Human Dental Pulpal Stem Cells: Clinical Potential as Mesenchymal Stem Cell Source

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Mesenchymal stem cells (MSCs) are a source of adult stem cells for regenerative medicine as they are extraordinarily plastic and when expanded into colonies, retain their multilineage potential. MSCs can differentiate into cells of mesodermal origin and can give rise to representative lineages of the three embryonic layers. MSCs are also found in dental pulp, only soft tissue of a tooth, encased by dental hard tissues. This review will inform about the stem cells, properties and types of human dental pulpal stem cells and their updated clinical potential in stem cell - based therapies.

Stem cells

Stem cells are pluripotent cells, having a property of self-renewal and differentiating into various types of cells of human body [1].

Embryonic stem cells are totipotent cells derived directly from the blastocyst during embryonic development. Embryonic stem cells can differentiate into any cell type. For ethical reasons, there is considerable controversy over the isolation of these as they come from live embryos. As a result, two other strategies have emerged: transdifferentiation, the transformation of a specialised cell into another kind of specialised cell, and induced pluripotent stem cells (iPSCs), the reprogramming of somatic cells into pluripotent stem cells. ***Adult stem cells*** (somatic or postnatal stem cells) are undifferentiated cells found between other cells in adult tissues including skin, adipose tissues, peripheral blood, bone marrow, pancreas, intestine, brain, hair follicles, as well as in the dental pulp cells. Adult stem cells exhibit multipotency (also known as plasticity) and self-renewal. They can differentiate into a cartilage, bone, adipose tissue, muscle, epithelial, or neural cell. These cells are characterised by cellular and molecular markers to understand their phenotypes. ***Mesenchymal stem cells*** (MSC) are adult stem cells that were initially identified and isolated from bone marrow (BMMSC) but have been isolated from almost every oral tissue including the dental pulp [2].

In the year 2012, Shinya Yamanaka and John Gurdon have won Noble prize award for their excellent work on induced pluripotent stem cells (iPSCs) derived from adult somatic cells. This work has resulted into development of innovated technology to make an iPSCs from individual patient who needs treatment for specific disease. [1]

Different sources of stem cells in orofacial region are dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), Periodontal ligament stem cells (PDLSC), dental follicle stem cells(DFSC), stem cells from apical papilla (SCAP), bone marrow

stem cells (BMSC), epithelial stem cells (EpSC), Induced pluripotent stem cells (IPSC), immature dental pulp stem cells (IDPS), oral epithelial stem cells (OESCs), gingiva derived MSCs (GMSCs), tooth germ progenitor cells (TGPCs), salivary gland stem cells (SGSCs), periosteum derived stem cells (PSCs) [3].

Properties and types of dental pulpal stem cells

Pulpal stem cells were initially isolated by Gronthos and his group in the year 2000, from third molars scheduled for extraction. They reported that these cells had properties in common with other mesenchymal cells including clonogenicity, self- renewal, and plasticity. These cells express specific surface markers such as CD 105, CD73, CD90, CD24, CD146, and STRO-1; they can be selected from the rest of the tissue by flow cytometry or magnetic beads. They can be isolated by sphere formation after growth in low-attachment flasks [2].

DPSCs were the first stem cells isolated from the dental pulp and identified in the perivascular niche in the dental pulp of permanent teeth. DPSCs are readily obtainable from extracted wisdom teeth or exfoliated deciduous teeth. These cells express endothelial and smooth muscle cell markers such as stromal derived factor-1 (STRO-1) and smooth muscle actin (SMA).They have the ability to differentiate into odontoblast-like cells and secrete a dentin-like tissue when implanted in a hydroxyapatite–tricalcium phosphate scaffold under the skin on the back of immunocompromised mice. These cells may be actively involved in recognition and response against both Gram-positive and Gram-negative bacteria as they express specific membrane receptors TLR-2 and TLR-4. DPSCs isolated from inflamed pulp tissues are diminished dentinogenic properties in comparison with stem cells extracted from healthy teeth. Dental pulp stem cells have been used not only to form mineralized connective tissues but also to form cells such as neurons and myocytes with great therapeutic potential. [2]. DPSCs could also be used for pulpal regeneration, tooth reconstruction, endocrinology, neurology, angiogenesis and vasculogenesis. Stem cell-based therapy holds a great promise to solve health problems from both systemic and oral diseases [1].

SHED cells were the second group of stem cells derived from the dental pulp. These cells were isolated from exfoliated deciduous teeth. Similar to DPSCs, SHED cells are able to form bone and dentine like tissues in vivo. Interestingly and unlike DPSCs, SHED cells express neural markers such as Nestin, Neural filament M (NFM), Neuronal nuclei (NeuN), and Glial Fibrillary Acidic Protein (GFAP) amongst others. SHED cells have a higher proliferation rate than DPSCs and have immunoregulatory properties similar to those of DPSCs [2].

SCAP are isolated from the apical papilla of immature permanent teeth. They express similar markers as DPSCs including STRO-1 and CD105, but unlike DPSCs, SCAP cells express neural markers including Nestin and NFM as well as the cell membrane marker and signaling transducer, CD24, whose expression will decrease when differentiation is induced. As a result of their origin (the developing dental papilla), they proliferate readily. SCAP are the main source of cells that can potentially survive at the apical papilla to be induced to form new dentin-like tissue inside the canal, thickening

dentinal walls and increasing root length [2].

Clinical potential of pulpal stem cells in stem cell-based therapies

It is proposed that dental pulp stem cells (DPSCs) can develop iPSCs which can be used for therapies of various diseases.

Stem cell-based therapies are currently being developed to treat diabetes, arthritis, atherosclerosis, Parkinson's, Alzheimer's, and neoplastic disease. Stem cells will be isolated and transplanted into a scaffold previously treated with specific growth factors. The concept of another strategy, cell homing, is to provide therapy without needing to implant stem cells. In this approach, host stem cells will be recruited into the implanted scaffold. The isolation and transplantation of stem cells is not needed and there will be less chance of rejection and contamination; therefore the procedure would be simpler and quicker [2].

A clinical trial, jointly led by Songtao Shi of the University of Pennsylvania and Yan Jin, Kun Xuan, and Bei Li of the Fourth Military Medicine University in Xi'an, China, found that children who received hDPSC treatment had more signs of healthy root development and thicker dentine than the control group treated by apexification. Blood flow increased as well. Examining a variety of immune-system components, the team found no evidence of safety concerns. They also found that the implanted stem cells regenerated different components of dental pulp, including the cells that produce dentin, connective tissue, and blood vessels. Now, Shi and colleagues are beginning to test the use of allogenic stem cells, or cells donated from another person, to regenerate dental tissue in adults. They are also hoping to secure FDA approval to conduct clinical trials using hDPSCs in the United States [4].

A team led by Dr. Praveen Arany, assistant professor of oral biology at the University of Buffalo in New York, is testing the use of low-power laser light to stimulate tooth regeneration. Arany has found that shining laser light directly on the remaining pulp can stimulate stem cells in the pulp to produce new dentin. This would still need to be capped, but is likely to be far more resilient. By regenerating the tooth so the pulp is coated in natural dentin again, it doesn't have the same risk of material failure [5].

Dr. Paul Sharpe, professor of stem biology at Kings College London and leader of the research found that dentin produced by stimulating stem cells with Tideglusib, a low cost experimental drug with an established safety record, integrates itself completely within the tooth so that there's no risk of the filling coming out. So far Tideglusib has been studied only in rats, but Sharpe expects to start human trials within the next year [5].

The Holy Grail for dental researchers is the ability to regrow an entire missing tooth. Sharpe has done this in mice, but doing the same in humans raises ethical and legal concerns. It would involve the creation of a so-called tooth primordium and implanting it in the jaw where the missing tooth had been. To create a tooth primordium, it is necessary to harvest stem cells from human embryos- which bump up against U.S. law. "Embryos have the only cells we know of that can make a tooth," Sharpe says. "Our adult mouths don't make teeth. These cells are no longer present." But if

regrowing entire teeth is impractical now, scientists believe they will make it happen one day but it's not going to be in the next few years. Sharpe says that we need to find another way which doesn't involve cells from embryos [5].

In a study published in 27 February 2012, in IOP Publishing's Journal of Breath Research, Japanese scientists, Dr. Ken Yaegaki and his group, from Nippon Dental University, have showed that hydrogen sulphide (H2S), odorous compound responsible for halitosis, increased the ability of adult stem cells to differentiate into hepatic (liver) cells, furthering their reputation as a reliable source for future liver-cell therapy. This is the first time that liver cells have been produced from human dental pulp and, even more impressively, have been produced in high numbers of high purity. "High purity means there are less 'wrong cells' that are being differentiated to other tissues, or remaining as stem cells. Moreover, these facts suggest that patients undergoing transplantation with the hepatic cells may have almost no possibility of developing teratomas or cancers, as can be the case when using bone marrow stem cells," said lead author of the study Dr. Ken Yaegaki [6].

Dr. Ying-Chu Lin and research team of the Kaohsiung Medical University School of Dentistry, Kaohsiung City, Taiwan have found that intravenous injections of stem cells derived from human exfoliated deciduous tooth pulp (SHED) have a protective effect against brain damage from heat stroke in mice. Their finding was safe and effective and so may be a candidate for successfully treating human patients by preventing the neurological damage caused by heat stroke. According to the research team, these cells have "significantly higher proliferation rates" than stem cells from bone marrow and have the added advantages of being easy to harvest and express several growth factors, including vascular endothelial growth factor (VEGF), and they can promote the migration and differentiation of neuronal progenitor cells (NPCs). Some drawbacks to the experimental therapy are a limited supply of SHED and SHED transplantation has been associated with cancer and immune rejection [7].

In ophthalmology, there has been increasing interest to differentiate DPSCs and PDLSCs towards ocular lineage. Both can commit to retinal fate expressing eye field transcription factors and generate rhodopsin-positive photoreceptor-like cells. This proposes a novel therapeutic alternative for retinal degeneration diseases [8].

Although stem cells can be isolated from a variety of tissues at various developmental stages with different stem cell capacities, human Dental Pulp Stem Cells (DPSCs), dental tissue-derived adult stem cells, have been widely studied due to their great clinical potential as a mesenchymal stem cell source, easy accessibility and less invasive harvesting. Recently, the applications of DPSC in the dental field have been widely used. Most common application is pulp regeneration since pulpal pathology is commonly seen in the dental clinics; in addition pulp regeneration is extremely needed to preserve the infected pulp and protect the tooth from being non-vital [9].

Since the first discovery of DPSCs in 2000, studying in DPSCs grows rapidly. Nevertheless, there are still questionable issues needed to be optimized and answered such as the variable biological capacity of DPSCs [9].

References

1. Potdar PD and Jethmalani YD.Human dental pulp stem cells: Applications in future regenerative medicine. WJSC. 2015June 26; 7(5):839-851

Available from:

URL:http://www.wjgnet.com/1948-0210/full/v7/i5/839.htm

2. Holland GRand Botero TM. (2014). Pulp biology: 30 years of progress. Endodontic Topics.2014; 31: 19-35.

3. Sharma R, Bhargava D, Yadav M, Rastogi P, Chandarvarkar V, Siddhartha M, Caroli P. Dental Stem Cells; Harnessing Newer Possibilities. J Indian Acd Forensic Med. 2013 October 28: Vol. 35, No. 4:378-82.

4. University of Pennsylvania. "Regrowing dental tissue with stem cells from baby teeth." ScienceDaily. (Cited 11 September 2018).

Available from:www.sciencedaily.com/releases/2018/09/180911132046.htm. Science News from research organizations

5. CoxD. The next revolution in dental care is about to begin. (cited 2018 Jan.15).

Available from:

https://www.nbcnews.com/mach/science/next-revolution-dental-care-about begin-ncna8 37706 (accessed 4 October 2018)

6. Institute of Physics (IOP). Dental pulp stem cells transformed by bad breath chemical. Science Daily. 2012 February 26

Available from:

<www.sciencedaily.com/releases/2012/120226225951.htm>

7. Eurek Alert. Globel Source for Science News. Future Heat Stroke treatment found in dental pulp stem cells.Cell transplantation Center of Excellence for aging and Brain Repair. Public release: 5-Jun-2014

Available from:

https//www.eurekalert.org/pub_releases/ 2014-06/ctco-fhs060514.php

8. Yam GH-F, Peh GS-L,Singhal S, Goh B-T, Mehta JS. Dental stem cell: a future asset of ocular cell therapy.

Available from:

https://doi.org/10.1017/erm.2015.16 (accessed 4 October 2018)

9. Aljamie M, Alessa L, Noah R, Elsayed L.Dental Pulp Stem Cells, a New Era in regenerative Medicine: A literature Review. Open Journal of Stomatology. 2016Jun 7; 155-163.

Available from:

https://file.scirp.org/pdf/OJST_20160 60717374 862.pdf