Stem cells in dentistry : An overview

Marawar PP*, Mani A**, Sachdev S***, Sodhi NK****, Anju A*****

Abstract

Stem cells are cells that have the ability to continuously divide and produce progeny that differentiate into various other types of cells or types of tissues. They are unspecialized and are capable of dividing and renewing themselves. The scope for application of stem cells in dentistry is vast and includes continued root formation, in pulp healing and regeneration, in replantation and transplantation, pulp/dentin tissue engineering and regeneration and bioroot engineering and reconstruction of the periodontium, in cancer management and research. This review highlights the origin, history and applications of stem cells in the field of dentistry.

Key words: *Dentistry, stem cells, classification, future directions, immunohistochemistry, stem cell funding.*

Introduction

Stem cells are defined as clonogenic cells capable of both self-renewal and multilineage differentiation since they are undifferentiated cells with varying degrees of potency and plasticity. They differentiate into one daughter stem cell and one progenitor cell[1]. Most of the 300 trillion cells of the body have completely specialized functions. Blood, lung, brain, skin or liver cells are all wonderfully specialized for what they do. By and large, they cannot do anything other than what they were designed for. On the other hand, stem cells exist mainly to maintain and repair cells in the areas where they are found. Stem cells are found in the blood, bone marrow, muscle, skin, and organs like the brain and liver[2].

History

The term stem cell was proposed for scientific use by Russian histologist Alexander Maksimov in 1908. Research on stem cells grew out of the work of Canadian scientists in the 1960s[3]. The history of stem cell research had a benign, embryonic beginning in the mid 1800s with the discovery that some cells could generate other cells. In the early 1900 real stem cells were discovered and it was found that some cells generate blood cells.[3] The history of stem cell research includes work with both animal and human stem cells. A prominent application of stem cell research has been bone marrow transplants using adult stem cells. In the early 1900's physicians administered bone marrow by mouth to patients with anemia and leukemia. Although such therapy was unsuccessful, laboratory experiments eventually demonstrated that mice with defective marrow could be restored to health with infusions into the blood stream of marrow taken from other mice.[4] This caused physicians to speculate whether it was feasible to transplant bone marrow from one human to another (allogenic transplant). Among early attempts to do this were several transplants carried out in France following a radiation accident in the late 1950's. Performing marrow transplants in humans was not attempted on a larger scale until a French medical researcher made a critical medical discovery about the human immune system. It was not until the 1960s that physicians knew enough about HLA compatibility to perform transplants between siblings who were not identical twins. The 1990s saw rapid expansion and success of the bone marrow program with more than 16,000 transplants to date for the treatment of immunodeficiencies and leukemia. In 1998, James Thompson (University of Wisconsin-Madison) isolated cells from the inner cell mass of early embryos, and developed the first embryonic stem cell lines. In the same

*Professor & Head, **Reader, **** Post Graduate Students
Dept. of Periodontology and Oral Implantology
*** Post Graduate Students, Dept. Oral Medicine
***** Post Graduate Students, Dept. Oral Pathology
Rural Dental College, Loni

Address for Correspondence :
Dr. Neha Kaur Sodi, Post Graduate Student,
Dept. of Periodontology and Oral Implantology
Rural Dental College, PIMS, Loni Tal Rahata Dist Ahmednagar,
Maharashtra. - 413736.
Email: dr.nehasodhi@gmail.com

year, John Gearhart (Johns Hopkins University) derived germ cells from cells in fetal gonadal tissue (primordial germ cells)[4]. Pluripotent stem cell "lines" were developed from both sources. Ongoing researchers are now focused on transplanting stem cells of non-self origin.

Present State of Knowledge

Stem cells differ from other cells in the body. All stem cells, regardless of their source, have three general properties, which make them different from other cells in the body:

(1) They are capable of dividing and renewing themselves for long periods

Unlike muscle cells, blood cells, or nerve cells, which normally do not replicate themselves, stem cells may replicate many times. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal.

(2) They are unspecialized

One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.

(3) They can give rise to specialized cell types:

When unspecialized stem cells give rise to specialized cells, the process is called differentiation. Scientists are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation

Classification of Stem cells :

I. Stem cells can also be classified according to their plasticity:

- Totipotent stem cell,
- Pluripotent stem cell,
- Multipotent stem cell.

II. Stem cells can be classified according to the growth stage[6].

- Embryonic stem cells : Located within the inner cell mass of the blastocyst stage of development.
- Postnatal stem cells : Cells that have been isolated from various tissues including bone marrow, neural tissue, dental pulp and periodontal ligament.

III. Stem cells are often categorized by their source:

- Autologous stem cells : Cells are obtained from the same individual in whom they will be implanted.
- Allogenic stem cells : Cells originate from a donor of the same species.
- Xenogenic cells : Cells that are those isolated from individuals of another species.

The reason why it is important to distinguish between embryonic and postnatal stem cells is because these cells have a different potential for developing into various specialized cells i.e. plasticity[2]. The plasticity of the stem cell defines its ability to produce cells of different tissues.

Quantity and Quality of Work Being Carried Out in the Field of Stem Cells :

Various sources of postnatal dental stem cells have been successfully studied:[30].

- Permanent teeth : Dental pulp stem cells (DPSC): derived from third molar[5].
- Deciduous teeth : Stem cells from human-exfoliated deciduous teeth (SHED): Stem cells are present within the pulp tissue of deciduous teeth[7].
- Periodontal ligament : Periodontal ligament stem cells (PDLSC)[8].
- Stem Cells from apical papilla (SCAP)[9].
- Stem cells from supernumerary tooth-Mesiodens[10].
- Stem cells from teeth extracted for orthodontic purposes[11].
- Dental follicle progenitor cells[12].
- Stem cells from human natal dental pulp-(hNDP)[13].

Future Directions of Stem Cell Therapy

Immunohistochemistry :

All types of postnatal dental stem cells studied have mesenchymal stem cell-like qualities, such as capacity for self-renewal and multilineage differentiation. Immunocytochemistry has proved the existence of stem cells in these cell populations using STRO-1, CD29 and CD44 express mesenchymal stem-cell markers[14]. These stem cells are isolated from specialized tissue with potent capacities to differentiate into odontogenic cells; however, they also have the ability to give rise to other cell lineages similar to but different in potency from that of bone marrow stem cells[15].

Current Scope of Application of Stem Cells in Dentistry:[2]

1. In continued root formation
2. In pulp healing and regeneration
3. In replantation and transplantation
4. Pulp/dentin tissue engineering and regeneration
5. Bioroot engineering and reconstruction of the periodontium.

Potential Role of Stem Cells in Continued Root Formation:

Using guinea pigs as a model, a pilot experiment was conducted. Although the finding suggests that root apical papilla is likely to play a pivotal role in root formation, further research is needed to verify the role of stem cells from apical papilla in continued root formation[16].

Potential Role of Stem Cells in Pulp Healing and Regeneration

Recent researches challenge the traditional approach in managing immature teeth by applying apexification treatment, where there is little to no expectation of continued root development[17]. Instead, it is possible that alternative biologically-based treatments may promote apexogenesis / maturogenesis. A common aspect of many of these reported cases is the preoperative presentation of apical periodontitis with sinus tract formation, a condition normally associated with total pulpal necrosis and infection that requires apexification.

Although Iwaya et al and Banchs and Trope applied the term 'revascularization' to describe this phenomenon, what actually occurred was physiological tissue formation and regeneration initiated by the stem cells[18].

Potential Role of Stem Cells in Replantation and Transplantation

Andreasen et al and *Kling* et.al, showed excellent radiographic images of the ingrowth of bone and periodontal ligament (PDL) (next to the inner dentinal wall) into the canal space with arrested root formation after the replantation of avulsed maxillary incisors, suggesting a complete loss of the viability of pulp, apical papilla, and/of HERS[19]. Skoglund et al observed revascularization of' the pulp of replanted and autotransplanted teeth with incomplete root development in dogs. Ingrowth of new vessels occurs during the first few postoperative days. After 10 days, new vessels are formed in the apical half of the pulp and, after 30 days, in the whole pulp[20].

Stem Cells for Pulp/Dentin Tissue Engineering and Regeneration

Dental pulp tissue engineering was first tested by Mooney's groups. Bohl et al reported that culturing pulp cells grown in vitro on poly glycolic acid (PGA) resulted in high cell density tissue similar to the native pulp. Burma et al found that pulp cells seeded in PGA and implanted into the subcutaneous space of immunocompromised mice produced extracellular matrix[21]. New blood vessels also penetrated the cells/ PGA implants in vivo, three weeks after the implantation. Since then the isolation and characterization of DPSCs and SHED using these stem cells for dentin/pulp tissue regeneration has drawn great interest. These findings provide new light on the possibility of generating pulp and dentin in pulpless canals.

Stem Cells for Bioroot Engineering:

Dental implants have recently gained momentum as a preferred option for replacing missing teeth instead of bridges or removable dentures. However, although dental implants have had great improvements over the past decades, the fundamental pitfall is the lack of a natural structural relationship with the alveolar bone (i.e. the absence of PDL)[19]. In fact, it requires direct integration with bone onto its surface as the prerequisite for success, an unnatural relation with bone as compared with a natural tooth. The lack of natural contours and its structural interaction with the alveolar bone make dental implants a temporary option until a better alternative is available. This alternative may be tooth regeneration. Using animal study models, cells isolated from tooth buds can be seeded onto scaffolds which then form ectopic teeth *in vivo*. Nakao et al recently engineered teeth ectopically, followed by transplantation into an orthotopic site in the mouse jaw[22]. Tooth regeneration at orthotopic sites using larger animals such as dogs and swine has also been tested. The study in dogs failed to show root formation whereas the swine model was able to show root formation with a 33.3% rate of success[2].

From both DPSCs and SHED, tissue similar to normal dentin-pulp have been reported to be regenerated, which can be later on used for regenerative endodontics[23]. But SHED are retrieved from a tissue that is 'disposable' and readily accessible. The best candidates for SHED are moderately resorbed canine and incisors with the presence of healthy pulp. In children, other sources of easily accessible stem cells are supernumerary teeth, mesiodens, over-retained deciduous teeth associated with congenitally missing permanent teeth and prophylactically removed deciduous molars for orthodontic indications. SHED also show higher proliferation capability, abundant cell supply and painless stem-cell collection with minimal invasion, so SHED could be a desirable option as a cell source for regenerative endodontics; however, in comparision, DPSCs show higher inclination towards neuronal lineage[24,25,26]. Stem cells can also be isolated from aging teeth, but it is observed that the number of cells and their proliferation rate decreases with age and it is maximum only when crown is formed (germ stage). SCAP have higher proliferation rate as compared to DPSCs. They appear to be the source of primary odontoblasts that are responsible for root dentin formation, whereas DPSCs are the likely source of replacement odontoblast. SCAP represent early progenitor cells, and therefore whether SCAP are a more suitable stem-cell source than DPSCs and SHED, requirs further investigation[27]. For regeneration of periodontium, PDLSCs are a better source of stem cell compared to cells isolated from the pulp. Viable periodontal ligament is reported to be generated from PDLSCs[28]. Instead of forming entire tooth, even a bio-root with periodontal ligament tissues has been generated by utilizing SCAP along with PDLSCs. This bio-root is encircled with periodontal ligament tissue which has natural relationship with the surrounding bone[29].

Stem Cell Funding

Stem cell research is not federally funded due to a ban placed on embryo research in 1995. Since then, stem cell research has continued mainly through private funding. In early 1999, the NIH announced that they would support research on embryonic stem cell lines that had already been previously established[30]. This was a monumental step, as the potential benefits of stem cell research are very large, but in order to reap these benefits, a large and sustained research investment is needed. The federal government is the only realistic source of such large funds.

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