



Stem cell-based regenerative medicine

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Abstract: Recent developments in the stem cell biology provided new hopes in treatment of diseases and disorders that yet cannot be treated. Stem cells have the potential to differentiate into various cell types in the body during age. These provide new cells for the body as it grows, and replace specialized cells that are damaged. Since mesenchymal stem cells (MSCs) can be easily harvested from the adipose tissue and can also be cultured and expanded *in vitro* they have become a good target for tissue regeneration. These cells have been widespread used for cell transplantation in animals and also for clinical trials in humans. The purpose of this review is to provide a summary of our current knowledge regarding the important and types of isolated stem cells from different sources of animal models such as horse, pig, goat, dog, rabbit, cat, rat, mice etc. In this regard, due to the widespread use and lot of attention of MSCs, in this review, we will elaborate on use of MSCs in veterinary medicine as well as in regenerative medicine. Based on the studies in this field, MSCs found wide application in treatment of diseases, such as heart failure, wound healing, tooth regeneration etc.

Keywords: Mesenchymal stem cells (MSCs); animal model; cell-based therapy; regenerative medicine

Received: 11 November 2018; Accepted: 17 March 2019; Published: 18 July 2019.

doi: 10.21037/sci.2019.06.04

View this article at: <http://dx.doi.org/10.21037/sci.2019.06.04>

Definition and history of stem cell

Stem cells are one of the main cells of the human body that have ability to grow more than 200 types of body cells (1). Stem cells, as non-specialized cells, can be transformed into highly specialized cells in the body (2). In the other words, Stem cells are undifferentiated cells with self-renewal potential, differentiation into several types of cells and excessive proliferation (3). In the past, it was believed that stem cells can only differentiate into mature cells of the same organ. Today, there are many evidences to show that stem cells can differentiate into the other types of cell as well as ectoderm, mesoderm and endoderm. The numbers of stem cells are different in the tissues such as bone marrow, liver, heart, kidney, and etc.

(3,4). Over the past 20 years, much attention has been paid to stem cell biology. Therefore, there was a profound increase in the understanding of its characteristics and the therapeutic potential for its application (5). Today, the utilization of these cells in experimental research and cell therapy represents in such disorders including hematological, skin regeneration and heart disease in both human and veterinary medicine (6). The history of stem cells dates back to the 1960s, when Friedenstein and colleagues isolated, cultured and differentiated to osteogenic cell lineage of bone marrow-derived cells from guinea pigs (7). This project created a new perspective on stem cell research. In the following, other researchers discovered that the bone marrow contains fibroblast-like cells with congenic potential *in vitro*, which were

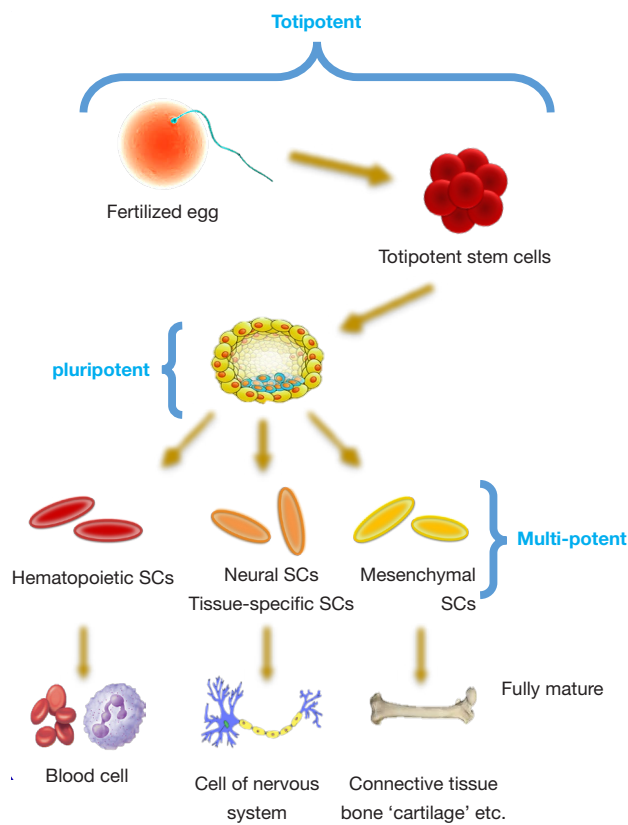


Figure 1 An overview of the stem cell classification. Totipotency: after fertilization, embryonic stem cells (ESCs) maintain the ability to form all three germ layers as well as extra-embryonic tissues or placental cells and are termed as totipotent. Pluripotency: these more specialized cells of the blastocyst stage maintain the ability to self-renew and differentiate into the three germ layers and down many lineages but do not form extra-embryonic tissues or placental cells. Multipotency: adult or somatic stem cells are undifferentiated cells found in postnatal tissues. These specialized cells are considered to be multipotent; with very limited ability to self-renew and are committed to lineage species.

capable of forming colonies (CFU-F) (8). For over 60 years, transplantation of hematopoietic stem cells (HSCs) has been the major curative therapy for several genetic and hematological disorders (9). Almost in 1963, Till and McCulloch described a single progenitor cell type in the bone marrow which expand clonally and give rise to all lineages of hematopoietic cells. This research represented the first characterization of the HSCs (10). Also, the identification of mouse embryonic stem cells (ESCs) in 1981 revolutionized the study of developmental

biology, and mice are now used extensively as one of the best option to study stem cell biology in mammals (11). Nevertheless, their application a model, have limitations in the regenerative medicine. But this model, relatively inexpensive and can be easily manipulated genetically (12). Failure to obtain a satisfactory result in the selection of many mouse models, to recapitulate particular human disease phenotypes, has forced researchers to investigate other animal species to be more probably predictive of humans (13). For this purpose, to study the genetic diseases, the pig has been currently determined as one the best option of a large animal model (14).

Classification of stem cells

Stem cells, based on their differentiation ability, are classified into different cell types, including totipotent, pluripotent, multipotent, or unipotent. Also, another classification of these cells are based on the evolutionary stages, including embryonic, fetal, infant or umbilical cord blood and adult stem cells (15). *Figure 1* shows an overview of stem cells classifications based on differentiation potency.

Toti-potent stem cells

Toti-potent cells have the potential for development to any type of cell found in the organism. In the other hand, the capacity of these cells to develop into the three primary germ cell layers of the embryo and into extra-embryonic tissues such as the placenta is remarkable (15).

Pluri-potent stem cells

The pluripotent stem cells are kind of stem cells with the potential for development to approximately all cell types. These cells contain ESCs and cells that are isolated from the mesoderm, endoderm and ectoderm germ layers that are organized in the beginning period of ESC differentiation (15).

Multi-potent stem cells

The multipotent stem cells have less proliferative potential than the previous two groups and have ability to produce a variety of cells which limited to a germinal layer [such as mesenchymal stem cells (MSCs)] or just a specific cell line (such as HSCs). Adult stem cells are also often in this group.

In the word, these cells have the ability to differentiate into a closely related family of cells (15).

Uni-potent stem cells

Despite the increasing interest in totipotent and pluripotent stem cells, unipotent stem cells have not received the most attention in research. A unipotent stem cell is a cell that can create cells with only one lineage differentiation. Muscle stem cells are one of the example of this type of cell (15). The word 'uni' is derivative from the Latin word 'unus' meaning one. In adult tissues in comparison with other types of stem cells, these cells have the lowest differentiation potential. The unipotent stem cells could create one cell type, in the other word, these cells do not have the self-renewal property. Furthermore, despite their limited differentiation potential, these cells are still candidates for treatment of various diseases (16).

ESCs

ESCs are self-renewing cells that derived from the inner cell mass of a blastocyst and give rise to all cells during human development. It is mentioned that these cells, including human embryonic cells, could be used as suitable, promising source for cell transplantation and regenerative medicine because of their unique ability to give rise to all somatic cell lineages (17). In the other words, ESCs, pluripotent cells that can differentiate to form the specialized of the various cell types of the body (18). Also, ESCs capture the imagination because they are immortal and have an almost unlimited developmental potential. Due to the ethical limitation on embryo sampling and culture, these cells are used less in research (19).

HSCs

HSCs are multipotent cells that give rise to blood cells through the process of hematopoiesis (20). These cells reside in the bone marrow and replenish all adult hematopoietic lineages throughout the lifetime of the human and animal (21). Also, these cells can replenish missing or damaged components of the hematopoietic and immunologic system and can withstand freezing for many years (22). The mammalian hematopoietic system containing more than ten different mature cell types that HSCs are one of the most important members of this. The ability to self-renew and multi-potency is another specific feature of these cells (23).

Tissue specific stem cell or adult stem cells

Adult stem cells, as undifferentiated cells, are found in numerous tissues of the body after embryonic development. These cells multiply by cell division to regenerate damaged tissues (24). Recent studies have been shown that adult stem cells may have the ability to differentiate into cell types from various germ layers. For example, bone marrow stem cells which is derived from mesoderm, can differentiate into cell lineage derived mesoderm and endoderm such as into lung, liver, GI tract, skin, etc. (25). Another example of adult stem cells is neural stem cells (NSCs), which is derived from ectoderm and can be differentiate into another lineage such as mesoderm and endoderm (26). Therapeutic potential of adult stem cells in cell therapy and regenerative medicine has been proven (27).

Cancer stem cells (CSCs)

For the first time in the late 1990s, CSCs were identified by John Dick in acute myeloid diseases. CSCs are cancerous cells that found within tumors or hematological cancers. Also, these cells have the characteristics of normal stem cells and can also give rise to all cell types found in a particular cancer sample (28). There is an increasing evidence supporting the CSCs hypothesis. Normal stem cells in an adult living creature are responsible for the repair and regeneration of damaged as well as aged tissues (29). Many investigations have reported that the capability of a tumor to propagate and proliferate relies on a small cellular subpopulation characterized by stem-like properties, named CSCs (30).

MSCs

Embryonic connective tissue contains so-called mesenchymes, from which with very close interactions of endoderm and ectoderm all other connective and hematopoietic tissues originate, Whereas, MSCs do not differentiate into hematopoietic cell (31). In 1924, Alexander A. Maximow used comprehensive histological detection to identify a singular type of precursor cell within mesenchyme that develops into various types of blood cells (32). In general, MSCs are type of cells with potential of multi-lineage differentiation and self-renewal, which exist in many different kinds of tissues and organs such as adipose tissue, bone marrow, skin, peripheral blood, fallopian tube, cord blood, liver and lung *et al.* (4,5). Today, stem cells are used

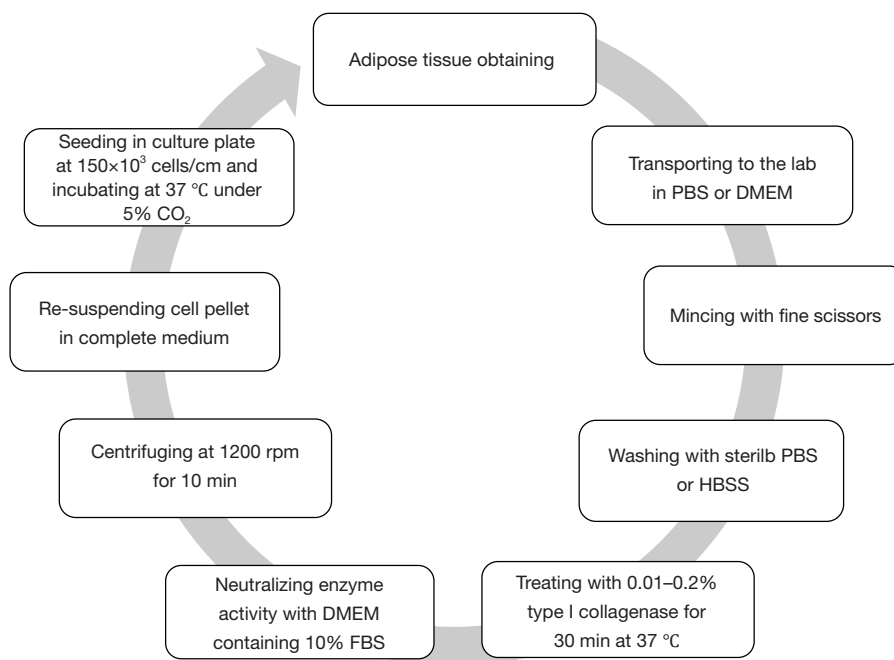


Figure 2 Diagram for adipose tissue-derived mesenchymal stem cell isolation (3).

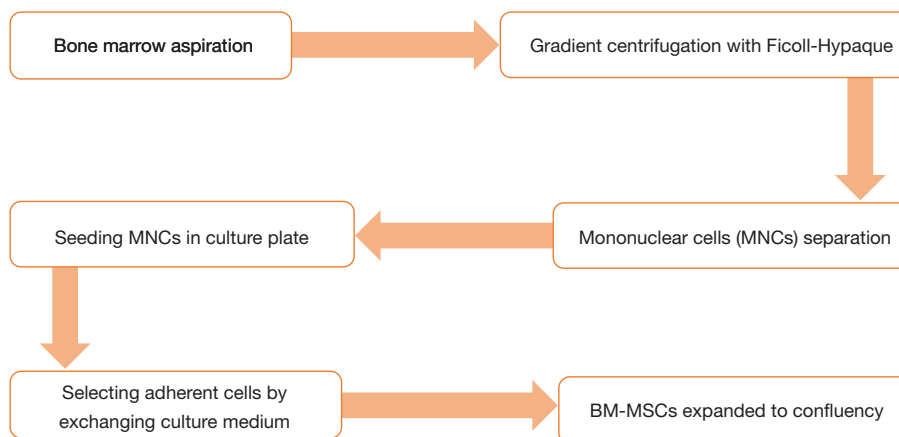


Figure 3 Diagram for bone marrow-derived MSCs isolation (33). MSC, mesenchymal stem cell.

for different applications. In addition to using these cells in human therapy such as cell transplantation, cell engraftment etc. The use of stem cells in veterinary medicine has also been considered. The purpose of this review is to provide a summary of our current knowledge regarding the important and types of isolated stem cells from different sources of animal models such as horse, pig, goat, dog, rabbit, cat, rat, mice etc. In this regard, due to the widespread use and lot of attention of MSCs, in this review, we will elaborate on

use of MSCs in veterinary medicine.

Isolation, culture and identification of MSCs

The isolation method, maintenance and culture condition of MSCs differs from the different tissues, these methods as well as characterization of MSCs described as *Figures 2-6* (36). MSCs could be isolated from the various tissues such as adipose tissue, bone marrow, umbilical cord,

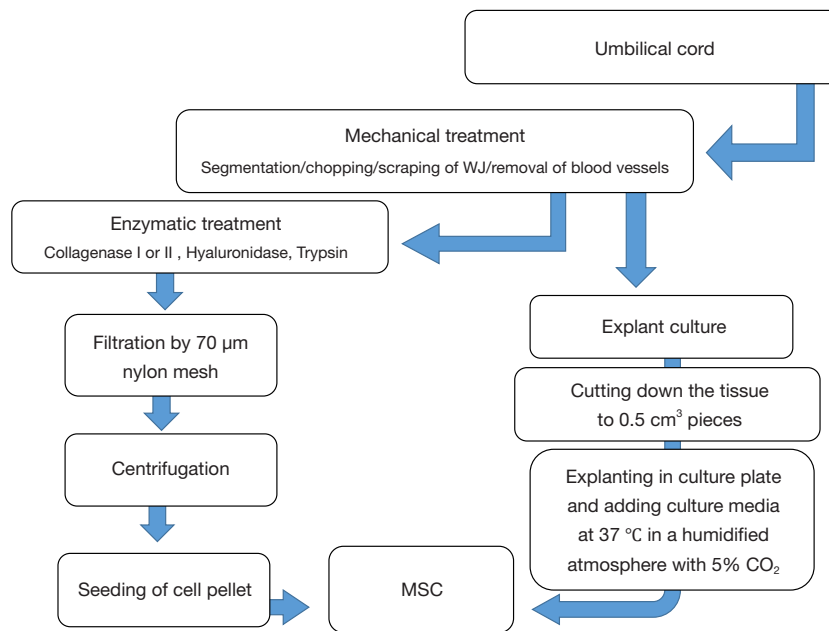


Figure 4 Diagram for umbilical cord-derived MSCs isolation (34). MSC, mesenchymal stem cell.

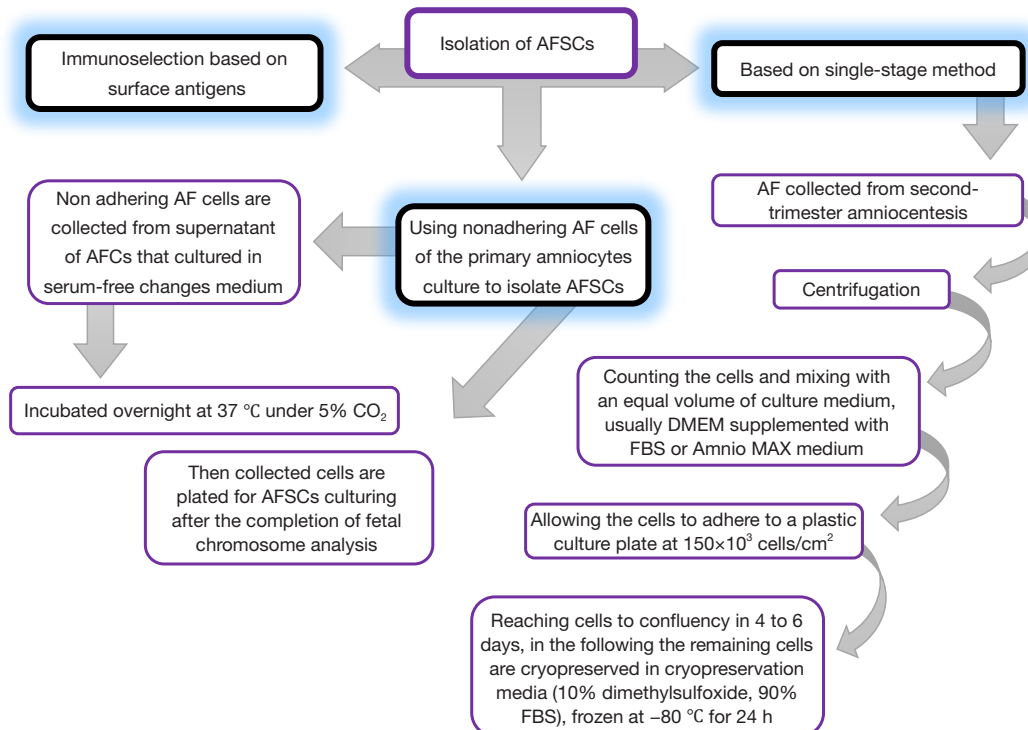


Figure 5 Diagram for isolation of amniotic fluid stem cells (AFSCs) (35).

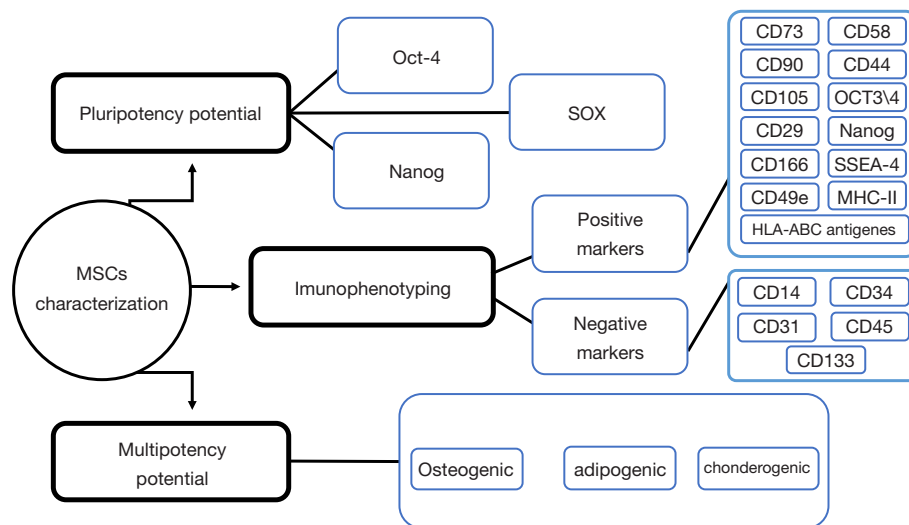


Figure 6 Diagram for MSCs characterization (35). MSC, mesenchymal stem cell.

amniotic fluid etc. (37).

Application of MSCs in regenerative medicine in animal models

The diversity of stem cell or MSCs sources and a wide aspect of potential applications of these cells cause to challenge for selecting an appropriate cell type for cell therapy (38). Various diseases in animals have been treated by cell-based therapy. However, there are immunity concerns regarding cell therapy using stem cells. Improving animal models and selecting suitable methods for engraftment and transplantation could help address these subjects, facilitating eventual use of stem cells in the clinic. Therefore, for this purpose, in this section of this review, we provide an overview of the current as well as previous studies for future development of animal models to facilitate the utilization of stem cells in regenerative medicine (14). Significant progress has been made in stem cells-based regenerative medicine, which enables researchers to treat those diseases which cannot be cured by conventional medicines. The unlimited self-renewal and multi-lineage differentiation potential to other types of cells causes stem cells to be frontier in regenerative medicine (24). More researches in regenerative medicine have been focused on human cells including embryonic as well as adult stem cells or maybe somatic cells. Today there are versions of embryo-derived stem cells that have been reprogrammed from adult cells under

the title of “pluripotent cells” (39). Stem cell therapy has been developed in the last decade. Nevertheless, obstacles including unwanted side effects due to the migration of transplanted cells as well as poor cell survival have remained unresolved. In order to overcome these problems, cell therapy has been introduced using biocompatible and biodegradable biomaterials to reduce cell loss and long-term *in vitro* retention of stem cells.

Currently in clinical trials, these biomaterials are widely used in drug and cell-delivery systems, regenerative medicine and tissue engineering in which to prevent the long-term survival of foreign substances in the body the release of cells are controlled (40).

Heart failure

Today, the incidence and prevalence of heart failure in human societies is a major and increasing problem that unfortunately has a poor prognosis. For decades, MSCs have been used for cardiovascular regenerative therapy as one of the potential therapeutic agents (41). Dhein *et al.* [2006] found that autologous bone marrow-derived mesenchymal stem cells (BMSCs) transplantation improves cardiac function in non-ischemic cardiomyopathy in a rabbit model. In one study, Davies *et al.* [2010] reported that transplantation of cord blood stem cells in ovine model of heart failure, enhanced the function of heart through improvement of right ventricular mass, both systolic and diastolic right heart function (42). In another study, Nagaya

Table 1 Advantages and disadvantages of small animal models (46)

Advantages of small animal modeling in cell based therapy of heart failure

- Lower maintenance costs
- Easier to handle and house
- Shorter gestation time and lifespan
- Suitable for proof-of-concept and “high-throughput” studies
- ischemia-reperfusion induced arrhythmias are infrequent and easy to reverse when they occur
- Suitable for genetic selection and production of transgenic strains

Disadvantages of small animal models

- Phylogenetically distant from humans
- Pathophysiology of disease may not be translatable to humans
- Different response to pharmaceuticals
- Not suitable for chronic studies

Table 2 Advantages and disadvantages of large animal models (47)

Advantages of large animal models

- Most physiologically and/or clinically relevant
- Allows for chronic studies to be undertaken
- Allows for cardiac function and responses to be assessed in the intact animal
- Responsive to all the techniques and measurements made in man
- Resembles more closely the human heart (young human heart is pig-like, older heart is dog-like)

Disadvantages of large animal models

- Higher maintenance costs
- Harder to handle and house-specialized infrastructure and trained personnel needed
- Longer gestation time and lifespan
- Dog and pig: ischemia-reperfusion induced arrhythmias are more frequent
- Less suitable than small animals for genetic selection and production of transgenic strains and less spontaneous disease models

et al. [2005] found that MSCs dilated cardiomyopathy (DCM), possibly by inducing angiogenesis and preventing cardiac fibrosis. MSCs have a tremendous beneficial

effect in cell transplantation including in differentiating cardiomyocytes, vascular endothelial cells, and providing anti-apoptotic as well angiogenic mediators (43). Roura *et al.* [2015] shown that umbilical cord blood mesenchymal stem cells (UCBMSCs) are envisioned as attractive therapeutic candidates against human disorders progressing with vascular deficit (44). Ammar *et al.*, [2015] compared BMSCs with adipose tissue-derived MSCs (ADSCs). It was demonstrated that both BMSCs and ADSCs were equally effective in mitigating doxorubicin-induced cardiac dysfunction through decreasing collagen deposition and promoting angiogenesis (45).

Small mammalian animal models for heart disease

There are many advantages of small animal models usage in cardiovascular research compared with large animal models. Small model of animals has a short life span, which allow the researchers to follow the natural history of the disease at an accelerated pace. Some advantages and disadvantages are listed in *Table 1* (46).

Large mammalian animal models for heart disease

Despite of the small animal model, large animal models are suitable models for studies of human diseases. Some advantages and disadvantages of using large animal models in a study protocol planning was elaborated in *Table 2* (47).

Wound healing

Chronic wound is one of the most common problem and causes significant distress to patients (48). Among the types of tissues that stem cells derived it, dental tissue-derived MSCs provide good sources of cytokines and growth factors that promote wound healing. The results of previous studies showed that stem cells derived deciduous teeth of the horse might be a novel approach for wound care and might be applied in clinical treatment of non-healing wounds (49). However, the treatment with stem cells derived deciduous teeth needs more research to understand the underlying mechanisms of effective growth factors which contribute to the wound healing processes (50). This preliminary investigation suggests that deciduous teeth-derived stem cells have the potential to promote wound healing in rabbit excisional wound models (49). In the another study, Lin

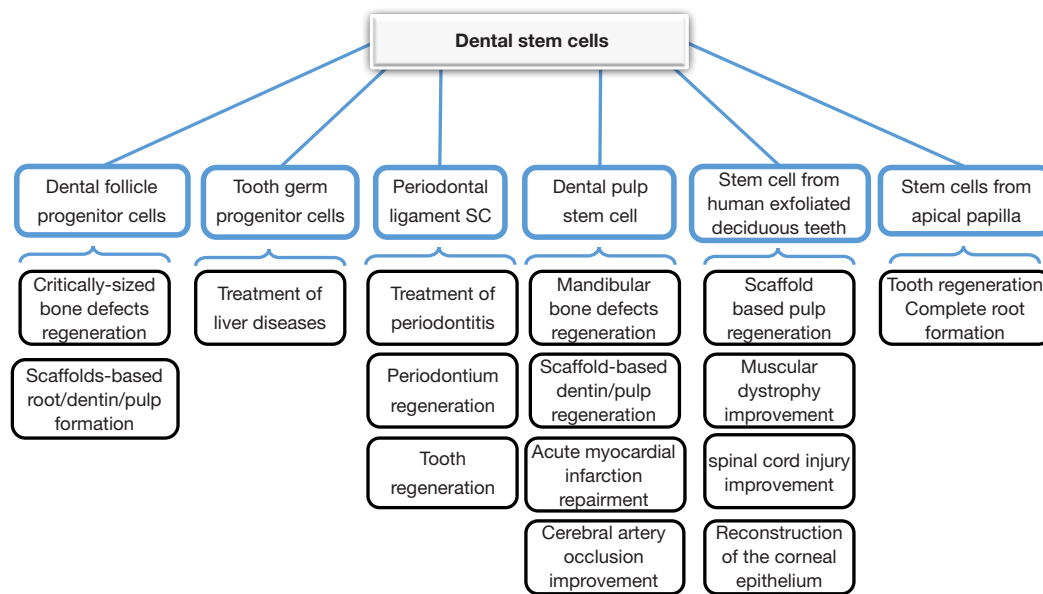


Figure 7 Diagram for application of dental stem cell in dentistry/regenerative medicine (53).

et al. [2013] worked on the mouse animal model and showed that ADSCs present a potentially viable matrix for full-thickness defect wound healing (51).

Tooth regeneration

Many studies have been done on dental reconstruction with MSCs. In one study, Khorsand *et al.* [2013] reported that dental pulp-derived stem cells (DPSCs) could promote periodontal regeneration in canine model. Also, it was shown that canine DPSCs were successfully isolated and had the rapid proliferation and multi-lineage differentiation capacity (52). Other application of dental-derived stem cells is shown in *Figure 7*.

Application of MSCs in neurodegenerative disease in animal model

As noted above, stem cells have different therapeutic applications and self-renewal capability. These cells can also differentiate into the different cell types. There is now a great hope that stem cells can be used to treat diseases such as Alzheimer, Parkinson and other serious diseases. In stem cell-based therapy, ESCs are essentially targeted to differentiate into functional neural cells. Today, a specific category of stem cells called induced pluripotent stem (iPS) cells are being used and tested to generate functional

dopamine neurons for treating Parkinson's disease of a rat animal model. In addition, NSC as well as MSCs are being used in neurodegenerative disorder therapies for Alzheimer's disease, Parkinson's disease, and stroke (54). Previous studies have shown that BMSCs could reduce brain amyloid deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease in mouse animal model. Lee *et al.* [2009] reported that BMSCs can increase the number of activated microglia, which effective therapeutic vehicle to reduce A β deposits in AD patients (55). In confirmation of previous study, Liu *et al.* [2015] showed that transplantation of BMSCs in brain of mouse model of Alzheimer's disease cause to decrease in amyloid beta deposition, increase in brain-derived neurotrophic factor (BDNF) levels and improvements in social recognition (56). In addition of BMSCs, NSCs have been proposed as tools for treating neurodegeneration disease because of their capability to create an appropriate cell types which transplanted. Åkerud *et al.* [2001] demonstrated that NSCs efficiently express high level of glial cell line-derived neurotrophic factor (GDNF) *in vivo*, suggesting a use of these cells in the treatment of neurodegenerative disorders, including Parkinson's disease (57). In the following, Venkataramana *et al.* [2010] transplanted BMSCs into the sub lateral ventricular zones of seven Parkinson's disease patients and reported encouraging results (58).

Conclusions

The human body is fortified with specialized cells named MSCs, which has the ability to self-renew and differentiate into various cell types including, adipocyte, osteocyte, chondrocyte, neurons etc. In addition to mentioned properties, these cells can be easily isolated, safely transplanted to injured sites and have the immune regulatory properties. Numerous *in vitro* and *in vivo* studies in animal models have successfully demonstrated the potential of MSCs for various diseases; however, the clinical outcomes are not very encouraging. Based on the studies in the field of stem cells, MSCs find wide application in treatment of diseases, such as heart failure, wound healing, tooth regeneration and etc. In addition, these cells are particularly important in the treatment of the sub-branch neurodegenerative diseases like Alzheimer and Parkinson.

Acknowledgments

The authors wish to thank staff of the Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Funding: The project described was supported by Grant Number "IR.TBZMED.REC.1396.1218" from the Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/sci.2019.06.04

Cite this article as: Rajabzadeh N, Fathi E, Farahzadi R. Stem cell-based regenerative medicine. *Stem Cell Investig* 2019;6:18.