

Dental-derived Stem Cells and Whole Tooth Regeneration: An Overview

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The World Journal of Medical Education and Research (WJMER) is the online publication of the Doctors Academy Group of Educational Establishments. Published on a quarterly basis, it's aim is to promote academia and research amongst all members of the multi-disciplinary healthcare team including doctors, dentists, scientists, and students of these specialties from all parts of the world. The principal objective of this journal is to encourage the aforementioned from developing countries in particular to publish their work. The journal intends to promote the healthy transfer of knowledge, opinions and expertise between those who have the benefit of cutting edge technology and those who need to innovate within their resource constraints. It is our hope that this will help to develop medical knowledge and to provide optimal clinical care in different settings all over the world. We envisage an incessant stream of information will flow along the channels that WJMER will create and that a surfeit of ideas will be gleaned from this process. We look forward to sharing these experiences with our readers in our subsequent editions. We are honoured to welcome you to WJMER.



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Introduction

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Dental-derived Stem Cells and Whole Tooth Regeneration: An Overview

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Abstract

Recent advances in the identification and characterisation of dental stem cells and in dental tissue- engineering strategies suggest that bioengineering approaches may successfully be used to regenerate dental tissues and whole teeth. As clinically relevant methods for generation of bioengineered dental tissues and whole teeth continue to improve, interest in the application of tissue regeneration increases. This paper describes dental derived stem cells and their characterization.

Introduction

Replacing teeth in modern dentistry utilizes titanium implants capped with a ceramic crown. Although these implants serve the purpose, factors that interfere with osteointegration (contact between bone and implant surface without the interposition of non-bone or connective tissue) may cause surgery failure. With advances in the stem cell biology and tissue engineering, 'biological teeth'¹ may become an alternative for replacing missing teeth. Stem cells are the 'Master cells' of the human body, and can differentiate into many types of cells, such as heart, muscle, bone or brain cells. They then proliferate, depending on the surrounding tissue, to form the specific desired tissue or organ. Stem cells are one of the most fascinating areas of biology today. They are unique cells and regardless of their source have three general properties – capacity to divide and renew

themselves for long periods, being 'unspecified', with the ability to give rise to specialized cell types².

Stem cells could be used to create a natural substitute for missing teeth. They would need to be programmed to adopt a dental lineage by cultivation with odontogenic induction signals, which work through epithelial mesenchymal interactions, and then developed over a scaffold matrix.

Stem Cell Classification

Stem cells are classed according to their 'potency', or ability to produce other specialised cell types:

1. **Totipotent** – these cells can differentiate into embryonic and extra-embryonic cell types. They are produced from fusion of the egg and the sperm cells and during the first few divisions of the fertilized egg.
2. **Pluripotent** – these cells can differentiate into cells derived from any of three germ layers. They are descendants of the totipotent stem cells and include some dental stem cells.
3. **Multipotent** - these can produce cells of closely related cell families e.g. hematopoietic stem cells can differentiate into red blood cells, white cells, platelets etc.
4. **Unipotent** - unlike the other stem cell types, these can produce only one cell type but are distinguished from non-stem cells by the property of self-renewal.

In dental research, there are two major categories of stem cells which are available for clinical application, embryonic and somatic stem cells. The isolation and use of human embryonic stem cells is ethically controversial. Somatic stem cells are easier to access and their uses do not bring up ethical concerns³, hence these are the most practical for use in dentistry. Mesenchymal stem cells (MSC) cells reside in post-natal organs and tissues like bone marrow, brain, liver, kidney, skin, adipose and dental pulp. These can be sourced by bone marrow biopsy (although often low yield), or by suction-assisted lipectomy. However, somatic stem cells number and function decreases with age, for example in new born it is 100%, by teens 10%, by 30 years 4%, by 50 years 2.5%. The functions decline in form of loss of lineage specificity, loss of self renewal, depletion due to senescence.

Stem Cell Isolation

Recently, it has been found that specific populations of dental stem cells can be isolated from three dental recourses, the dental follicle, the dental pulp stem cells (DPSCs) from exfoliated deciduous teeth (SHED), and the developed periodontal ligament.

Stem cells have been successfully cultured from both dental pulp tissue and periodontal ligament by Vagra and co-workers⁴. They demonstrated that both cell cultures showed typical fibroblast-like morphology, with clonogenic activity, and were STRO-1 positive on immunoreactivity testing. These results mean DPSCs are capable of self-renewal and multilineage differentiation.

The commonly known sources of stem cells are umbilical cord and bone marrow. However, it is a tedious process to retrieve stem cells from bone marrow and the umbilical cord requires preserving at the time of birth if for this purpose. Dental stem cells therefore provide a

useful and simpler option for retrieval of stem cells (Figure 1).

Stem Cell Preservation

The milk teeth of children (6 to 12 years of age) and the wisdom molars of adults are potent sources of dental stem cells. However, other teeth can be viable sources, particularly in young patients. If stem cells are to be preserved to be used in potential disease treatments, they are best taken sooner, in younger patients. Examples of disease where stem cells therapy may be future therapy include heart diseases, myocardial infarction, arthritis, Parkinson's disease, bone defects, liver diseases and multiple sclerosis. Banking stem cells can increase the chances of better life expectancy and is a mode of 'Biological Insurance' (Figure 2)

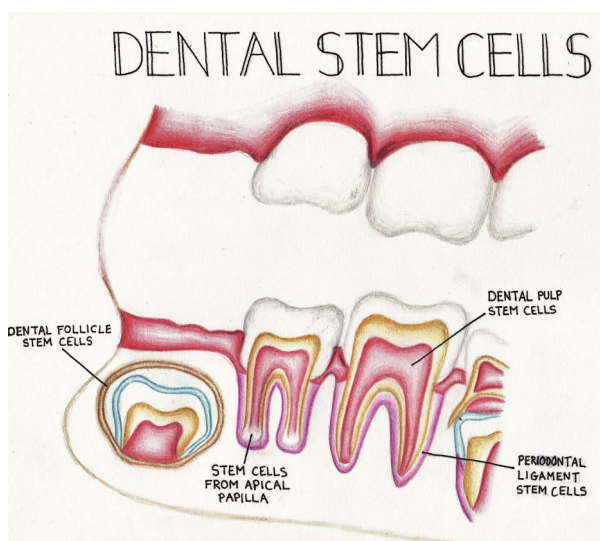


Figure 1: Location of Dental Stem Cells

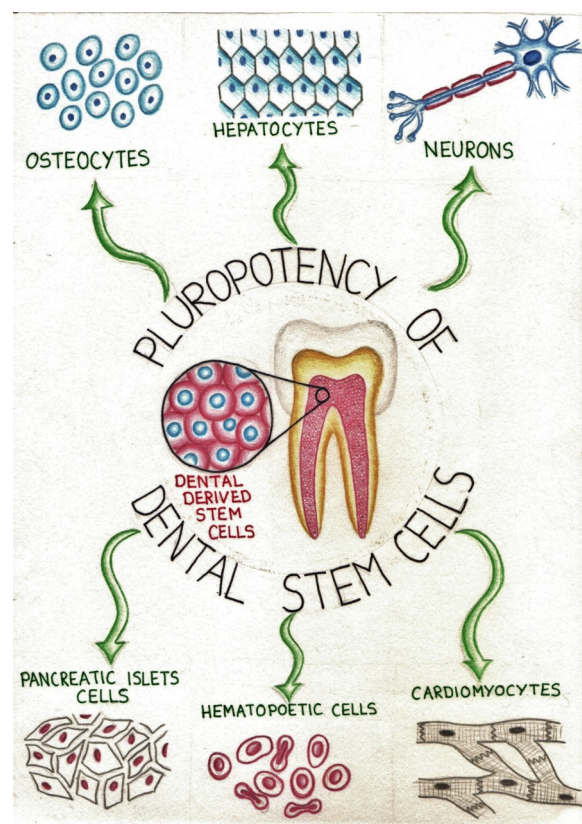


Figure 2: Pluripotency of Dental Stem Cells

Stem Cell Characterisation

It is important to be able to identify the odontogenic stem cells from dental tissue samples. Gronthos et al. first described a method of identification in 2000⁵, based on their clonogenic ability, rapid proliferation rate and capacity to form mineralized tissue both in vitro and vivo. Subsequent studies have isolated single cell colony-derived DPSC populations which demonstrate multipotentiality, forming adipocytes, neural precursors and the dentine-like tissues.

interactions that occur between neighbouring cells and include growth factor receptors, cell adhesion molecules and other cell surface markers expressed by MSCs are summarized in (Table 1).

Bone marrow stem cells and DPSCs, express similar putative surface markers, including CD4, CD106, CD146, 3G5 and Stro1. Both also express matrix proteins associated with mineral tissue formation, such as alkaline phosphatase, osteocalcin and osteopontin. However, in contrast to bone marrow stem cells, DPSCs have been shown to maintain a 30% higher proliferation rate and a higher growth potential.

Marker Type	Examples
Surface Markers	CD13,CD29,CD44,CD73, CD90,CD105,CD106, Stro-1,Stca-1
Cytokine receptors	IL-1R, IL-3R, IL-6R, IL-7R
Extracellular matrix receptors	ICAM-1, ICAM-2, VACM-1, ALCAM, endoglin, hyaluronate receptor integrins $\alpha 1, \alpha 2, \alpha 3, \alpha A, \alpha V, \beta 1, \beta 2, \beta 3, \beta 4$
Growth factor receptors	BFGF-R, PDGF-R
Other receptors	Thy-1, IFN- γ R, TGF- β R, TNF-R
<i>Commonly used cell surface proteins/receptors that are characteristic markers for isolation and characterization of MSC are shown. Fluorescently tagged antibodies to most of there are commercially available and can be used in a flow cytometry setting.</i>	

Table 1: Kind courtesy ofnAous Dannan. "Dental derived stem cells and whole teeth regeneration. An overview: 1 clinical Med Res" 2009, 1(2): 63-71}

Tissue Regeneration

Stem cells are considered tools for replacing, repairing, regenerating, and rejuvenating dead, degenerating or injured tissue and cells. Lifelong treatment is possible by engrafting stem cells into tissue or organs, such as liver, bone, kidney, lungs, heart, spinal cord etc.

Once implanted, stem cells interact with the surrounding micro-environments, facilitating regeneration by secreting certain factors. An extracellular matrix is required to provide physical support, nutrient, growth factors, cell migration, proliferation and cell adhesion⁶. Three dimensional scaffolds are used for growing mineralized tissues. The scaffold has regulated microporosities, are hydrophylic, biocompatible and biodegradable. They are fabricated out of a co-polymer

of polylactic acid and polyglycolic acid. Although for cartilage and bone growth collagen sponges, hydroxyapatites can be used.

Replacement Tooth Engineering

The concept of engineering a whole tooth is theoretically feasible and has exciting potential. Significant clinical challenges remain however, with issues about tooth shape and size, availability of the dental epithelium, growth and eruption of the tooth require resolution.

Research is currently in progress on developing complex scaffolds with bioengineered components to enhance

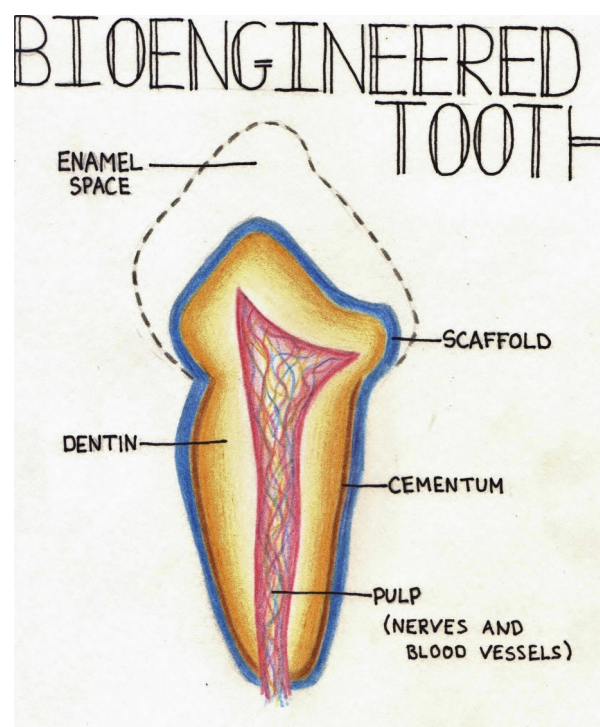


Figure 3: Potential bio-engineered tooth

stem cell and tooth regeneration (Figure 3).

The regeneration process requires identification and guidance of epithelial and mesenchymal cells interactions, to form a natural tooth. An ideal scaffold material has appropriate porosity, biocompatibility and biodegradability (usually degrading within weeks to one year). It requires the ability to support cell growth and act as a controlled gene and protein vehicle.

Two approaches to culturing stem cells are now possible now. In the first approach, stem cells are grown in vitro on a designed three-dimensional scaffold, composed of pores and intercommunicating channels. The second approach grows stem cells in vivo, in the organism itself for example as a subcutaneous transplant or in the kidney capsule. These culture sites provide nutrient and oxygen to nurture tooth-germ; a small tooth is cultivated there before it is implanted in to their anatomical sites.

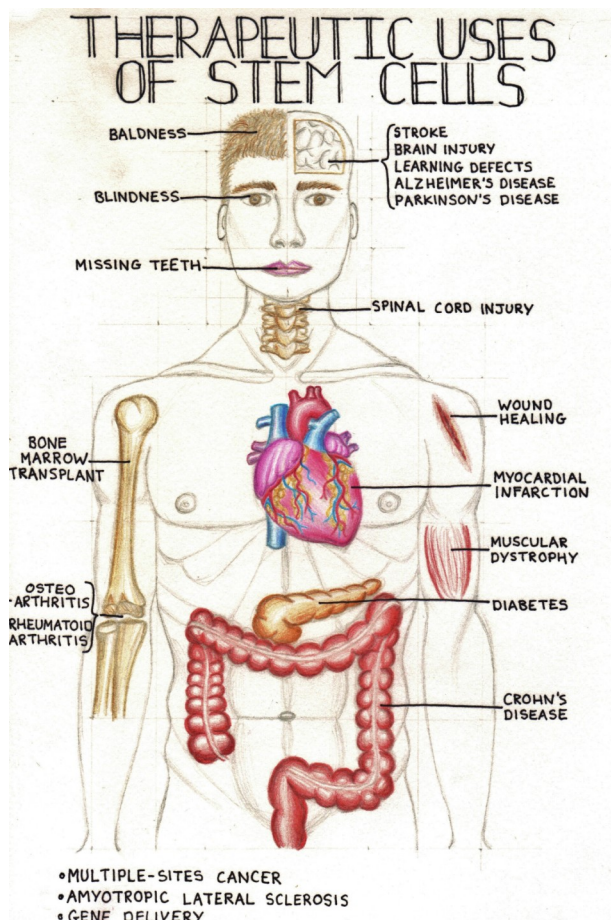


Figure 4: Therapeutic Uses of Stem Cells

Conclusion

In conclusion, regeneration of dental tissues provides an attractive alternative to traditional approaches for patients with missing teeth (replacement using natural tissues). The development of new approaches requires precise regulation of regenerating events to maintain tooth structure. There is an opportunity to move restorative dentistry into a new era, harnessing the biological activity of dental tissue, stem cells and tissue regeneration. Already, isolation, collection and cryopreservation of dental stem cells for banking and clinical use is now feasible and commercially possible. Stem cells are not yet fully understood but have great potential therapeutically. There needs to be careful research before routine clinical use is possible.

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