REVIEW ARTICLE

DENTAL STEM CELLS

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In dentistry the first procedures to regenerate pulp started almost half a century ago by introducing blood clots at the apical foramen (Östby, 1961). The key elements of tissue engineering are a set of regenerative cells, morphogens and physical framework scaffolding for cell attachment in 3D. It then serves as a platform for the laying down of tissues by those attached cells coating the frameworks. Regeneration occurs via the intricate interplay of these 3 components. If these components have been formulated properly they can promote the formation of complete mature tissues.

STEM CELLS

Stem cells can be categorized into embryonic and adult/ somatic cells and induced pluripotent stem cells (IPS). Induced pluripotent stem cells are a special class of stem cells. They are the direct products of adult somatic cells that have been re-programmed into embryonic like cells (Oct3/4, SOX-2, Klf 4, c-myc) (Takahashi and Yamanaka, 2006). They can be also categorized according to the number of tissue types they can differentiate into like totipotent, pluripotent, multipotent, oligopotent and unipotent categories. Their high capacity to reproduce and proliferate into various cell lineages is what makes them so potent and so significant in cell therapy and tissue engineering strategies. However, clinical implementation has been slow and challenging. Currently, induced pluripotent stem cells (iPS) are of significant interest because the total number of stem cells that can be generated is much greater than the quantity extracted from adult or embryonic tissues.

DENTAL STEM CELLS

These cells have self-renewal and multilineage differentiation characteristics isolated from teeth and other regions of the oral cavity. These include dental pulp stem cells (DPSC), stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), dental follicle progenitor stem cells (DFPCs) and stem cells from the apical papilla (SCAPs) (Table 1).

Table 1: Various oral dental derived stem cells

Cells	Source	Lineage	Reference
DPSC	Pulp of permanent teeth	Osteogenic/ dentinogenic, adipogenic, neurogenic, chondrogenic, myogenic	(Gronthos et al.,2000; Gronthos et al., 2002)
SHED	Exfoliated deciduous teeth	Osteogenic/ dentinogenic, chondrogenic, myogenic, neurogenic, adipogenic	(Miura et al., 2003)
SCAP	Apical papilla	Dentinogenic, adipogenic and neurogenic	(Sonoyama et al.,2008)
PDLSCs	Periodontal ligament	Osteogenic/ cementogenic, adipogenic, neurogenic, chondrogenic	(Seo et al., 2004)
DFPCs	Dental follicle	Odontogenic, cementogenic, adipogenic, chondrogenic	(Morsczeck et al., 2005)

They have been used extensively after 2000 since the use of hESC (human embryonic stem cells) has been attached with it ethical and legal hurdles. These dental stem cells also have a better clinical potential due also to their higher immune tolerance compared with HESCs.

These dental cells have odontogenic lineage characteristics compared to any other mesenchymal stem cell like the BMSC. Dental pulp stem cells (DPSCs) isolation DPSCs are extracted from the pulp of permanent extracted tooth (wisdom teeth, supernumerary teeth or extracted teeth for orthodontics) by one of two methods: by "enzymatic digestion" or by an "outgrowth" method. A heterogeneous Cells Source Lineage population of cells that is obtained from isolating cells from the dental pulp can adhere and proliferate in the scaffold. This population of cells has shown multiple cell lineage characteristics. The use of heterogenous population of cells has a number of advantages over using immuneselective cells. A likely advantage is of eliminating immunoselection as these cells will later be used for clinical application and thus

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should be devoid of any contaminant. Cell specific markers are used to obtain pure stem cells from tissue extracts containing a mixed population of cells according to their specific immunophenotypes. Two methods used include FACs (fluorescent activated cell sorting) or MACs (magnetic activated cell sorting). It is still debatable as to what is better to isolate the cells by MACs or FACs (Gronthos et al., 2000) or the heterogeneous population of cells. DPSCs seeded onto biomaterial frameworks and then placed inside a canal of the cross-sectioned tooth have shown to generate pulp-like structures (Demarco et al., 2010) and when implanted in non-dentine surface they failed to differentiate to odontoblasts.

DPSCs are almost identical to bone marrow mesenchymal stem cells (BMMSCs). However, they show higher cell proliferation capacity as compared to BMMSCs in vitro (Gronthos et al., 2000). It was shown that when DPSC implanted in immune compromised mice dentinelike structure surrounding a pulp-like structure was formed that was not seen in case of BMSCs. Studies have shown that they can differentiate into odontogenic, osteogenic lineages, chondrogenic, adipogenic, neurogenic and endothelial lineage. The DPSCs also have differences in properties when compared to other dental stem cells. They can form a dentine-pulp like complex. However, DPSCs have lower proliferation rate as compared to SHEDs (Miura et al., 2003). Recently, a study showed third molars stored in saline overnight at 40C elutes DPSCs. These can be isolated and cultured for clinical use in medium devoid of FBS and also retain its phenotypic characteristics. The analogy behind using FBS free medium is to make sure that the DPSCs don't come in contact with animal serum. This is one way of making them clinically more feasible and acceptable to use. Human serum (HS) has been used as an alternative to fetal bovine serum (FBS) for culturing DPSCs. When fibronectin was added for initial DPSCs isolation it produced higher proliferation rate, however the expression of CD73, CD 90, CD105 or multipotency characteristics remained unaltered irrespective of the type of serum (Eubanks et al., 2014).

Cryopreservation of DPSCs is a technique by which the cells or the whole tooth are stored at -1960C, a temperature where all the cell activities are stopped, thereby achieving a high cell survival rate (Chen et al., 2011). Even after 120 hours of extraction of tooth viable DPSC could be isolated when the tooth is cryopreserved. Currently many companies are storing these dental stem cells with a potential to be used by the patient for the treatment of various diseases currently being researched upon. Unlike human embryonic stem cells, Dental stem cells are ethical and have no legal complication associated with its storage.

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