translation to the clinic.

Bone Defects:

Quarto et al. used a graft of hydroxyappatite and MSCs stabilized by external fixation in three patients to reconstruct 4 to 7 cm long bone defects with satisfactory incorporation and bone formation [29]. These reports were successful since the constructs encompassed the fundamental principles of bone regeneration; osteogenesis, osteoinduction and osteoconduction along with final functional bonding between the host bone and substitute material which is called Bajada et al. Stem cells for regeneration In future more complex constructs should incorporate effective mechanical stimulation and better orchestration of neovascularisation.

Fracture non-union:

It is estimated that 10% of the fractures lead to non-union [30]. Even though this is a well known condition the pathogenesis is still a "mystery". A possible effective therapy is the use of MSCs to reactivate the fracture healing mechanism.

Osteogenesis imperfect:

Bone marrow derived MSCs might be effective for genetic disorders when injected systemically. This is due to the homing capability of these cells. These not only engraft to the host bone marrow but also to other multiple sites such as bone, cartilage, lung and spleen [31]. This novel therapy can be used for osteogenesis imperfecta (OI), currently an untreatable genetic disorder caused by defects in the major bone extracellular matrix structural protein, type I collagen. There are six types of OI, though the symptoms range from person to person. Type I is the most common and mildest form, followed by Type II, Type III and Type IV. Types V and VI have been more recently classified, and they share the same clinical features of IV, but each have unique histological findings. Horwitz et al. used allogenic bone marrow transplantation in three children suffering from the disorder. After three months the total bone mineral content increased, fracture rate decreased and trabecular bone showed new dense bone formation [32]. The authors concluded that this improvement is

possibly due to engraftment of transplant bone marrow derived MSCs, which generate osteoblast capable of secreting normal extracellular proteins.

Cartilage:

Articular cartilage is vulnerable to injury with a poor potential for regeneration leading to early degeneration and later arthritic changes. Even though joint arthroplasties have improved considerably over the last decade, cell based therapy to repair cartilage defects at an earlier stage is needed. Procedures using stem cells are available; 'Microfracture' introduced by Steadman et al. leads to penetration of subchondral bone. When the tourniquet is released, possible recruitment of stem cells from the underlying bone marrow leads to the formation of a "super clot". A report shows 11% of biopsies being predominantly hyaline cartilage and 17% a mixture of fibrocartilage and hyaline [33]. However, this technique is not adequate for large lesions and results are not always consistent. Another available therapy is autologous chondrocyte. This leads to an alternative cell based therapy for the treatment of chondral and osteochondral defects. In this technique differentiated chondrocytes are isolated from autologous non-weight bearing cartilage and expanded to millions of cells by tissue culture. The cells are then re-implanted into the defect under a periosteal or more recently under a biodegradable membrane. Even though, chondrocytes in two-dimensional cell cultures are known to alter their phenotype and dedifferentiate to fibroblast cells losing the ability for collagen II and proteoglycan formation clinical results at 11 years follow-up are rated as good or excellent in 84% of patients. Autologous matrix induced chondrogenesis (AMIC) is a novel therapy which uses a porcine collagen I/III matrix patch over a defect which has been microfractured. This patch is supposed to keep the "super clot" contents i.e. stem cells, protected in the early post-operative stage and thus accommodate chondrogenic differentiation [34].

When compared to ACI, AMIC avoids the need for time consuming and costly tissue culture while exploiting the stem cell potential from the subchondral bone. The main criticism for ACI is that it requires an invasive procedure to harvest chondrocytes from adjacent intact areas. MSCs are an alternative source of cells. These can be derived from several sources such as the bone marrow and fat. Utilising MSCs and directing them into chondrogenic differentiation might lead to the formation of higher quality cartilage, that is a larger composition of hyaline, adequate structural reorganization and thus better biomechanical properties. Wakitani et al. used successfully MSCs in a type I collagen gel to repair carpine chondral defects. This was translated successfully to clinical practice. Autologous bone marrow derived MSCs transplantation was used for the repair of full-thickness articular cartilage defects in the patellae of two patients. Wakitani et al. also reported on twelve patients suffering from knee osteoarthritis (OA) who received MSCs injected into cartilage defects of the medial femoral condyle at the time of high tibial osteotomy. These were then covered by periosteum. The control group underwent the same procedure but received no cells. Although the clinical improvement was not significantly different, MSCs treated patients had better arthroscopic and histological grading scores [35].

In the near future a novel approach for OA could be the use of MSCs to inhibit progression of the disease. In OA, it was found that stem cells are depleted and have reduced proliferation and differentiation capabilities. Thus, the systemic or local delivery of stem cells, thus, might augment the regenerative cell population and possibly induce repair or inhibit progression of the condition. Murphy et al. percutaneously injected MSCs suspended in sodium hyaluronan into a carpine OA model. It was shown that the MSCs stimulated regeneration of meniscal tissue with implanted MSCs detected in the regenerate. Degenerated cartilage, osteophytic remodelling, and subchondral sclerosis were reduced in the cell treated joints compared with the control [36]. These experiments implicate that MSCs hold exciting promise for regenerating meniscus and preventing OA. There is a group in Singapore that uses this procedure clinically with success.

Cardiac Muscle:

The discovery of an endogenous repair system questions the old paradigm that describes the heart as a post-mitotic organ and introduces the notion that cardiac regeneration can be regulated by stem cells. In fact dividing cells with large mitotic figures were found in cardiac muscle. However, their proportion is very low

(0.015-0.08%). The origin of these cells is uncertain. They can be endogenous, derived from the epicardium or even be extracardiac. The latter is suggested by investigations in sex-matched heart transplant patients were male patients who received female hearts showed cardiomyocyte biopsies carrying the Y chromosome [37]. This leads upto hypothesise that circulating stem cells are homing for regeneration.

Regenerating ischaemic heart disease can be achieved by delivering culture expanded MSCs into the coronary arteries or directly into the myocardium to expand the endogenous regenerative pool. Janssens et al.[38] reported the first randomised controlled trial of autologous bone marrow MSCs implantation for patients with ST-elevation myocardial infarction. Stem cell therapy provided significant reductions in myocardial infarct size and better recovery rates of regional systolic function after four months follow up. However, there was no significant benefit in terms of left ventricular ejection fraction, myocardial perfusion and cardiac metabolism. In addition, there is no evidence to date that MSCs produce contractile structures in the cardiac muscle following implantation. Despite these mixed results the use of stem cells is a promising option for treating patients with acute myocardial infarction.

Urinary Tissues – Bladder:

Urologists have always been faced with the problem of bladder replacement. Traditionally, this has been undertaken with intestinal segments. However, this involves complicated bowel resection and possible complications such as adhesions, mucus secretion, metabolic derangements and malignant transformation [39]. Thus, an adequate alternative is needed. Cell based regeneration of bioengineered bladder has been reported in several animal models. Atala et al. reported the first clinical trial of engineered bladders in seven patients with myelomeningocele suffering from high-pressure or poorly compliant bladders. Autologous urothelial and smooth muscle cells were cultured for six weeks, and then seeded on biodegradable 3D matrices made of collagen or a composite of collagen and polyglycolic acid (PGA). Thereafter, augmentation cystoplasty utilising the engineered construct was undertaken. Over a mean follow-up of almost four years all patients showed improved overall bladder function with no complications. The patients who had an omentum wrapped around the construct showed the best results [40]. Most probably, the omentum was a source of neovascularisation; a vital element in regenerative medicine. Bladder tissue engineering using MSCs might show better results than differentiate cells. MSCs were shown to migrate to the bladder grafts and differentiate into smooth muscle. These achieved fast repopulation of the grafts, exhibited appropriate neural function and showed less fibrosis. Utilising autologous bladder cells might be inadequate if bladder cancer is present [41]. Clinical application of bladder tissue engineering made important steps. However, more needs to be done for achieving the target of whole organ regeneration and transplantation in urology.

Spinal Cord:

Pluripotent cells have the ability to differentiate into neural tissue including neurons, astrocytes and oligodendrocytes. The presence of endogenous stem cells in the mammalian spinal cord, suggest an inherent capacity for regeneration [42]. Animal models showed axonal regeneration and functional recovery after spinal cord injury. Akiyama et al [43] found that MSCs can remyelinate spinal cord axons after direct injection into the lesion. Traumatic spinal cord injury (SCI) can lead to severe neurological damage. Even though endogenous stem cells are present, recovery from this injury is difficult. A strategy to increase axonal regeneration could involve transplantation of stem cells into the injured spinal cord.

1) Type 1 Diabetes

A clinical trial under way at the University of Florida is examining how an infusion of autologous cord blood stem cells into children with Type 1 diabetes will impact metabolic control over time, as compared to standard insulin treatments. Preliminary results demonstrate that an infusion of cord blood stem cell is safe and may provide some slowing of the loss of insulin production in children with type 1 diabetes [44].

2) Cardiovascular

The stem cells found in a newborn's umbilical cord blood are holding great promise in cardiovascular repair.

Researchers are noting several positive observations in pre-clinical animal studies. Thus far, in animal models of myocardial infarction, cord blood stem cells have shown the ability to selectively migrate to injured cardiac tissue, improve vascular function and blood flow at the site of injury, and improve overall heart function [45].

3) Central Nervous System

On May 17, 2012, Osiris Therapeutics announced that Canadian health regulators approved Prochymal, a drug for acute graft-versus-host disease in children who have failed to respond to steroid treatment. Prochymal is the first stem cell drug to be approved anywhere in the world for a systemic disease. Graft-versus-host disease, a potentially fatal complication from bone marrow transplant, involves the newly implanted cells attacking the patient's body [46].

Heparan Sulfate Analogues:

Heparan sulfates glycosylaminoglycans bind to the heparan sulfate binding domain of matrix proteins such as collagens and fibronectin on the extracellular matrix. Heparan sulfate consist of a chain of subunits of 85kD which is negatively charged and can therefore interact with the slightly positively charged basic amino acids of growth factors and cytokines, protecting and holding them in the process. In any wound area heparan sulfates are degraded by glycanases and heparanases. This disrupts the normal tissue homeostasis because the different growth factors and cytokines cannot be held and protected by the heparan sulfate.Heparan sulfate analogue is a synthetic heparan sulfate mimetic [47]. Due to a different coupling of subunits it is resistant to enzymatic degradation: the β2-4 carbon-carbon binding of the subunits of heperan sulfate is prone to enzymatic cleavage whereas the α1-6 carbon-carbon binding of the subunits of heparan sulfate analogues are resistant to cleavage by all known glycanases and heparanases [48]. Heparan sulfate analogues have shown significant improvement on different kind of wounds in pre-clinical research. Animal research has shown that heparan sulfate analogues help the wounds heal but retain the normal tissue structure and prevent scarring [49].

Retinal Regeneration :

The retina has been called the "approachable part of the brain," owing to its relatively simple structure and its location near the body surface, and for these reasons it serves as a useful and experimentally amenable model of the central nervous system. Until very recently, it was thought that, in adult mammals, the retina was entirely incapable of regenerating [50], but we now know that at least new retinal neurons can be generated after being damaged. This has opened up new hope that the ability to regenerate neurons and even to reconstitute the neural network may be retained in the adult retina.

Opportunities and Goals for Regenerative Medicine in Developmental Biology:

- ✓ Understand mechanisms that underlie embryonic development, morphogenesis and regenerative capacity
- ✓ Identify mechanisms to restore regenerative capacity to differentiated or aged tissues in vivo
- ✓ Produce replacement cells or tissues in vitro for transplantation
- ✓ Permit modeling of human specific diseases or capabilities in vitro
- ✓ Move towards early intervention or new therapies for inherited developmental defects
- ✓ Enhance human organ functions, reverse effects of aging, increase strength in patients suffering from wasting disease, improve cognitive or immune system function

V. CONCLUSION

Stem cells are at the frontier in therapeutics as part of a multidisciplinary approach of cell therapy, gene therapy and regenerative medicine. The extraordinary research done with stem cells has come a long way, and practical utility of stem cells in clinical settings can only be realized through intensive and additional studies on all types of stem cells. It is important to be able to direct the differentiation of pure cell populations in large quantities and safety concerns must be met, as well. The hESCs should not cause teratomas or carcinomas when transplanted in vivo or immunologically rejected. To have ESCs available for research or clinical purposes, moral and bioethical aspects should be taken into

consideration. A great deal of basic research needs to be continued to explore the full potential of stem cells in regenerative medicine for efficient and effective ways to treat diseases.

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