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Review Article

Stem Cells -The Biomedicine in Orthodontics

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Abstract: Background: The growth and fusion of various embryonic primordia give rise to the most complex three-dimensional structure of the human body i.e. the face. These primordia are highly populated with the adult stem cells or mesenchymal stem cells (MSCs). Description: As tissue engineering has gained momentum, these MSCs have been used in reconstruction of craniofacial and oro-dental defects. This review article will focus on the recent updates of stem cells and their scope in craniofacial Orthodontics. Conclusion: Even though in everyday Orthodontics is not much influenced by MSCs therapy but with the evolving technology, possibility does exist for its use in everyday Orthodontic procedures too.

Keywords: Stem cells, Orthodontics, Tissue engineering.

INTRODUCTION

Stem cells are undifferentiated, or "blank," cells which can develop into cells that serve numerous functions in different parts of the body. They have the capacity either to remain as stem cells or become specialized differentiated cells. (Stem Cell Research) Stem cells as a phrase was first coined by E.D. Wilson in 1896 (Svendsen, C.N., & Ebert, A.D. 2008). Stem cells can be categorized into three types as multipotent, totipotent and pluripotent, to serve different purposes. Multipotent cell type is the most differentiated type of stem cell thereby have limited capacities of developing into a complete organism. While, totipotent cells can differentiate into any cell type of the body. After several cell division cycles, totipotent cells will develop into pluripotent cells. Embryonic stem cells are known as pluripotent stem cells (Zainal Ariffin, S. H. *et al.*,2011). These cells can give rise to virtually any other type of cell in the body. Adult stem cells or extra-embryonic stem cells are partly specialized cells, as they are not capable of forming all types of cells (Xie, T., & Spradling, A. 2001).

MSCs are found in bone marrow, muscle, liver, placenta, peripheral blood, synovial fluid, dental pulp, and adipose tissue (Yoshimura, H. *et al.*,2007). Bone marrow–derived MSCs (BMSCs) are an abundant source of osteogenic precursors for bone tissue engineering. The healing of local bone defects by MSCs transplantation allows for maximal MSCs attachment, proliferation, and osteogenic differentiation and formation of mineralized matrix deposition. BMSCs have been shown to increase periodontal regeneration (Prockop, D.J. 1997; Krebsbach, P. H. *et al.*, 1997; Quarto, R. *et al.*,2001; Hu, B. *et al.*, 2006). Dental stem cells (DSCs), such as dental pulp stem cells and periodontal ligament stem cells, were also used in regeneration of dental tissues, including alveolar bone. Although DSCs are promising for regenerative dentistry, their availability is limited compared with BMSCs (Liu, H. C. *et al.*, 2011). This review interprets the critical role of adult stem cells on craniofacial bone, teeth, periodontium and TMJ, in postnatal growth and development and regeneration of the craniofacial tissues or organs.

Role of MSCs in Tissue Engineering

The most common craniofacial problems such as cleft lip and palate, ear microtia, craniofacial microsomia, and head and neck cancers often require a multi-staged multidisciplinary team approach. Though, the current surgical therapies attempt to reduce the morbidity and social/emotional impact, yet their outcomes can still be unpredictable and unsatisfactory (Mohammadi, B., & Tony, A. P. 2016). Craniofacial reconstructive surgery manipulates available tissues in a three dimensional field, either by transferring tissue from a donor site or supporting and shaping the repair

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with artificial scaffolds and biomaterials (Dudas, J. R. *et al.,* 2006 Yoon, E. *et al.,* 2007). With the addition of these materials, an artificial environment thus created, will allow MSCs renewal, proliferation, and differentiation and promoting vascularization, integration, adhesion, and survival of the newly generated (Rossi, C. A. *et al.,* 2010). Scaffolds provide a 3D framework for cells and serve as an extracellular matrix for a finite period of time. These scaffolds are biodegradable and biocompatible.

With the advancements in tissue engineering over the last decade has provided a plethora of materials to the craniofacial reconstructive surgeon, that may be suitable for the healing of craniofacial defects like the cleft palate. Tissue engineering scaffolds can be classified into three groups: autografts, allografts, and xenografts. Today the reconstructive surgeon makes best use of the autograft category, taking bone from another site (*e.g.*, iliac crest, rib) and transplanting it into the cleft defect (Mohammadi, B., & Tony, A. P. 2016).

MSCs as a tool in General Dentistry

With the understanding of the stem cell biology and its recent advancements, its scope in general dentistry and orthodontics has gained much popularity. To test the safety and effectiveness of new medications differentiated stem cells have been used thereby eliminating the need to test them on animals.

Unlike bone, most hard tissue in the tooth does not undergo constant renewal once formation; only dentin can regenerate itself internally upon injury, suggesting the existence of stem cell populations within the tooth pulp (Gronthos, S. *et al.,* 2000). One of the first dental related stem cell populations identified are the Dental pulp stem cells (DPSCs), which are capable of differentiating into multiple tissue types namely odontoblast, bone, adipocyte, and neuron (Gronthos, S. *et al.,* 2002). This multilineage capacity of these DPSCs suggests that they have a broader therapeutic application than lineage restricted adult stem cells (Ferro, F. *et al.,* 2014).

Regenerating the periodontium is a challenge in the treatment of periodontal diseases due to its complex structure. Studies on different animal models demonstrated some regeneration activity in periodontal tissues, suggesting the existence of stem cell population within the periodontium. (Nyman,S. *et al.,* 180; Parlar, A. *et al.,* 2005). Not only the periodontal ligaments, but also cementum and alveolar bone, can be regenerated, suggesting the presence of multi potential stem cell populations (Hollinger, J.O., &Winn, S.R. 1999; Alsberg, E. *et al.,* 2001; Shi, S. *et al.,* 2005). In an animal study, Periodontal ligament stem cells (PDSCs) were found helpful in regeneration of the wounded periodontium; surpassing the repair capacity of embryonic cells (Nayak, B. N. *et al.,* 2008).

MSCs as a tool in Orthodontics

The most fascinating part the of MSCs for orthodontists is that they provide a shorter treatment time, i.e. the bioactive factors secreted suppress the local immune system, inhibit fibrosis and apoptosis, enhance angiogenesis, and stimulate mitosis and differentiation of the tissue intrinsic reparative process (Caplan, A.I., & Dennis, J.E. 2006). This process increases the healing and regeneration, thereby treatment time is reduced.

One of the iatrogenic cause of Orthodontic treatment is the External apical root resorption (Pizzo, G. *et al.,* 2007; McNab, S. *et al.,* 2000; Sameshima, G.T., & Sinclair, P.M. 2001). 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 (Brudvik, P., Rygh, P. 1994). According to recent studies, odontoblasts derived from MSCs, stem cells from an exfoliated deciduous tooth (SHED), DPSCs, and apical papilla stem cells (SCAP), while cementoblasts from MSCs and dental follicular stem cells (DFSC); these cells may be used prior to the treatment, to prevent root resorption or post treatment to repair the damage (Bluteau, G. *et al.,* 2008).

Cases have been reported in the literature where TMJ replacement has been achieved with conventional approaches such as: autogenous bone grafting in Degenerative joint disorders. With the recent advances in stem cell therapy, bioengineered TMJ can be constructed for the replacement, which is biocompatible and capable of withstanding the physiological loads required for this joint (Yaun, K. *et al.,* 2010). 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 (Bailey, M. M. *et al.,* 2007; Schek, R. M. *et al.,* 2005).

Distraction osteogenesis deals with new bone growth in an area subjected to gradual tension and stress occurs by deliberate separation of the fragments by traction and ischemia holds the most common limiting factor (Dheeraj, K. *et al.,* 2011; Cetrulo Jr, C. L. *et al.,* 2005). 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 (Qi, M. *et al.,* 2006).

Stem cell therapy also holds as a promising treatment modality for cleft palate cases. Treatment with conventional secondary bone graft is followed by some complications if not performed with care. So, stem cells can be an alternative to this which has been proved clinically: 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 (Waite, P. D., & Waite, D. E. 1996, September).

Stem cell research controversy

MSCs don't present any ethical problems. However, in recent years, there has been controversy surrounding the way human embryonic stem cells are obtained. Two schools of thought exist regarding their use in clinical dentistry. The first school thinks that the embryo is destroyed during the process of harvesting embryonic stem cells hence, raises ethical concerns for people who believe that the destruction of a fertilized embryo is morally wrong. While, the supporters of stem cell research, on the other hand, believe that the embryos are not yet humans (Stem Cell Research; Liu, H. C. *et al.,* 2011; Dudas, J. R. *et al.,* 2006). Hence, their use has been limited by ethical issues, dysregulated ES cell differentiation, and immune rejection. All this further requires pre planning to use ES cells for clinal research (Rossi, C. A. *et al.,* 2010).

With the breakthrough discovery of induced pluripotent stem cells (iPSCs), there may be less of a need for human embryos in research. This may help ease the concerns of those who are against using embryos for medical research.

However, if iPSCs have the potential to develop into a human embryo, researchers could theoretically create a clone of the donor. This presents another ethical issue to take into consideration.

CONCLUSION

Nowadays stem cell therapy is one of the most favored areas of research in craniofacial tissue engineering. It is pertinent for the orthodontists to be prepared for paradigm shifts in craniofacial regeneration for optimal and efficient manipulation in conjunction with techniques of the future. Also, this therapy if used by craniofacial orthodontists on a daily basis to treat patients indeed would be great.

CONFLICTS OF INTEREST

There is no conflict of interest.

DECLARATION

- **Ethics approval and consent to participate-** NOT APPLICABLE
- **Consent for publication-** NOT APPLICABLE
- **Availability of data and material-** The datasets generated and/or analysed during the current study are available in the Google Scholar and Pubmed repository
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ABBREVIATIONS

- MSCs- Mesenchymal stem cells
- BMSCs- Bone marrow–derived MSCs
- DSCs- Dental stem cells
- DPSCs- Dental pulp stem cells
- PDSCs- Periodontal ligament stem cells
- SCAP- apical papilla stem cells
- DFSCs- dental follicular stem cells
- iPSCs- induced pluripotent stem cells

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