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Stem cells, regenerative dentistry and their current trends: A narrative review

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Abstract
Periodontal disease is a worldwide problem that affects people of all classes. It is caused by a bacterial infection of the periodontium and results in a degeneration of tissue. Current methods used to repair any damage due to periodontal disease have poor efficacy, can be harmful, painful and expensive. The future therapeutic methods may involve tissue engineering using stem cells found in the Periodontal Ligament. The reason that the PDLSC's hold such great importance is that most of the cells are able to differentiated into a mixture of periodontal ligament -including the specific fiber bundles that attach tooth to bone - and the mineralized tissue called cementum that covers the roots of our teeth. These cells are also beneficial in a clinical point of view because they are so easily accessible. In theory, people could one day preserve these stem cells and bank them from their own wisdom teeth that they have had extracted. These can then be used later in life to treat advanced periodontal disease. The idea of preserving one's own cells for later use is the ideal for the future of tissue engineering via stem cells.

Keywords: Stem cell, regeneration, tissue engineering, periodontal ligament

Introduction
The periodontium is the area of specialized tissue surrounding the tooth and anchoring it to the underlying alveolar bone. It is composed of four regions; the cementum, periodontal ligament (PDL), gingival (gums), and the alveolar bone. The cementum is a layer of bone that surrounds the root of the tooth. Its main function is to serve as the site to which the PDL attaches. The other end of the PDL then attaches to the alveolar bone, therefore anchoring the tooth in place. The PDL is composed of cells that have either fibroblastic or osteoblastic properties. Periodontal disease is a bacterial infection that leads to tissue damage of the periodontium and is the major cause of tooth loss. The PDL goes through limited regeneration and repair if there is no therapeutic involvement. The current therapeutic methods are also somewhat ineffective in that they have variable efficacy as well as safety issues among other things. There are novel approaches to PDL regeneration that involve tissue engineering. It is in these new methods that the potential for the use of stem cells can be applied. A stem cell is a special kind of cell that has a unique capacity to renew itself and that have a remarkable potential to develop into many different cell types in the body. Serving as a sort of repair system for the body, they can theoretically divide without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential to either remain as a stem cell or become another type of cell with a more specialized function e.g a muscle cell, brain cell or red blood cell. Although most cells of the body such as cardiac cells or skin cells are committed to conduct a specific function whereas stem cells are uncommitted until they receive a signal to develop into specialized cells. Stem cell research has the potential to impact not just one disease but numerous ones e.g. Diabetes, Cancer, Cardiovascular disease, Alzheimer's disease, Burn victims, Leukemia, tooth regeneration, bone regeneration and many more but to be able to harness such therapeutic potential of stem cells, scientists need to learn how to direct them to differentiate appropriately, their therapeutic potential and to ensure that they do not continue to multiply in an uncontrolled way.[1] The goal of modern restorative dentistry is to functionally and cosmetically restore the tooth structure. Identification of adult stem cells has thrown a light on regenerative dentistry and has provided insight to replace damaged structures including dentin and root structures, as well as the cells of the pulp-dentin complex.

Background

Stem cell is a broad term that refers to any number of cells that are able to self renew and are not committed to being any one specific cell type. Adult stem cells are multipotent and can differentiate into any number of different cells, though this potential to differentiate is more limited than in embryonic stem cells. Mesenchymal stem cells (MSC) differentiate into different types of connective tissue such as muscle, endothelial cells, fibroblasts, osteoblasts, adipocytes and chondroblasts Since, it is these types of cells that make up the tissue of the periodontium, it is determined that the PDL cells are derived from mesenchymal stem cells. Generally when stem cells differentiate into committed cells, they go through different phases of development. Before they can become fully differentiated cells the stem cells go through an intermediate phase. At this point the cells are somewhat differentiated and are considered progenitor cells. These progenitor cells must undergo further replications and differentiation before they reach the stage at which they are considered fully differentiated and committed cells. The PDLSC differentiate into three different cells in order to make up the tissues of the cementum, PDL, gingival and alveolar bone. These include cementoblasts, fibroblasts and osteoblasts. [2] (Fig-1)

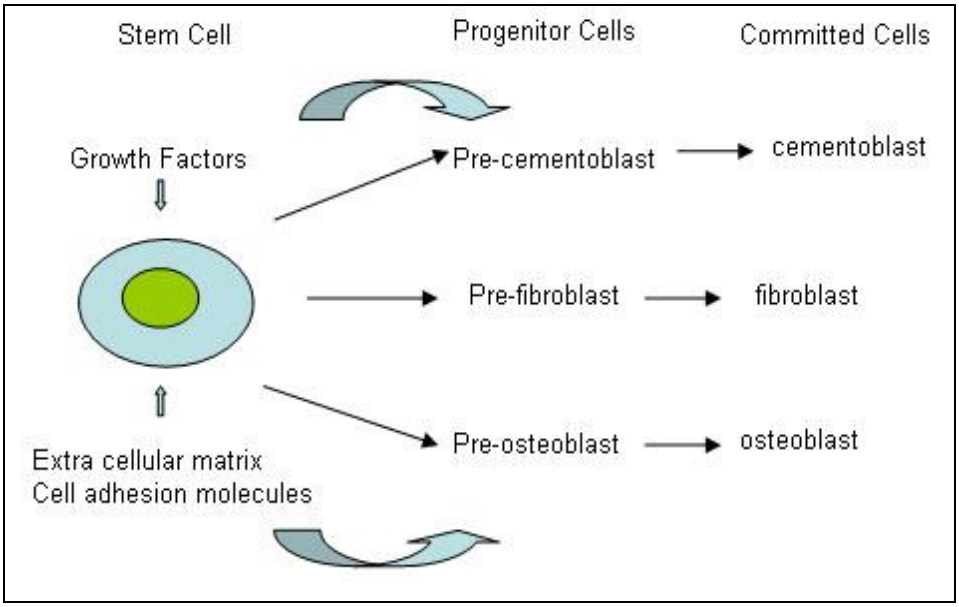


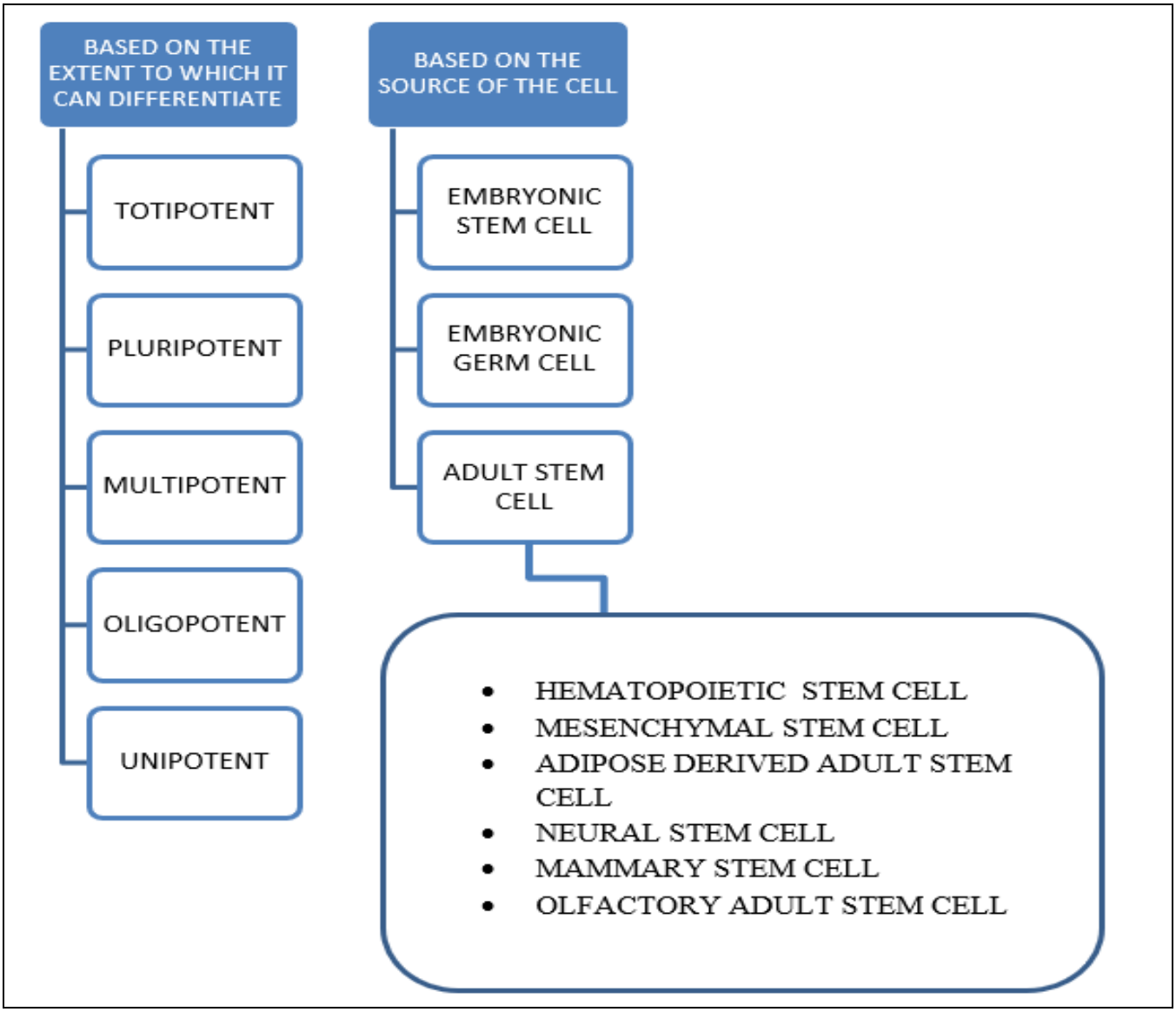
Fig 1: Differentiation of adult mesenchymal stem cells and progenitor cells.

History of Stem Cells [3-6]

1878	The first attempts were made to fertilize mammalian eggs outside the body.
1908	The term "stem cell" was proposed for scientific use by the Russian histologist Alexander Maksimov (1874-1928) at congress of hematologic society in Berlin. It postulated existence of haematopoietic stem cells.
1959	First animals made by in-vitro fertilization (IVF).
1968	The first human egg is fertilized *in vitro*.
1978	The first IVF baby is born in England.
1978	Haematopoietic stem cells are discovered in human cord blood.
1997	Leukemia is shown to originate from a haematopoietic stem cell, the first direct evidence for cancer stem cells.
1998	A new era in stem cell biology began. James Thomson and co workers reported methods of deriving and maintain human embryonic stem cells from the inner cell mass of human blastocysts donated by couples undergoing treatment for infertility. They derive the first human embryonic stem cell line at the University of Wisconsin-Madison.
2003	MIURA *et al.* identified the multipotent stem cell [SHED – stem cell from human exfoliated deciduous teeth].
2004	SEO *et al.* reported multi potent stem cell from human periodontal ligament.
2005	SAITO *et al.* developed bovine cementoblast cells.
2007	Mario Capecchi, Martin Evans, and Oliver Smithies win the 2007 Nobel Prize for Physiology or Medicine for their work on embryonic stem cells from mice using gene targeting strategies producing genetically engineered mice (known as knockout mice) for gene research.

Properties of Stem Cells [7, 8]

Self-division and self-renewal	Stem cells have a special ability to divide and renew themselves for extended periods of time. In fact an initial population of stem cells can produce millions of cells within few months in a laboratory setting. When the produced cells remain unspecialized for a longer duration - that indicates the long term self-renewal capacity of the cells.
Unspecialized	Stem cells lack the specific parts that allow them to perform specialized functions in the body. A stem cell does not have a specialized function but it has the capacity to differentiate into a specialized cell that can carry out these functions.
Can Give Rise to Specialized Cells	By the process of differentiation, unspecialized stem cells produce specialized cells.



Classification of Stem Cells: [5, 7, 9, 10]

1. Totipotent cells: From Latin 'totus', meaning entire {total} because it has the potential to generate all the cells and tissues that make up an embryo and that support its development in utero. Cells produced by the first few divisions of the fertilized eggs are totipotents. These cells can differentiate into embryonic and extra embryonic cell types. These are the most versatile of the stem cell types. When a sperm cell and an egg cell unite, they form a one-celled fertilized egg. This cell is totipotent, meaning it has the potential to give rise to any and all human cells, such as brain, liver, blood or heart cells etc. It can even give rise to an entire functional organism. The first few cell divisions in embryonic development produce more totipotent cells. After four days of embryonic cell division, the cells begin to specialize into pluripotent stem cells.

2. Pluripotent cells: "Pluri"—derived from the Latin plures—means several or many. Thus, pluripotent cells have the potential to give rise to any type of cell, unlike totipotent stem cells which cannot give rise to an entire organism. These are descents of totipotent cells and can differentiate into cells derived from the three germ layers. As these pluripotent stem cells continue to divide, they begin to specialize further.

3. Multipotent cells: These are true stem cells but differentiate into a limited number of types e.g the bone marrow contains multipotent stem cells that give rise to all the cells of the blood but not to other types of cells. Multipotent stem cells are found in adult tissues; perhaps most organs in the body (e.g brain, liver) contain them where they can replace dead or damaged cells.

4. Oligopotent stem cells: The ability to differentiate into a few cells. Examples include adult lymphoid or myeloid stem cells.

5. Unipotent stem cell: A unipotent stem cell refers to a cell that can differentiate along only one lineage.

6. Hematopoetic Stem Cells (HSCs): HSCs from bone marrow were the first type of adult stem cells to be identified. The HSC is a well characterised multipotent stem cell type. Their main location is in specific niches in the red bone marrow. The niches function both as a sanctuary and stimulatory site where the stem cells can get signals for both proliferation and differentiation into different blood cell lineages at a rate of about 10^{11} to 10^{12} new blood cells every day. HSC is also found in blood and umbilical cords, however here they don't proliferate.

7. Mesenchymal Stem Cells (MSCs): Mesenchymal stem cells are another important stem cells residing in bone marrow. MSCs from the bone marrow that give rise to stromal cell, fat cells and type of bone cells. Sources of adult stem cells have been found in the bone marrow, blood stream, cornea and retina of the eye, the dental pulp of the tooth, liver, skin, gastrointestinal tract, and pancreas.

8. Adipose derived adult stem cells: Adipose derived stem cells have also been isolated from human fat, usually by method of liposuction. This cell population seems to be similar in many ways to MSCS derived from bone marrow. However, it is possible to isolate many more cells from adipose tissue and the harvest procedure itself is less painful than the harvest of bone marrow. Human ASC's have been shown to differentiate in the laboratory into bone, cartilage, fat, muscles and might be able to differentiate into neurons, making them a possible source for future application in the clinic.

9. Mammary stem cells: Mammary stem cells provide the source of cells for growth of the mammary gland during puberty and gestation and play an important role in carcinogenesis of the breast. Mammary stem cells have been isolated from human and mouse tissue as well as from cell lines derived from the mammary gland. A single such cells can give rise to both luminal and myoepithelial cell types of the gland and has been shown to regenerate the entire organ in mice.

10. Neural stem cells: The existence of stem cells in the adult brain has been postulated following the discovery that by process of neurogenesis, birth of new neurons continues into adulthood in rats. It has since been shown that new neurons are generated in adult mice, songbirds and primates, including humans.

11. Olfactory adult stem cells: Olfactory adult stem cells have been successfully harvested from the human olfactory mucosa cells, the lining of the nose involved in the sense of smell and they have the ability to develop into many different cell types if they are given the right

Markers to Identify PDLSC [11, 12]

PDLSC are a specialized mesenchymal stem cell (MSC). Therefore, they express markers that are similar to those used to identify MSCs. A specific antigen marker does not exist for MSC's or PDLSC's. Therefore, a combination of markers that are found on MSC's but not on hemopoietic stem cells, must be used in order to identify the cells. (Fig-2)

Positive Markers	Function
CD105	A component of the TGFBeta receptor complex and is highly expressed on the surface of endothelial cells. It is important in angiogenesis.
CD146	Belongs to the Immunoglobin superfamily. It is a potential adhesion molecule in endothelial cells.
CD44	Involved in cell-cell interactions as well as adhesion and migration of cells.
Scleraxis	A tendon specific transcription factor. PDLSC express a higher level of scleraxis than other stem cells found in teeth, making them unique from other mesenchyal stem cells.
CD166	A adhesion molecule that binds to CD.
STRO-1	An immunoglobulin antibody also used to detect stromal cells in human bone marrow.

Fig 2: Markers for PDLSC

Methods to Identify Stem Cell

Two methods are nowadays used which include the combination of the chemical properties of fluorescence and unique receptor patterns on cell surfaces to identify specific populations of stem cells. One approach for using markers as a research tool is with a technique known as fluorescence-activated cell sorting.

First Method – FACS (Fig-3)

1) This technique uses a suspension of tagged cells (i.e., bound to the cell surface markers are fluorescent tags) is sent under pressure through a very narrow nozzle so that cells must pass through one at a time. Upon exiting the nozzle, cells then pass, one-by-one, through a light source, usually a laser, and then through an electric field. The fluorescent cells become negatively charged, while non fluorescent cells become positively charged. The charge difference allows stem cells to be separated from other cells. The researchers now have a population of cells that have all of the same marker characteristics, and with these cells they can conduct their research.

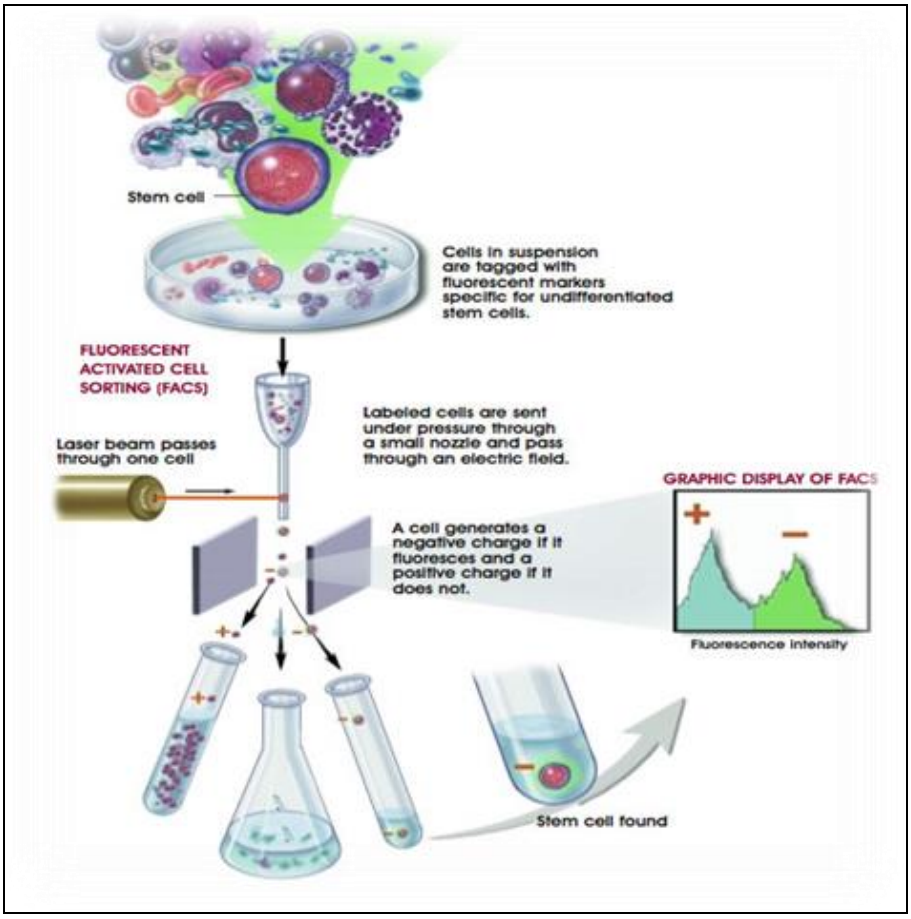


Fig 3: Fluorescence-activated cell sorting (FACS)

Second Method (Fig-4)

A second method uses stem cell markers and their fluorescent tags to visually assess cells as they exist in tissues. In this method, a thin slice of tissue is prepared, and the stem cell markers are tagged by the signaling molecule that has the fluorescent tag attached. The fluorescent tags are then activated either by special light energy or a chemical reaction. The stem cells will emit a fluorescent light that can easily be seen under the microscope.

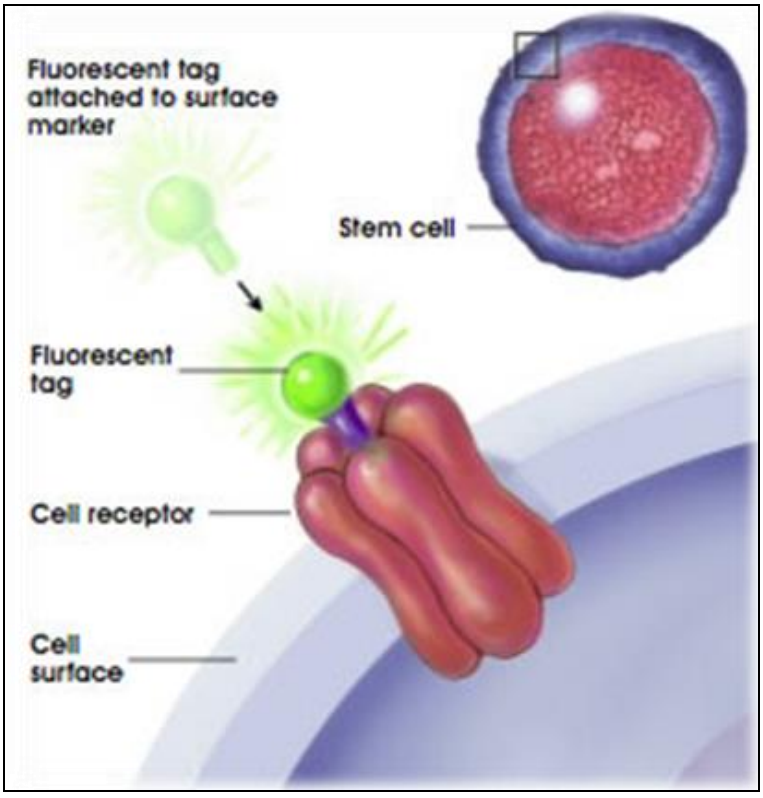


Fig 4: Cell Surface Markers Using Fluorescent Tags

Stem Cell Culturing [3, 12-14]

Various methods to culture stem cells are Petridishes, Spinner Bottles, Rotating Bioreactor, Hollow fiber module, Perfusion containers, Tissue carrier etc.

Stem Cell Research Centers In India [15]

All India institute of medical sciences – New Delhi	Post-graduate institute of medical sciences and research, Chandigarh
CMC-DBT center for stem cell research, Vellore	Sanjay Gandhi post graduate institute, Lucknow
In stem, Bangalore national centre for biological sciences, Bangalore	Tata institute of fundamental research, Mumbai
Indian institute of science, Bangalore	National institute for research in reproductive health, Mumbai
NIMHANS, Bangalore	Tata memorial center, Mumbai
National institute of immunology, New Delhi	Centre for cellular and molecular biology (CCMB) Hyderabad
National brain research center, New Delhi	LV Prasad eye institute, Hyderabad
Drdo-Inmass, New Delhi	Stem cell research centre, Hyderabad
National centre for cell science, Pune	Advanced neuroscience allies pvt. Ltd
Rajiv gandhi center for biotechnology, Trivandrum	Stempeutics research pvt. Ltd
Advanced center for treatment, research and education in cancer (ACTREC), Navi Mumbai	Reliance life sciences pvt. Ltd.
Sree Chitra Tirunal institute of medical sciences and technology.	Amrita institute of medical sciences
Indian institute for chemical biology, Kolkata	Ansa research foundation
Bose institute, Kolkata	Manipal institute of regenerative medicine

Stem Cells & Regenerative Dentistry

Regenerative dentistry is a dental field comprising biomedical, translational and clinical research on the use of stem cells for regeneration of defective tissues in the oromaxillofacial region [16] Prevention of dental diseases will also gain new ground as more insight is gained into the genetic makeup of microbial pathogens, their interactions with the host, and the host repair mechanisms.

Dental Mesenchymal Stem Cells: Dental tissues are specialized tissues that do not undergo continuous remodeling as shown in bony tissue; therefore, dental-tissue-derived stem/progenitor cells may be more committed or restricted in their differentiation potency in comparison with bone marrow derived mesenchymal stem cells (BMMSCs). Dental mesenchyme is termed 'ectomesenchyme' due to its earlier interaction with the neural crest. From this perspective, ectomesenchyme-derived dental stem cells may possess different characteristics than those of neural crest cells or mesenchymal cells taken separately (Fig-5, 6) [17]

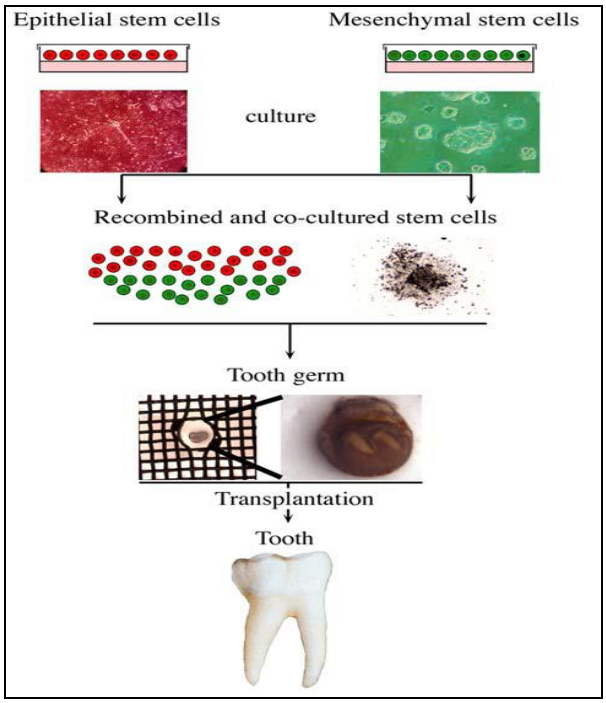


Fig 5: Epithelial and mesenchymal stem cells

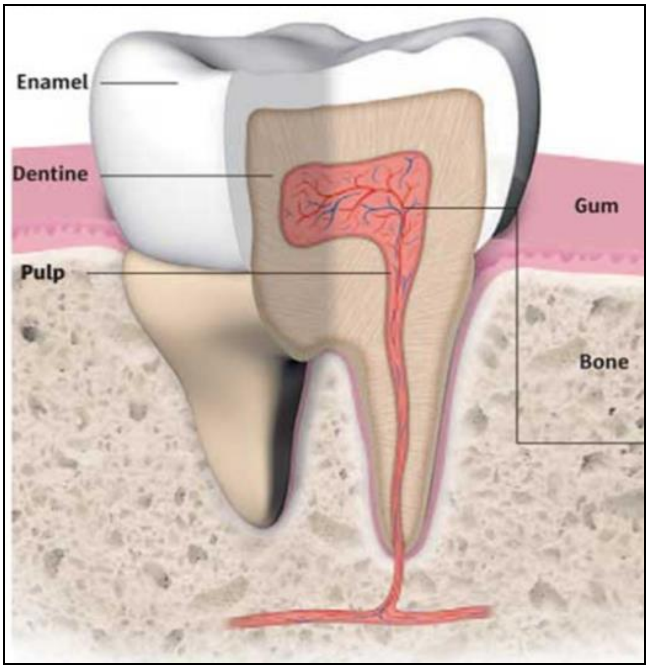


Fig 6: Stem cells are in areas next to nerves and blood vessels within the pulp of a tooth

Sources of Stem Cells in Oral Tissues [17]

1. Dental pulp stem cells (DPSCs)
2. Stem cells from Human exfoliated deciduous teeth (SHED)
3. Periodontal stem cells (PDLSCs)
4. Stem cells from apical papilla (SCAP)
5. Dental follicle progenitor cells (DFPCs)

Periodontal Ligament Stem Cells (Pdlscs)

Earlier evidence has shown that PDL contains cell populations that can differentiate into either cementum-forming cells (cementoblasts) or bone-forming cells (osteoblasts). The presence of multiple cell types within PDL suggests that this tissue contains progenitor cells that maintain tissue homeostasis and regeneration of periodontal tissue.

In vitro **characterization of PDLSCs-Multilineage differentiation potential:** PDLSCs express the MSC-associated markers STRO-1, CDs, and scleraxis - a tendon-specific transcription factor, which is expressed at higher

levels in PDLSCs than in BMMSCs and DPSCs. Immunohistochemical staining and Western blot analysis showed that cultured PDLSCs expressed an array of cementoblastic/osteoblastic markers. Similar to the other dental stem cells described above, PDLSCs exhibit osteogenic, adipogenic, and chondrogenic characteristics under defined culture conditions [18-20].

***In vivo* characterization of PDLSCs—Formation of cementum- and PDL-like Tissue:**

Typical cementum /PDL-like structure can be regenerated after transplantation of ex vivo expanded PDLSCs into immunocompromised mice. A thin layer of cementum-like tissue is formed along with condensed collagen fibers with sparse cells resembling PDL structures. The cementum/PDL-like structures are totally different from typical bone/marrow structures generated by BMMSCs and dentin/pulp-like structures generated by DPSCs.

Transplanted human PDLSCs form a dense type I collagen-positive PDL-like tissue within the transplants. More importantly, collagen fibers generated *in vivo* were able to connect with newly formed cementum-like structures that mimicked physiological attachment of Sharpey's fibers responsible for the functional attachment of cementum/PDL structures. From these findings, one can infer that PDLSCs may contain a subpopulation of cells capable of differentiating into cementoblasts/cementocytes and collagen-forming cells *in vivo*. After transplantation of hPDLSCs into the periodontal defects of immunocompromised mice, PDL like tissue was regenerated, and these human stem cells were also identified to be closely associated with the trabecular bone next to the regenerated PDL, suggesting their involvement in alveolar bone regeneration [21]

Potential Implications of Stem Cells in Dentistry

1. Regeneration of dental hard tissues

A. Dentine regeneration
B. Cementum regeneration
C. Enamel formation
D. Regenerative endodontics

2. Bone regeneration

a) Regenerating of bone from autologous stem cells
b) Implant associated bone regeneration
c) Condyle regeneration

3. Periodontal tissue regeneration
4. Stem cells in sinus augmentation
5. Repair of cleft lip & palate defects
6. Regeneration of irradiated salivary glands:
7. Peripheral nerve regeneration
8. Management of oral cancer

Tissue Engineering: Defined by Langer and Vacanti, "an inter disciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function". MacArthur and Oreffo, defined tissue engineering as "understanding the principles of tissue growth and applying this to produce functional replacement tissue for clinical use". [22]

Tissue Engineering Triad [23]

Bioengineered scaffolds: The basic role of scaffolds is to act as carriers for cells, to maintain the space and to create an environment in which the cells can proliferate and produce the desired tissue matrix. Scaffolds can be Natural scaffolds, Mineral scaffolds or Synthetic scaffolds (Fig-7).

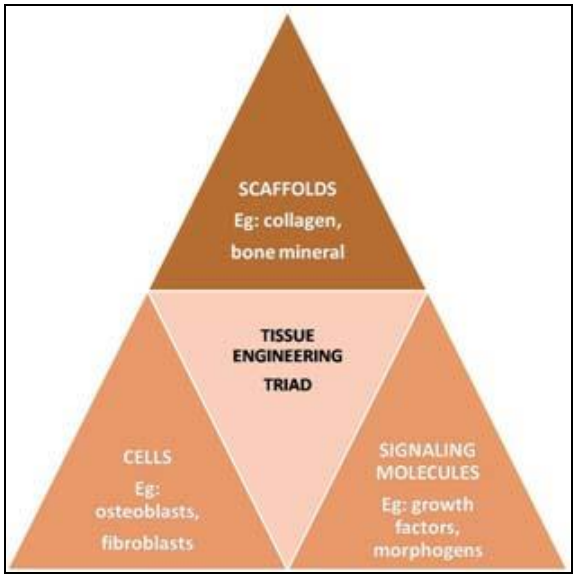


Fig 7: Tissue engineering triad

1. **Natural scaffolds:** The examples for natural scaffolds are collagen, hyaluronic acid, chitosan and chitin. These natural scaffolds have been used in several craniofacial and dental applications. These lack the desired structural rigidity for use in the load bearing region.
2. **Mineral scaffolds:** These are composed of calcium phosphates in the form of hydroxyapatite or _ tricalcium phosphate. These scaffolds are brittle and hence, are prone to fracture.
3. **Synthetic scaffolds:** The most widely used synthetic materials are polymers of polyglycolicacid, polylacticacid and polydioxanone.

Signaling molecules: These are the molecules that transmit signals between cells, functioning as stimulators/inhibitors of growth, as well as the modulators of differentiation. These consist of growth factors (PDGF, TGF), differentiation factors, Bone Morphogenic Protiens (BMPs) and stimulating factors [22].

Stem Cells in Periodontal Regeneration [22]

In periodontal diseases healing by repair results in a tissue that does not completely restore the architecture or function of the original tissue, whereas healing by regeneration produces a new tissue that is identical in both structure and function to the original tissue. Identification of stem cells in postnatal dental tissues has presented exciting possibilities for the application of tissue engineering and cell based therapies in reconstructive dentistry. Recently multipotent stem cell population, termed PDLSCs have been isolated from the PDL of extracted human third molar teeth which give rise to adherent clonogenic clusters that resemble fibroblasts and are capable of developing into adipocytes, osteoblast and cementoblast-like cells *in vitro*, and demonstrate the capacity to produce cementum and periodontal ligament like tissues *in vivo*. PDLSCs express an array of cementoblast and osteoblast markers as well as the BMSCCs associated markers, STRO-1 and CD146 antigens, which are also present on dental pulp stem cells. The similarity between PDLSCs, DPSCs and BMSCCs suggests that PDLSCs represent another MSC-like

population. A potential tissue engineering approach to periodontal regeneration involves incorporation of progenitor cells and instructive messages in a prefabricated 3-dimensional construct, which is subsequently implanted into the site of defect.

In another study by Zhenhua Yang, *et al.* it has been shown that a multilayered human periodontal ligament cell sheet could reconstruct the physiological architecture of a periodontal ligament–cementum complex. Human periodontal ligament cells were isolated and cultured to allow cell detachment as a cell sheet. In the case group, human periodontal ligament cells were cultured in Dulbecco's modified Eagle's minimal essential medium containing 10% fetal bovine serum and 1% antibiotics. After 3 weeks, scanning electron microscopy was carried out, in addition to staining for alkaline phosphatase activity and for calcium (using the Von Kossa stain). Human periodontal ligament cells produced mineral-like nodules and also showed positive staining for alkaline phosphatase, calcium (Von Kossa) and mRNA expression of type I collagen. By contrast, in the control group only weak alkaline phosphatase staining was observed, the Von Kossa stain was negative and there was no mRNA expression of type I collagen. Six weeks after transplantation with human periodontal ligament cells cultured in osteodifferentiation medium, most of the dentin surfaces showed a newly immature cementum-like tissue formation and periodontal ligament with perpendicular orientation inserted into the newly deposited cementum-like tissue [24].

Stem Cells in Sinus Augmentation

In a study conducted by Yadollah S.S *et al.* it is shown that sinus augmentation can successfully be done using beta-tricalcium phosphate, hydroxyl apatite and human mesenchymal stem cells, or MSC's. Mesenchymal stem cells (MSCs) are a better source because they are able to proliferate under low oxygen tension and differentiate when the oxygen level rises. Depending on the micro-environment MSCs have the ability to differentiate into osteoblasts. In animal experiments stem cell application in combination with a bio material (BioOss) show lamellar bone formation and bone invasion into the micropores [24].

Future Studies

There still remains a lot that has to be learned about PDLSC. An experiment on the exact number of PDLSC that exist and the exact location of these stem cells within PDL tissues is still needed. The experiments that have been performed so far, have taken PDL tissue from extracted teeth, cultured this tissue to favor the expansion of PDLSC and then identified markers of PDLSC within the culture to guarantee quality. However, a specific structure of the periodontal ligament at the cellular level has not been created. More information is still needed on what conditions and cytokines favor *in vivo* differentiation of PDLSC into the different types of tissues within the periodontium. Although there are some protein factors that are known to play a role in differentiation of PDLSC, the specific pathway is not understood yet.

Another study that still has to be performed is the discovery of specific markers for PDLSC. Currently, markers that are found within mesenchymal stem cells are used to distinguish PDLSC. These markers are also found at variable levels within the PDL tissue, further illustrating that the PDL tissue is heterogenic and composed of cells that are found at different points of the differentiation process. The heterogeneous nature of the PDL tissue also brings up another important topic that has to be looked into further, which is the difference in the properties of the stem cells in perspective donors and recipients. This difference in properties could be a possible source of an immune response in a case where the PDLSC is transplanted to two people who have a significant difference amongst the properties of the stem cell. As mentioned earlier, experiments have been done to cryopreserve the PDL while still keeping the tissue viable for later use of the PDLSC's. Another piece of information that is still needed is the maximum length of cryopreservation storage that is possible for PDL tissue and still capable of supporting PDLSC that can differentiate into their lineages. Due to the fact that PDL tissue is so easy to obtain from a variety of donors, these cells can be used to optimize cryopreservation techniques and the techniques may later be applied to other types of stem cells. This makes the PDL very important not just for the study of PDLSC's but also for other types of stem cells. PDLSC are mesenchymal stem cells so studies that are done with them may also apply to other mesenchymal stem cells which are more difficult to obtain due to more invasive procedures. People have their wisdom teeth removed everyday, which opens up an untapped source of stem cells from a variety of donors, without having to face the ethical issues involved with the procurement of many other types of stem cells.

Conclusion

Stem cells have more roles to play in medicine and dentistry. The complete restoration of the physiologic, structural & mechanical integrity of the native tissue structure is fascinating fact and it's a way far to reach the hands of mankind. Advances in adult stem cell biology have provided a great deal of impetus for the biomedical community to translate these findings into clinical application.

Given the fact that researchers have in hand populations of stem cells that reproducibly reform bone and its marrow, cementum, dentin, and perhaps even periodontal ligament, it is possible to obtain complete restoration of the hard tissues in the oral cavity using the patient's own cells, thereby avoiding issues of histocompatibility. Furthermore, advances in techniques to genetically modify the gene activity of stem cells during their *ex vivo* expansion offers the unique possibility to make a patient's own stem cells even better.

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