

Reforming craniofacial orthodontics via stem cells

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Abstract

Stem cells are the most interesting cells in cell biology. They have the potential to evolve as one of the most powerful technologies in the future. The future refers to an age where it will be used extensively in various fields of medical and dental sciences. Researchers have discovered a number of sources from which stem cells can be derived. Craniofacial problems are very common and occur at all ages. Stem cells can be used therapeutically in almost every field of health science. In fact, many procedures will be reformed after stem cells come into play. This article is an insight into the review of the current researches being carried out on stem cells and its use in the field of orthodontics, which is a specialized branch of dentistry. Although the future is uncertain, there is a great possibility that stem cells will be used extensively in almost all major procedures of orthodontics.

Key words: *Orthodontics, periodontium, root resorption, stem cells, Temporomandibular joint defects*

INTRODUCTION

Nowadays faster orthodontic treatment is one of the major demands of the patient population, which is not adequately met by the orthodontists. Low friction and self-ligating bracket systems, robot preformed arch wires, rapid canine retraction, and alveolar corticotomies are some examples of the approaches that aim to reduce the time required by orthodontic therapy.^[1] These procedures have definitely brought better results, but they are not the ultimate solution to all our problems — newer and better technologies are always welcome. Technologies such as stem cell therapy hold a great potential and can bring a revolutionary change in the field of health science. The knowledge of stem cells and its implications will help the orthodontists to modify their treatment planning, which

will be acknowledged by the patient. This article will review the literature on the potential clinical use of stem cells in craniofacial deformities, with reference to the orthodontic field.

STEM CELLS

It was E.D. Wilson who in his classic textbook, “The Cell in Development and Inheritance,” first coined the phrase ‘stem cell,’ in 1896.^[2] Stem cells are ‘undifferentiated cells that can proliferate and have the capacity for self-renewal and the ability to produce one or more highly differentiated progenitors’.^[3,4] However, this definition is not fully accepted after the introduction of concepts like de-differentiation and transdifferentiation. In 2007, Dr. James Thomson, in the United States, and Dr. Yamanaka, in Japan, simultaneously discovered that adult human cells could be reprogrammed back to an embryonic state by overexpressing the powerful stem cell genes. These new type of stem cells are called induced pluripotent stem cells (iPSC).^[2,5]

Essentially, stem cells are of two types: Embryonic stem cells and Adult stem cells. The embryonic cells are pluripotent and can differentiate to all cell lineages

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in vivo.^[6] Human embryonic stem cells are derived from the inner cell mass of a blastocyst that has been fertilized *in vitro*.^[7,8] They are virtually immortal due to their high expression of telomerase, the enzyme complex responsible for maintaining telomere lengths and chromosomal stability during cellular division.^[9] However, their growth is difficult to control and they are fairly sensitive.^[2,10]

An adult stem cell can be defined as a cell residing within an adult tissue that divides, either autonomously or in response to regulated signals, to produce cells that contribute to organismal homeostasis.^[11] Adult stem cells or extra-embryonic stem cells are partly specialized cells, as they are not capable of forming all types of cells. The list of adult tissues containing stem cell repositories are growing and include the bone marrow, peripheral blood, brain, spinal cord, dental pulp, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, retina, liver, and pancreas.^[11] Unfortunately, the isolation of adult stem cells with sufficient purity and quantity is still complicated.^[12]

THE NEED OF STEM CELLS

Worldwide there is a significant percentage of the population suffering from oral and craniofacial defects, which demand oral and craniofacial tissue engineering. Techniques like autografts, allografts, and biomaterial are used to repair these defects. Taking these into consideration, each of them has some limitations. Although autografts are considered as the 'gold standard' for bone regeneration procedures, yet the failure rate is as high as 30%.^[13] The allograft has a great potential for rejection and infection transfer. Freeze-drying, demineralization, and irradiation to reduce graft immunogenicity can also reduce the structural integrity; leading to a graft fracture.^[14-16] Bone allografts are not osteogenic and there is slower integration in the host bed.^[17] Besides this, grafting procedures include risks such as donor site morbidity, unpredictable resorption, limited quantities available, and the need to include additional surgical sites.^[18] Alloplasts have only an osteoconductive property and lack osteoinductive and osteogenic properties,^[19] therefore, bone formation is uncertain in this case. Biomaterials, such as implants, and bone substitutes such as bovine and the like, for long-term complications, include, stress shielding, loosening, and mechanical or chemical breakdown of the material itself.^[20] Thus, there is a demand for a method or material that is less invasive, reduces the risk of morbidity, has the ability to adapt itself along with the tissue, and can be in a harmonious relationship with the adjacent hard and soft tissues.

Stem cells have three specific properties:^[21]

- They are unspecialized cells that renew themselves for long periods through cell division
- Under certain conditions stem cells can be induced to become cells with special functions, with the capability of self-renewal
- Stem cells give rise to specialized cells.

Thus, their properties of differentiating into any kind of cells and self-renewal can pave new pathways for treatment.

THE PROMISE OF STEM CELLS TO ORTHODONTISTS

With the recent advances in the understanding of stem cell biology, certain opportunities can be provided to the orthodontist such as:

Shorter treatment time

In a study,^[22] embryonic stem cells have been differentiated into cartilage cells and implanted on artificially created cranial osseous defects. In comparison to the control group, the group that received the implanted tissue had a significantly faster response. It is known that for any damaged tissue to recover there should be regeneration of blood vessels in that region. Mesenchymal stem cells (MSCs) express and secrete stromal cell-derived factor 1 (SDF-1), the vascular endothelial growth factor (VEGF); the basic fibroblast growth factor (bFGF); matrix metalloproteinases (MMPs), and other cytokines that are important for angiogenesis.^[23] Thus, stem cells can provide a sufficient substrate for neoangiogenesis. In a study, primary marrow-derived, cultured mesenchymal cells that were introduced into ceramic showed a strong osteogenic potential, with bone forming in the pore regions of the ceramic as early as two weeks after *in vivo* implantation.^[24] Stem cells also secrete bioactive factors that suppress the local immune system, inhibit fibrosis and apoptosis, enhance angiogenesis, and stimulate mitosis and differentiation of the tissue intrinsic reparative process.^[25] From these studies it is clear that stem cells can enhance the treatment by increasing the rate of healing and regeneration, thereby, reducing the treatment time.

Periodontal health consideration

The periodontium is the only supporting system of the tooth. Nowadays, many people suffer from periodontal disease. 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, and black triangles.^[26] One such example — band impingement — may directly compromise the local resistance related to subgingival pathogens in susceptible patients and result in damage to both interproximal gingival tissues and alveolar crestal bone.^[27] This is the reason why it becomes very essential for an orthodontist to maintain the ortho–perio relationship while carrying out any orthodontic procedures. Surprisingly, periodontal ligament stem cells (PDSCs) are capable of regenerating the wounded periodontium in rats; surpassing the repair capacity of embryonic cells.^[28] Thus, stem cells can be used to regenerate and repair periodontal tissues.

In a study,^[29] human periodontal cell sheets were transplanted into a mesial dehiscence model, in athymic rats, where the periodontal ligament-like tissues — which included an acellular cementum-like layer and fibrils anchoring into this layer — were identified at their site of placement. Such regeneration was not observed in the nontransplanted controls. Another *in vivo* study was conducted using human adult PDSCs and transplanted into an athymic rat model, and the data showed that human adult PDSCs were capable of regenerating elements of bone and collagen fibers.^[30] However, complete regeneration of the periodontal complex was a big challenge to overcome, especially in a diseased state with inflammatory factors, including cytokines.^[31] Human PDLSCs were transplanted into surgically created defects in the periodontal area of the mandibular molars in immunocompromised rats. They were integrated into the PDL tissue, which resulted in them homing to the surfaces of the alveolar bone and tooth root.^[32] When the PDLSCs were treated with dentin noncollagenous proteins, they showed an increased proliferation and adhesion ability.^[33] Dental pulp stem cells (DPSCs) have the highest osteogenic potential among bone marrow mesenchymal stem cells (BMSCs) and periosteal cells, indicating a useful cell source for tissue engineered bone around the dental implants.^[34] These look promising, but there is still a long way to go before they enter the clinics.

Lesser root resorption

External apical root resorption is the most common^[35] and undesirable sequela of orthodontic treatment.^[36] In most studies of root resorption, treatment factors top the list of the ‘usual suspects’.^[37] They are probably caused on account of the removal of the necrotic tissue from areas of the periodontal ligament that have been

compressed by an orthodontic load.^[38] 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.^[39–41] According to recent studies, odontoblasts can be derived from mesenchymal stem cells (MSC), stem cells from an exfoliated deciduous tooth (SHED), dental pulp stem cells (DPSC), and apical papilla stem cells (SCAP), while cementoblasts can be derived from mesenchymal stem cells (MSC) and dental follicular stem cells (DFSC).^[42] Thus, these kinds of stem cells may be used prior to the treatment, to prevent root resorption or post treatment to repair the damage.

Patient benefits

Using stem cell therapy instead of bone graft surgery will relieve the patient from the extra major surgical procedures and the pain of iliac crest bone grafts. It is a minimally invasive technique.^[43] Other advantages include, less failure cases as the body’s own cells are used and there is of course natural regeneration. Stem cells can also accelerate the healing process, as has been done in a study by Wu *et al.*^[44] It has been found that bone marrow mesenchymal stem cell (BM-MSC)–treated wounds exhibit significantly accelerated wound closure, with increased re-epithelialization, cellularity, and angiogenesis.

ORTHODONTIC IMPLICATIONS OF STEM CELL THERAPY

Repair of the alveolar bone

Unwanted alveolar bony defects are often created after orthodontic extractions and repair of these defects is needed to avoid the risk of dehiscence and other periodontal insults at a later stage, after the teeth have been retracted into the extraction site.^[45] Resorption of an edentulous or partially edentulous alveolar ridge or bone loss on account of periodontitis or trauma will require alveolar bone augmentation prior to placement of the implant.^[46] Stem cells can be a potential treatment for rehabilitation of these types of defects. For example, in an experiment conducted on animal models (rats) with traumatic alveolar bone defects on the maxilla, bilaterally, it was found that a composition of bone marrow stem cells (BMSCs) and fibrin glue (FG) had been suggested as a promising method to repair the alveolar bone defect.^[47]

In a recent study,^[48] the tissue repair cells were grafted into the osseous defects of the jaw of 12 patients and the biopsies were harvested for analysis at six and

twelve weeks. Reconstruction was completed with an oral implant therapy and was observed for 12 months postoperatively. It was demonstrated clinically, radiographically, and histologically that the cell therapy accelerated the regenerative response. There was also significant reduction in the need for secondary bone grafting procedures in this group.

The alveolar cleft is a highly prevalent congenital malformation, where 75% of the patients with cleft lip and palate display osseous defects of the premaxilla alveolar bone.^[49] Contemporary treatments of patients with alveolar cleft defects involve autologous bone grafting at the defect site.^[50] These patients often require a secondary bone graft procedure, to allow for eruption of the anterior teeth and orthodontic treatment.^[45] However, in 10–36% of the cases there is graft resorption and later on surgical procedures are needed.^[51,52] Late complications such as chronic pain, unesthetic scarring at the harvest site, and gait disturbance have often been associated.^[53,54] Thus, there is a need for an alternative to combat these complications so that the orthodontic treatment of these patients becomes facile and at the same time effectual. In an alveolar cleft osteoplasty of a nine-year-old female patient, mesenchymal stem cells were used instead of bone grafts. After six months the cleft bridged with 79.1% of the grafted region and after nine months the canine and lateral incisor in the affected side erupted in the reconstructed alveolar ridge.^[49]

DISTRACTION OSTEOGENESIS

Distraction osteogenesis is a surgical approach by which the development of new bone growth in an area subjected to gradual tension and stress occurs by deliberate separation of the fragments by traction.^[55] Ischemia is a limiting factor during distraction osteogenesis, which can be overcome by using stem cells.^[56] It has even been suggested that using stem cells in distraction osteogenesis may prove to be a potential method to accelerate bone regeneration in the distraction gap and enhance consolidation.^[57]

In a study,^[58] 54 New Zealand white rabbits underwent osteodistraction of the left mandible and were randomly divided into group A, group B, and group C ($n = 18$ in each group). At the end of the distraction, bone marrow mesenchymal stem cells (BMMSCs) transfected with osterix (OSX), autologous BMMSCs, and physiological saline were injected into the distraction gap in groups A, B, and C, respectively. It was observed that there was excellent bone callus formation in groups A and B. The group C animals showed poor bone formation in the distracted callus, when compared to groups A and B.

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.^[59] The primary methods used to reconstruct the temporomandibular joint (TMJ) include autogenous bone grafting, such as, harvesting from the rib or the use of alloplastic materials, with neither being ideally suited for the task and sometimes leading to unwanted adverse effects.^[60] The recent advances in stem cell technology assure the construction of a bioengineered TMJ replacement, which is biocompatible and capable of withstanding the physiological loads required for this joint.^[61] Cells from various sources, including articular cartilage cells, fibroblasts, human umbilical cord matrix cells, and mesenchymal stem cells, have been used in efforts to reconstruct the TMJ.^[62,63] In many studies, a tissue-engineered mandibular condyle was constructed, with stratified layers of cartilage and bone from a single population of BMMSCs, which was molded into the shape of a human cadaver mandibular condyle, with dimensions of $11 \times 7 \times 9$ mm (length \times width \times height).^[64-67]

THE PHASE OF TRANSITION

Stem cells are still controversial and of course their use is uneconomical. One requires high skill and knowledge to handle and use them. There are also no proper studies done on how many stem cells are required to treat a defect. Variable results are seen, for example, implantation of osteo-induced rabbit adipose-derived stem cells (ASCs) and gelfoam scaffolds into rabbit calvarian defects have not significantly improved bony healing when compared with the controls.^[68] In contrast to this, a study has reported improved calvarial defect healing upon implantation of poly lactic-co-glycolic acid scaffolds seeded with human ASCs maintained *in vitro*, in the presence of osteogenic factors, before implantation.^[69] There are many records of using different kinds of stem cells with different scaffolds, but to date no standard cell-scaffold system exists, which is accepted universally. This is a phase of transition and problems will exist, but they can only be solved by conducting more detailed researches and studies on them.

CONCLUSION

Nowadays stem cell therapy is one of the most favored areas of research in craniofacial tissue engineering. However, the fact is that our exposure to this technology remains limited, as it is extremely expensive. Isolation

and storage requires a lot of experience, as also high storage and good transport facilities. Stem cell therapy is a multidisciplinary approach. Support from the regulatory bodies, funding agencies, advocacy bodies, ethic bodies, and manufacturing agencies is also needed to make it easily acceptable in our clinical conditions. It will be really fascinating to see craniofacial orthodontists using this therapy on a daily basis to treat patients.

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