Review Article

Extending the envelope of regenerative medicine in orthodontics by stem cells

ABSTRACT

Stem cell (SC) therapy has become a buzz word in several debilitating diseases in medicine. This rapidly evolving cutting-edge technology has slowly extended its tentacles in dentistry without sparing orthodontics. There are several conditions in orthodontics which are only being partly answered by human-engineered techniques. With the hope of getting a complete solution to several such problems, research in SC therapy has gained momentum in orthodontics for the past few decades. Electronic databases were searched for the material collection; language restriction was not followed. The following keywords were used: stem cell and orthodontics. The search was not limited to any particular type of study design. This review article describes various possible areas in orthodontia where SC therapy will and can be applied in future based on the evidence from a collection of several such studies conducted in those areas.

Keywords: Accelerated orthodontics, regenerative medicine, stem cell

INTRODUCTION

The distinctive potentiality of stem cell (SC) to differentiate into the sort of cell in demand makes it a promising candidate in future for several regenerative and reparative therapies. Research on the extensive application of SC therapy in medical and dental sciences has geared up in the past few decades. There are many situations in orthodontics which are only being partially answered by the human-engineered techniques. The interesting features of SCs theoretically prove us that it would be an absolute answer to several of those unsolved problems, however yet to be established much and proven practically for it to be followed in day-to-day practice. This article reviews the various possible areas in orthodontia wherever SC therapy will and can be applied in future and also focuses on the current researches being carried out in this perspective. Electronic databases were searched for the material collection; language restriction was not followed. The following keywords were used: stem cell and orthodontics. The search was not limited to any particular type of study design.

Access this article online	
Website: www.orthodrehab.org	Quick Response Code:
DOI: 10.4103/ijor.ijor_20_19	

STEM CELL

The term stem cell was coined by E.D. Wilson[1] in 1896. SCs are cells that can self-renew by dividing and developing into more mature, specialized cells. SCs may be unipotent, multipotent, pluripotent, or totipotent, depending on the number of cell types to which they can give rise [Figure 1].

Totipotent

Capability to form all cell lineages of the organism including extraembryonic tissues like placenta.

Pluripotent

Capability to form all the lineages of the embryo, but not the extraembryonic tissues like placenta.

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How to cite this article: Tania SD, George AM. Extending the envelope of regenerative medicine in orthodontics by stem cells. Int J Orthod Rehabil 2019;10:82-7.

Multipotent

Potential to form limited number of cells restricted to an embryonic layer, particularly cell lineage.

Unipotent

Capability to form one particular cell type.

Commonly, SCs come from two main sources:

1. Embryonic SCs: The embryonic cells are pluripotent and can differentiate to all cell lineages *in vivo*.

Sources:

   a. *In vitro* fertilization-produced blastocyst which is produced 5 days after fertilization
   b. Somatic cell nuclear transfer.

2. Adult SCs: These are multipotent cells that can give rise to specialized cells such as nerve and cardiac. They are immune by nature. They can be classified as follows:
   a. Hematopoietic SCs
   b. Nonhematopoietic SCs/mesenchymal cells.

STEM CELL SOURCES

Muscle, dermis, bone marrow, adipose tissue, periosteum, blood, umbilical cord, synovial membrane, and teeth are the various available sources of SC. SCs of dental origin are obtained from dental pulp, periodontal ligament (PDL), or human exfoliated deciduous teeth [Figure 2]. The SCs are either directly planted into the defect site or into the scaffolds used for supporting these cells. Extraction of teeth being the common treatment procedure carried out, teeth can be used as an important source of SC for dental purposes without extramorbidity.

ORTHODONTIC IMPLICATIONS OF STEM CELL THERAPY

Alveolar bone repair and periodontal ligament regeneration

Orthodontic tooth movement (OTM) is a unique mechanism which takes place as a result of complex biological reactions such as deposition and resorption of the alveolar bone in response to the mechanical load. A healthy alveolar bone and PDL are prime requisites for a successful orthodontic treatment. Unwanted alveolar bony defects are often created after orthodontic extractions, and hence repair of these defects is needed to avoid the risk of dehiscence and other periodontal insults at a later stage, probably after the retraction of teeth into the extraction site.[2] Repair of the alveolar bone is mandatory before undergoing orthodontic treatment. The reparative potential of SCs (bone marrow SCs) in alveolar defect was proven in an experiment conducted on animal models (rats) with bilateral traumatic alveolar bone defects on the maxilla.[3] SCs have the potential to generate different tissues, including bone; therefore, SC therapy is a promising approach to alveolar bone regeneration.

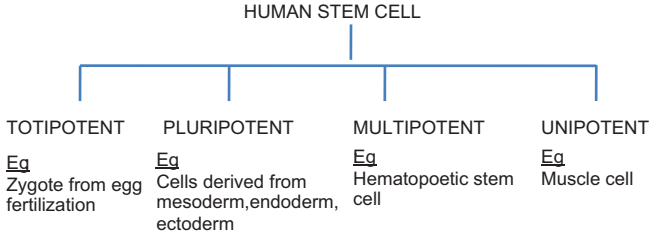

Figure 1: Classification of stem cell based on differentiation potential

Periodontal complications are one of the most common side effects linked to orthodontics; they occur in various forms, from gingivitis to periodontitis, dehiscence, fenestrations, interdental fold, gingival recession, or overgrowth. Studies conducted in rats have proven the regenerative potential of periodontal ligament stem cells (PDLSCs). An *in vivo* study was conducted using human adult PDLSCs and transplanted into an athymic rat model, and the data showed that human adult PDLSCs were capable of regenerating elements of bone and collagen fibers.[4] Based on the differential potential capability of SCs and their ability of renewal via mitosis, they have the quality to regenerate damaged tissues; hence, they can be used for the regeneration of periodontium.

The capability of human adult periodontal ligament stem cells to regenerate elements of bone and collagen can be applied in cases of periodontitis. Thus, the use of PDLSC transplantation in periodontal therapies can reduce treatment time and produce better outcomes followed by patient comfort; however, due to the complex structure of periodontium, regeneration is a feasible yet complicated procedure and may need pluripotent SCs and more investigations.

Accelerated orthodontic tooth movement

The initiating inflammatory event at compression sites is caused by constriction of the PDL microvasculature, resulting in a focal necrosis, followed by recruiting of osteoclasts from the adjacent marrow spaces.[5] These osteoclasts are mostly derived from hematopoietic SCs.[6] Hence, SCs could be used to accelerate OTM by providing progenitor cells. In a study, an increase in PDL progenitor cells with suppressed expression of type I collagen (Col-I) was observed during orthodontic force application, whereas after force withdrawal, there was an increase in Col-I expression, which suggests that PDLSCs can respond to orthodontic mechanical forces with suppressed collagen expression.[7] This ability of SCs could be used to accelerate OTM in response to orthodontic

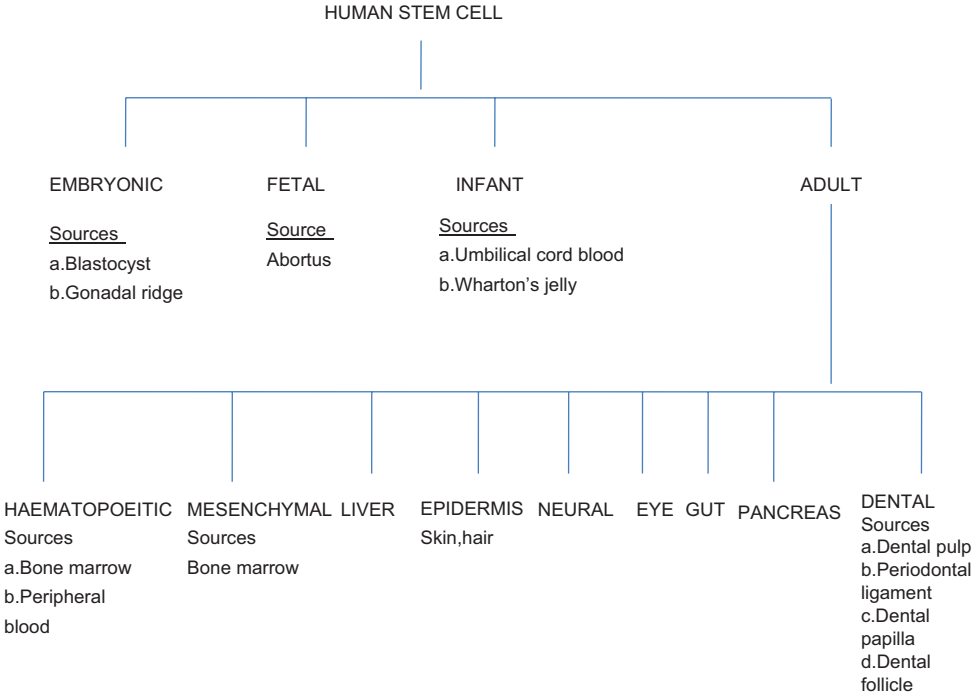

Figure 2: Classification of stem cell based on origin

forces. When orthodontic force is applied, tooth movement is hindered until the necrosis is removed, leading to the clinical manifestation of a delay period. Hypothetically, transplantation of SCs in pressure sites may speed up the process, resulting in accelerated OTM.

Lesser root resorption

External apical root resorption is the most common and undesirable sequel of orthodontic treatment.[8] In most studies of root resorption, treatment factors top the list of the "usual suspects."[9] They are probably caused on account of the removal of the necrotic tissue from areas of the PDL that have been compressed by an orthodontic load. However, root resorption is multifactorial, with a complex etiology, but the condition appears to result from a combination of individual biological variability, genetic predisposition, and the effect of a mechanical factor. According to recent studies,[10-12] odontoblasts derived from mesenchymal SCs (MSCs) and cementoblasts derived from MSCs and dental follicular SCs are capable of preventing root resorption when used prior to treatment, promoting the repair of the damage post treatment.

Cleft

Alveolar cleft occurs as a result of divergence from normal development during front nasal prominence growth, contact, and fusion. Autologous bone grafting of the defect is the contemporary management of patients with alveolar cleft. However, in 10%–36% of the cases, there is graft resorption and later on, surgical procedures are needed.[2] Late complications such as chronic pain, unesthetic scarring at the harvest site, and gait disturbance have often been associated.[13,14] SC therapy would be an alternative to combat these complications. In an alveolar cleft osteoplasty of a 9-year-old female patient, MSC were used instead of bone grafts.[15] After 6 months, the cleft bridged with 79.1% of the grafted region and after 9 months, the canine and lateral incisors in the affected side erupted in the reconstructed alveolar ridge.

Composite scaffold of demineralized bone mineral and calcium phosphate loaded with MSCs showed 34.5% regenerated bone in the cleft area in one case and in the other, there was 25.6% presentation of bone integrity.[16] Several other studies have also proven the benefits of SC over autograft for cleft repair. Thus, the bone regenerative potential of SC can be successfully applied in repairing alveolar defect,[16-18] with less postoperative morbidity compared to the conventional autogenous bone grafting, facilitating the eruption of teeth in the defect area.

Hemifacial microsomia

Hemifacial microsomia (HFM) is a frequently encountered form of congenital facial malformation presenting with unilateral hypoplasia of the craniofacial skeleton and its overlying soft tissue. Autologous fat grafting is considered to reconstruct soft-tissue defect in the treatment of congenital malformations as well as posttraumatic malformations.[19]

Unpredictable results and low graft survival rate are some of the problems associated with autologous grafting. To overcome these effects, many innovative efforts and refinements of surgical techniques have been tried. Adipose-derived stromal cells (ASCs) for tissue regeneration have attracted the attention these days.

A study conducted on patients with HFM[20] who have been grafted with supplementation of ASCs showed 88% of fat volume survival after 6 months in comparison to control group which was only 54%.

Studies are ongoing, and as results are reported, it will be crucial to evaluate the long-term outcome of such procedures. The current evidence[21] suggests that the use of ASCs for soft-tissue reconstruction may enhance angiogenesis, improve the survival of grafts, and thus reduce atrophy.

Distraction osteogenesis

Distraction osteogenesis (DO), a procedure of generating new bone in several skeletal deformities and reconstructive surgery, has the advantage of avoiding the complications of other treatments such as bone grafting but with the major disadvantage of lengthy time needed for bone consolidation. The osteogenic potential of MSCs has been documented by researchers, with successfully proving the efficiency of SCs on promoting bone formation and shortening the consolidation period during distraction. For this purpose, different sources of SCs such as human exfoliated deciduous teeth,[22] bone marrow,[23] and fatty tissue[24] were employed in studies. In some studies, MSCs, in the others, gene-transferred MSCs, and factors were used to enhance bone regeneration following DO. The modifications such as use of scaffolds,[25] demineralized bone matrix,[26] and platelet-rich plasma[27] have been done in some studies.

Rapid maxillary expansion

Rapid maxillary expansion (RME) is analogous to DO histologically. During RME, a gap within the midpalatal suture is formed that is stuffed with blood and granulation tissue, followed by active bone formation. The expanded arch dimension relapses unless followed by an adequate retention period. Therefore, providing a method to accelerate bone formation within the midpalatal suture may shorten treatment and retention periods, attain stability, and prevent relapse. Due to the ability of SCs to differentiate into osteogenic cells, injection of SCs seems to have the power to accelerate the process of bone formation. In an animal study,[28] local injection of MSCs into intermaxillary suture after force application resulted in augmented new bone formation within the suture by increasing the amount of osteoblasts and new vessel formation. Thus, regionally applied MSCs to the expanded maxilla can be a helpful and useful treatment strategy to accelerate new bone formation in midpalatal suture and to shorten the treatment and retention periods for patients undergoing orthopedic maxillary expansion.

Regeneration and repair of temporomandibular joint defects

Temporomandibular joint disorders (TMD) manifest as pain, myalgia, headaches, and structural destruction, collectively known as degenerative joint disease. The conventional methods of temporomandibular joint (TMJ) reconstruction include autogenous bone grafting with bone harvesting from rib bone or use of alloplastic materials, but neither being ideally suited for the task and sometimes leading to unwanted adverse effects.[29] The recent advances[30] in SC technology assure the construction of a bioengineered TMJ replacement, which is biocompatible and capable of withstanding the physiological loads required for this joint. Cells from various sources,[31] including articular cartilage cells, fibroblasts, human umbilical cord matrix (HUCM) cells, and MSC, have been used in efforts to reconstruct the TMJ.

Engineering a TMJ-like osteochondral graft has been studied in several studies. The culture of HUCM SCs in growth medium containing chondrogenic factors showed that the HUCM SCs can outperform the TMJ condylar cartilage cells.[32] Rat bone marrow MSCs encapsulated in poly (ethylene glycol)-based hydrogel, which are molded into the shape of a cadaver human mandibular condyle, demonstrated two stratified layers of histogenesis of cartilaginous and osseous phenotypes.[33,34] Porcine MSCs which had been cultured in osteogenic induction medium and seeded onto a poly DL-lactic–co-glycolic acid scaffold, formed the construct that had a shape which closely resembled the model of condyle.[35] Thus, these studies have proven the role of SCs in TMJ reconstruction.

Cranial osseous defects

SCs enhance the repair of cranial osseous defects by increasing the rate of healing and regeneration. In a study, where embryonic SCs differentiated into cartilage cells were implanted on artificially created cranial osseous defects,[36] it was found that, in comparison to the control group, a significantly faster response was observed in the group that received the implant. It is known that, for any damaged tissue to recover, there should be regeneration of blood vessels in that region. MSCs express and secrete stromal cell-derived factor 1, vascular endothelial growth factor, basic fibroblast growth factor, matrix metalloproteinases, and other cytokines that are crucial for angiogenesis. Thus, SCs can provide a sufficient substrate for neoangiogenesis.[37] Therefore, it is clear that SCs

can enhance the treatment by increasing the rate of healing and regeneration, thereby reducing the treatment time.[38]

CONCLUSION

The regenerative potential of SC has increased the scope of SC therapy, widening the therapeutic possibilities in medicine and dentistry. However, certain limitations such as rejection, high cost of treatment, and ethical issues associated with this therapy have the potential of holding the research back. Although research in dentistry has been evolving expressively in this field which is on the cutting edge of biological science today, it is still in its infancy. Detailed studies of both embryonic and adult human SCs will be required to most efficiently advance the scientific and therapeutic potential of regenerative medicine. The days are not far when SC therapy will be extensively used in day-to-day practice.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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