

Dental stem cells

Vashisht N¹, Vashisht D²

¹Dr Neha Vashisht

MDS, Oral Medicine and Radiology
Private Practitioner, Shimla

²Dr Divy Vashisht

Senior Lecturer, Prosthodontics
H P Government Dental College and
Hospital
Shimla, Himachal Pradesh, India

Received: 07-09-2013

Revised: 22-09-2013

Accepted: 31-10-2013

Correspondence to:

Dr Neha Vashisht

0 9736020571

dr_nehamahajan26@yahoo.in

ABSTRACT

While the regeneration of a lost tissue is known to mankind for several years, it is only in the recent past that research on regenerative medicine/dentistry has gained momentum and eluded the dramatic yet scientific advancements in the field of molecular biology. The growing understanding of biological concepts in the regeneration of oral/dental tissues coupled with experiments on stem cells is likely to result in a paradigm shift in the therapeutic armamentarium of dental and oral diseases culminating in an intense search for “biological solutions to biological problems.” Stem cells have been successfully isolated from variety of human tissues including orofacial tissues. Mesenchymal stem cells (MSCs) are multipotent stem cells which differentiate into a variety of cell types. The potential MSCs for tooth regeneration mainly include stem cells from human exfoliated deciduous teeth (SHEDs), adult dental pulp stem cells (DPSCs), stem cells from apical part of the papilla (SCAPs), stem cells from the dental follicle (DFSCs), periodontal ligament stem cells (PDLSCs) and bone marrow derived mesenchymal stem cells (BMSCs). This review article outlines the recent progress in mesenchymal stem cells used in tooth regeneration.

Keywords: Dental stem cells, tooth engineering

Introduction

The term “tissue engineering” was coined in 1993 by Langer and Vacanti to describe the process by which tissues and organs are regenerated by cell transplantation with or without a scaffold. [1] Tissue engineering aims to stimulate the body either to regenerate tissue on its own or to grow tissue outside the body which can then be implanted as natural tissue. [2]

Stem cells are defined by their capacity to generate daughter cells with different and more restricted properties. [3] According to developmental stages, stem cells can be divided into embryonic stem cells and adult stem cells. Differentiation and proliferation of embryonic stem cells constitute the basis of animal development. The further differentiation of adult stem cells is the prerequisite of tissues and

organs repair and regeneration. Embryonic stem cells are the progenitors of undifferentiated cells, which are “totipotent” (totipotency is the ability of a single cell to divide and produce all the differentiated cells in an organism, including extraembryonic tissues) and can differentiate into a variety of cells to form various organs, also known as the “all-competent cells”. In the process of cell differentiation, they can gradually differentiate into a stable form of “pluripotent stem cells”. With the features of highly proliferative capacity and plasticity, stem cells are regarded as a new source of seed cells in tissue engineering in a wide range of applications. [2] Numerous attempts have been made to “create” tooth and very promising results been made. In the field of tooth engineering, efforts have

been made to explore mesenchymal stem cells (MSCs) such as stem cells from human exfoliated deciduous teeth (SHEDs),^[4] adult dental pulp stem cells (DPSCs),^[5] stem cells from the apical part of the papilla (SCAPs),^[6] stem cells from the dental follicle (DFSCs),^[7] periodontal ligament stem cells (PDLSCs),^[8] bone marrow derived mesenchymal stem cells (BMSCs)^[9] and epithelium-originated dental stem cells.^[10] These dental stem cells are derived from the neural crest, and thus have a different origin from bone marrow-derived MSCs, which are derived from mesoderm.

Stem cells from human exfoliated deciduous teeth (SHEDs)

The discovery of stem cell in deciduous teeth sheds a light on the intriguing possibility of using dental pulp stem cells for tissue engineering.^[4] The obvious advantages of SHEDs are: higher proliferation rate compared with stem cells from permanent teeth, easy to be expanded in vitro, high plasticity since they can differentiate into neurons, adipocytes, osteoblasts and odontoblasts, readily accessible in young patient, especially suitable for young patients with mixed dentition.^[2,4]

Miura et al^[4] demonstrated that SHEDs could not differentiate directly into osteoblasts but did induce new bone formation by forming a template to recruit murine host osteogenic cells. SHEDs are distinctive with the osteoinductive ability and high plasticity.

Adult dental pulp stem cells (DPSCs)

The dental pulp is a highly specialized mesenchymal tissue characterized by the presence of odontoblasts and by the fact that it is surrounded by a rigid mineralized

tissue.^[11] The dental pulp is infiltrated by a network of blood vessels and nerve bundles emanating from the apical region. Damage to the dental pulp by mechanical, chemical, thermal, and microbial irritants activate various types of inflammatory responses involving complex vascular, lymphatic, and local tissue reactions.^[12]

Gronthos^[5] first identified adult dental pulp stem cells in human dental pulp and found that they could regenerate a dentin-pulp-like complex, which is composed of mineralized matrix with tubules lined with odontoblasts, and fibrous tissue containing blood vessels in an arrangement similar to the dentin-pulp complex found in normal human teeth.

DPSC cells are characterized by their ability to differentiate into multiple stromal cell lineages and to their clonogenic capacity.^[13] It has been demonstrated that DPSCs are able to adhere and proliferate in scaffolds and they can also differentiate into odontoblastic lineage cells. In vitro, DPSC demonstrate high frequency of colony formation, producing calcified nodules.^[13,14]

In a study by Zhang et al., 2006, DPSCs were seeded onto different 3-dimensional scaffold materials (a spongy collagen, a porous ceramic, and a fibrous titanium mesh) and implanted in nude mice for 6 or 12 weeks, the formed tissue was not dentin-pulp-like complex but something resembled connective tissue. These studies indicate the potential of DPSCs in tooth tissue engineering.^[15]

Stem cells from dental follicle (DFSCs)

The dental follicle is a mesenchymal tissue that surrounds the developing tooth germ. During tooth root formation, periodontal components, such as cementum,

periodontal ligament (PDL), and alveolar bone, are created by dental follicle progenitors. [2] Stem cells from dental follicle (DFSCs) have been isolated from follicle of human third molars and express the stem cell markers: Notch1, STRO-1 and nestin. [16, 3] DFSCs were found to be able to differentiate into osteoblasts/cementoblasts, adipocytes, and neurons. In addition, immortalized dental follicle cells were transplanted into immunodeficient mice and were able to recreate a new periodontal ligament (PDL)-like tissue after 4 weeks. [2] These cells may be a useful research tool for studying PDL formation and for developing regeneration therapies.

Luan [17] indicated that DFSCs lines were heterogeneous. The three main lineages were highly undifferentiated state of periodontal ligament-type lineage and cementoblastic or alveolar bone osteoblastic lineage. The profound cellular heterogeneity of DFSCs suggests that heterogeneous cellular constituents might play a role in tissue regeneration as much as the individual lineages might do.

Bone marrow derived mesenchymal stem cells (BMSCs)

Human bone marrow-derived stem cells originate from cell populations in the bone marrow and are capable of differentiating along multiple mesenchymal lineages. The bone marrow derived cells are a mixed population which consists of fibroblasts, osteoblast, adipocyte progenitors and up to 0.01% stem cells. [18]

BMSCs have been tested for their ability to recreate periodontal tissue and restore periodontal defects. It was proved that auto-transplantation of BMSCs are able

to form in vivo cementum, periodontal ligament, and alveolar bone after implantation into defective periodontal sites. Thus, bone marrow provides an alternative source of MSC for the treatment of periodontal diseases. [19, 2]

Hu and his colleagues [20] investigated the possibility that BMSCs give rise to different types of epithelial cells and their potential to serve as a source for ameloblasts. Their results showed, for the first time, that BMSCs can be reprogrammed to give rise to ameloblast-like cells.

Periodontal ligament stem cells (PDLSCs)

The periodontal ligament is a specialized connective tissue, derived from dental follicle and originated from neural crest cells. Recent studies have shown that mesenchymal stem cells obtained from periodontal ligament are multipotent cells with similar features of the BMSCs and DPSCs, capable of developing different types of tissues such as bone and tooth associated tissues. It was reported that PDLSCs could differentiate into cells that can colonize and grow on biocompatible scaffold, suggesting an easy and efficient autologous source of stem cells for bone tissue engineering in regenerative dentistry. [2]

Ex vivo-expanded PDLSCs are capable of regenerating a typical cementum/periodontal ligament-like structure when transplanted into immunocompromised mice using hydroxyapatite/tricalcium phosphate (HA/TCP) as a carrier. [21] Because of their periodontal ligament derivation and their capacity to differentiate into osteoblasts, cementoblasts, and fibroblasts, PDLSCs were

the first candidate stem cells for periodontal tissue engineering. More importantly, these cells have the potential to form collagen fibers and generate cementum/PDL-like structures in vivo and, thus, serve as reliable sources for periodontal tissue reconstruction.

Adipose-derived stromal cells (ADSCs)

Adipose-derived stromal cells are considered to contain a group of pluripotent mesenchymal stem cells and manifest multilineage differentiation capacity, including osteogenesis, chondrogenesis and adipogenesis.^[2] ADSCs exhibit stable growth and proliferation kinetics in vitro. Adipose tissue can be obtained by less invasive methods and in larger quantities than bone marrow cells, making the use of hADSCs as a source of stem cells very appealing.

In 2005, a research team^[22] first proposed the hypothesis that adipose derived stem cells could be induced into odontogenic lineage and might be used as suitable seeding cells for tooth regeneration to replace the lost tooth of elderly patient. The team holds the opinion that the seeding cells for tooth regeneration such as odontoblasts from dental germ, stem cells from dental pulp and deciduous teeth, and ectomesenchymal cells from the first branchial arch are difficult, even impossible to harvest in clinic. Bone marrow mesenchymal stem cells have odontogenic capacity, but their differentiation abilities significantly decrease with the increasing age of the donors. Therefore, the cells mentioned above are not practical in the clinical application of tooth regeneration in the old. They tried to find ideal alternative seeding cells and an appropriate inducing

method to overcome the problems mentioned above. The team reported that overexpression of DSPP enhanced expression of genes related to mineralization, such as Cbfa1, Osx, BSP, OCN and DMP1 in ADSCs and early odontogenic marker genes, such as Msx1, Msx2, Lhx7 and Pax9, which implied that these cells may differentiate into functional odontoblast-like cells. It was reported that ADSCs expressed bone marker proteins including alkaline phosphatase, type I collagen, osteopontin, and osteocalcin and produce mineralized matrix.

In a study,²³ the ADSCs ability to form osteoid matrix in vivo was determined, proved them a novel therapeutic for bone repair and regeneration.

Tooth Engineering

A therapeutic option that was unthinkable a few years ago seems an achievable goal today. Tooth engineering is possible now. Since teeth are formed from two different tissues, building a tooth logically requires the association/cooperation of odontogenic mesenchymal and epithelial cells. The recombination of dissociated dental epithelial and mesenchymal tissues leads to tooth formation both in vitro and in vivo.^[18]

Conclusion

There has been great interest in mesenchymal stem cells and their roles in maintaining the physiological structure of tissues. Since these cells are considered as candidates for regenerative medicine, the knowledge of the cell differentiation mechanisms is imperative for the development of tooth engineering.

Stem cell therapy is no longer science fiction. Recent developments in the technique of stem cell isolation and expansion together with advances in growth factor biology and biodegradable polymer constructs have set a stage for successful tissue engineering of tooth/tooth-related tissues. Stem cell therapy has brought in a lot of optimistic hope amongst researchers, doctors, and not to forget the patients who are the chief supportive and beneficiary of this innovation.

References

1. Langer R, Vacanti JP. Tissue engineering. *Science* 1993;260:920-926.
2. Li Peng, Ling Ye, Xue-dong Zhou. Mesenchymal Stem Cells and Tooth Engineering. *International Journal of Oral Science* 2009;1(1):6-12.
3. Masaki J. Honda, Mari Imaizumi, Shuhei Tsuchiya, Christian Morsczech. Dental follicle stem cells and tissue engineering. *Journal of Oral Science* 2010;52:541-552.
4. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG et al. SHED: stem cells from human exfoliated deciduous teeth. *Proc Natl Acad Sci USA* 2003;100:5807-5812.
5. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc Natl Acad Sci USA* 2000;97:13625-13630.
6. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. *J Endod* 2008;34:166-171.
7. Yao S, Pan F, Prpic V, Wise GE. Differentiation of stem cells in the dental follicle. *J Dent Res* 2008;87:767-771.
8. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004; 364:149-155.
9. Li ZY, Chen L, Liu L, Lin YF, Li SW, Tian WD. Odontogenic potential of bone marrow mesenchymal stem cells. *J Oral Maxillofac Surg* 2007;65(3):494-500.
10. Bluteau G, Luder HU, De Bari C, Mitsiadis TA. Stem cells for tooth engineering. *Eur Cell Mater* 2008;16:1-9.
11. Nor JE. Tooth regeneration in operative dentistry. *Oper Dent* 2006;31:633-642.
12. Nakashima M, Akamine A. The application of tissue engineering to regeneration of pulp and dentin in endodontics. *J Endod* 2005;31:711-718.
13. Flávio Fernando. Dental Pulp Tissue Engineering. *Braz Dent J* 2011;22:3-14.
14. Gronthos S, Brahim J, Li W, Fisher LW, Cherman N, Boyde A et al. Stem cell properties of human dental pulp stem cells. *J Dent Res* 2002;81:531-535.
15. Zhang W. The performance of human dental pulp stem cells on different three-dimensional scaffold materials. *Biomaterials* 2006;27:5658-5668.
16. Morsczech C, Gotz W, Schierholz J, Zeilhofer F, Kuhn U, Mohl C et al. Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biol* 2005; 24(2):155-165.
17. Luan X, Ito Y, Dangaria S, Diekwisch TG. Dental follicle progenitor cell heterogeneity in the developing mouse periodontium. *Stem Cells Dev* 2007;15(4):595-608.
18. G. Bluteau. Stem Cells for Tooth Engineering. *European Cells and Materials* 2008;16:1-9.
19. Kawaguchi H, Hirachi A, Hasegawa N, Iwata T, Hamaguchi H, Shiba H et al.

- Enhancement of periodontal tissue regeneration by transplantation of bone marrow mesenchymal stem cells. *J Periodontol* 2004;75(9):1281–1287.
20. Hu B, Unda F, Bopp-Kuchler S, Jimenez L, Wang XJ, Haikel Y et al. Bone marrow cells can give rise to ameloblast-like cells. *J Dent Res* 2006;85(5):416– 421.
21. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet* 2004;364:149-155.
22. Jing W, Wu L, Lin Y, Liu L, Tang W, Tian W. Odontogenic differentiation of adipose-derived stem cells for tooth regeneration: necessity, possibility, and strategy. *Med Hypotheses* 2008;70(3):540–542.
23. Hicok KC, Du Laney TV, Zhou YS, Halvorsen YD, Hitt DC, Cooper LF et al. Human adipose-derived adult stem cells produce osteoid in vivo. *Tissue Eng* 2004;10:371–380.

Cite this article as: Vashisht N, Vashisht D. Dental stem cells. *Int J Med and Dent Sci* 2014; 3(1):376-381.

Source of Support: Nil
Conflict of Interest: No

