STEM CELL THERAPY IN DENTISTRY

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ABSTRACT

Stem cells are cells with a unique capacity for self renewal. Stem cells can be transformed into desirable cells. Regeneration of oral and maxillofacial structures is earned out by using stem cell therapy and this has gained momentum in recent days. Future tissues like tissue engineered bone grafts, engineered joints and cranial sutures can be developed with stem cell therapy. Emphasis is been given to the possibilities of stem cell therapy in the oral and maxillofacial region including regeneration of tooth and craniofacial defect.

KEYWORDS: Stem cells, Dentistry, Therapy, Regeneration.

INTRODUCTION

Stem cell therapy is an intervention strategy that introduces new adult stem cells into damaged tissue in order to treat diseases or injury. Stem cells are biological cells found in all multi cellular organisms, that can divide and differentiate into diverse specialized cell types and can self renew and produce more cells. There are two types of stem cells embryonic and adult stem cells. The mesenchymal stem cells are widely used in dentistry. Many researchers believe that they have potential to change human disease and alleviate sufferings. They can self renew and produce new cells which differentiate to take up
various functions to replace diseased and damaged areas in body with minimal risk of rejection and side effects. Stem cell therapies exist, but are at experimental stages, costly or controversial with an exception of bone marrow transplantation. Mesenchymal stem cells, in particular, have gained interest due to their differentiation potential and their availability. They represent a potential key component in autologous graft for tissue regeneration. Cell therapy based on tissue engineering has two approaches such as direct implant of cells and by use of scaffold acting as both templates of tissues and carrier of cells. The increase in technology continues to increase in dentistry as a substitute for traditional treatments and artificial components. Postnatal stem cell therapy was launched in 1968, which were stem cells donated by patients themselves or their close relatives. This was used when the first bone marrow transplant was successfully used in the treatment of severe combined immune deficiency. The bone marrow, adipose tissue, periodontal ligament and pulp will be described as potential sources for stem cells. Thus in this review, we would like to infer the importance of stem cell in dentistry.

WHAT IS STEM CELLS
Stem Cells are the master cells of the body. There are two major types of Stem Cells, Embryonic stem cells, and Adult stem cells. A single embryonic stem cell has the potential to differentiate into all 220 types of specialized cells that make up the human body. Adult stem cells are responsible for the regeneration and replacement of tissue damaged by disease or injury. There are two properties of stem cells that make it different from any other specialized cells the body. These properties are self-renewal (the ability to go through numerous cycles of cell division while maintaining their undifferentiated state) and the ability to differentiate into a Specialized cell type. Another unique property of stem cells is their ability to grow in vitro (Outside of the body) by the right culture medium and under the right controlled conditions, stem Cells are able to proliferate indefinitely.

TYPES OF STEM CELLS
Stem cells can be broadly divided into:
1. Embryonic stem cell
2. Adult stem cell which is further divided into:
   • Hematopoietic stem cell
   • Mesenchymal stem cell (MSC).
Embryonic Stem Cell
Embryonic stem cells are capable of multi potential differentiation. The inner cell mass of the embryo is used to form embryonic cell lines.\textsuperscript{[4]} Embryonic stem cells has a potential to differentiate into germ layers namely ectoderm, endoderm and mesoderm.\textsuperscript{[5]} Tumor genesis and immune rejection is common with embryonic stem cells.\textsuperscript{[6]}

Adult Stem Cell
Adult stem cells are multi potent stem cells.\textsuperscript{[1]} They have been harvested from different kind of tissues like bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas, cornea, dental pulp and adipose tissue. Adult stem cells are comparatively easier to isolate. Immune rejection and teratoma formation is also rare with adult stem cells. Adult stem cells are commonly used in current day practice.

STEM CELLS FROM DENTAL ASPECTS
The first type of dental stem cell was isolated from the human pulp tissue and termed dental pulp stem cells (DPSCs).\textsuperscript{[6]} Subsequently, four more types of dental stem cells were identified:
\begin{itemize}
  \item Stem Cells from Exfoliated Deciduous Teeth (SHED).\textsuperscript{[6]}
  \item Periodontal Ligament Stem Cells (PdSCs),
  \item Stem Cells from Apical Papilla (SCAP)\textsuperscript{[3-7]}
  \item Dental tissue from human third molar\textsuperscript{[8]}
\end{itemize}

In teeth, two different stem cells have been suggested: the cervical loop of rodent incisor for epithelial stem cell and a perivascular niche in adult dental pulp for mesenchymal stem cells (MSC). In addition to the dental pulp MSC, other MSC populations have been isolated from human dental tissues such as the periodontal ligament and the dental follicle but nothing is known about the existence of these tissues. In the dental pulp, MSCs are thought to reside in a perivascular niche, but little is known about the exact location and molecular regulation of this niche.\textsuperscript{[5, 8, 9]}

DPSCs, on the other hand, are thought to be arising from two different sources: ectomesenchyme of the neural crest or ectoderm of the dental lamina and thus possess two different cell lines.\textsuperscript{[7]}
The comparison of the osteogenic and adipogenic potential of MSC from different origins shows that, even if cells carry common genetic markers, they are not equivalent and are already committed toward a specific differentiation pathway.\cite{10, 11} Commitment could arise from the conditioning of stem cells by their specific microenvironment or stem cell niche.\cite{2, 7, 8} A brief account of different sources of stem cells in orofacial region and their properties is as follows:\cite{2-17}

**Dental Pulp Stem Cells (DPSC)**

Their source is dental pulp mesenchyme (neural crest mesenchyme). They slow cycling cells, have restricted potential and represent mature adult pulp stem cells. They have better immunologic/host acceptance. In vitro, they formed odontoblasts, osteoblasts, endothelial cells, adipocytes, Chondrocytes, neurons and smooth muscle cells. While in vivo, various directions like odontogenic, myogenic, adipogenic, angiogenic and osteogenic are found and were able to form complete dentin-pulp complex. It’s in vitro developmental capability and in vivo therapeutic targeting is yet to be explored.

**Stem Cells From Human Exfoliated Deciduous Teeth (SHED)**

Their source is human exfoliated deciduous teeth (coronal pulp). They are multipotent cells with very high proliferative potential and higher cell doublings. In vitro, they can differentiate odontogenic, osteogenic, adipogenic, chondrogenic, or neural tissues. In vivo, they can form neurons, adipocytes, odontoblasts and osteoinductive and endothelioid cells. But they failed to form complete dentin-pulp complex in vivo.

**Periodontal Ligament Stem Cells (PDLSC)**

They can be extracted from periodontal ligament of the roots of the extracted teeth. They are the primary source for treatment of periodontal disease. These cells are multipotential. In vitro, PDLSCs differentiate into osteoblasts, cementoblasts and adipocytes. In vivo, after transplantation into mice, structures resembling bone, Cementum, cartilage and periodontal ligament have been found. They can contain multiple stem cells lineages. But their utility is yet to be explored.

**Dental Follicle Stem Cells (DFSC)**

They are extracted from dental follicle of the impacted teeth and possess multiple potentialities. They have lesser ability to form adipocytes and their potential yet to be identified for forming odontoblasts, neural cells and other tissues.
Stem Cells from Apical Papilla (SCAP)
They are taken from extraction sites of third molars or other teeth. They are easily accessible and have a higher proliferative potential than PDLSC.

ADVANTAGES OF DENTAL STEM CELLS
a. Increasing the success rate of tooth auto-transplantation\(^{[18,19]}\)
b. Better proliferation and immunoregulation than bone marrow-derived mesenchymal stem cells\(^{[20]}\)
c. Dental stem cell-based tissue engineering in tooth regeneration\(^{[21]}\), pulp/dentin regeneration\(^{[22]}\), periodontal regeneration.\(^{[23]}\)
d. Efficient and easy to access source of MSCs
e. Potential for commercial banking.
f. Medical applications in bone formation\(^{[24]}\), stroke therapy\(^{[25]}\), heart disease.\(^{[26]}\)

APPLICATIONS OF STEM CELL IN DENTISTRY
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 periodontium

ROLE OF STEM CELLS IN CONTINUED ROOT FORMATION
Stem cells from the apical papilla have been used in vitro studies for continued root formation.

ROLE OF STEM CELLS IN PULP HEALING AND REGENERATION
Stem cell based treatment promotes apexogenesis or maturogenesis. It is also useful in revascularization of the dental pulpal tissues in regenerative endodontic. Since the discovery and isolation of the different types of dental stem cells, there have been many attempts to use them in the regeneration of the dental pulp tissue. Using a tooth slice model, pulp-like tissue was engineered using SHEDs seeded onto synthetic biodegradable scaffolds. SHEDs were able to differentiate into odontoblast-like cells, and also endothelial-like cells.

In another study using the same tooth slice model, DPSCs were seeded on collagen scaffold supplemented with dentin matrix protein (DMP-1) and were able to regenerate pulp-like
tissue. These findings suggest that SHED and DPSCs can be considered as reliable sources of stem cells for dental pulp tissue engineering and regeneration.\cite{27,28}

**ROLE OF STEM CELLS IN RE IMPLANTATION AND TRANSPLANTATION**

Andresen et al showed excellent radiographic images of the in growth of bone and periodontal ligament into the canal space with arrested root formation after the re implantation of avulsed maxillary incisors suggesting a complete loss of viability of the pulp, apical papilla and / or Hertwig’s epithelial root sheath.\cite{29}

**STEM CELLS FOR DENTIN / PULP TISSUE REGENERATION**

Isolation and characterization of DPSC and SHED using these stem cells for dentin/pulp tissue regeneration have drawn great interest. These findings provide new insight on the possibility of generating pulp and dentin in pulp less canals.

**STEM CELLS FOR BIOROOT ENGINEERING**

Using animal study models, cells isolated from tooth buds can be seeded on to scaffolds and form ectopic tooth in vivo, demonstrated the use of combined mesenchymal stem cell populations for root/periodontal tissue regeneration.\cite{29} They loaded root shaped hydroxyapatite/tricalcium phosphate (HA/TCP) block with swine SCAPs. They then coated the HA/TCP block with gel foam containing swine PDLSCs and inserted the block in the central incisor socket of swine. Three months post-implantation, histological and computerized tomography scan revealed a HA/SCAP-gel foam/PDLSC structure growing inside the socket with mineralized root-like tissue formation and periodontal ligament space. These findings suggest the ability of combined autologous SCAP/PDLSCs generating a bio-root, which can be an alternative to dental implants in replacing missing teeth.\cite{28}

**CHALLENGES ENCOUNTERED IN STEM CELL DENTISTRY**

The challenges encountered in stem cell dentistry can be broadly categorized in to three types:

- Biological challenges
- Technical challenges
- Clinical challenges
BIOLOGICAL CHALLENGES

Despite biological evidence showing that regeneration can occur in humans, complete and predictable regeneration still remains an elusive clinical goal, especially in advanced periodontal defects.

- Periodontal regeneration, based on replicating the key cellular events that parallel periodontal development, has not been possible because of our incomplete understanding of the specific cell types, inductive factors and cellular processes involved in the formation of the dental tissues.
- Furthermore, most basic discoveries on Dental stem cells have emerged from cell culture and animal models which do not always translate to the human situation.
- Thus, not all findings in animal models can be directly extrapolated to humans. In addition, the molecular pathways that underlie stem cell self-renewal and differentiation are also largely unknown.
- Further research is needed to elucidate the cellular and molecular events involved in restoring lost periodontal tissues before a reliable biologically-based therapy can be developed. [30,31]
- In light of these concerns, the isolation and characterization of dental stem cells may provide a good starting point to investigate the role of stem cells in wound healing and their potential applications in regenerative therapy, including tissue engineering.

TECHNICAL CHALLENGES

- Biologically, the matrix scaffold should have good biocompatibility for the cellular and molecular components normally found in regenerating tissues.
- There is evidence to suggest that cultured human PDLSCs in a suitable scaffold and implanted into surgically created periodontal defects can result in the formation of a periodontal ligament-like structure.
- However, the optimal mechanism of propagation and incorporation of these cells into a carrier scaffold still needs further refinement. In addition, further studies are needed to understand the conditions that induce lineage-specific differentiation and efficacy of in vitro expanded stem cells derived from regenerating periodontal defects.
- Possible karyotypic instability and gene mutations can limit the usefulness of cell lines after prolonged culture.
- There are also difficulties in providing clinical-grade stem cell lines using animal free media to prevent cross-infection in humans.
- Thus, refinement of current techniques to facilitate laboratory handling of these cells and to maximize their regenerative potential represents a long-term endeavor if these cells are to be used in clinical situations.\(^{[32]}\)

**CLINICAL CHALLENGES**

- There are a number of clinical barriers in MSC-based clinical therapy that must be understood and overcome: Immune rejection, tumor growth and efficacy of cell transplantation.
- Firstly, it is important to understand how the immune system will respond to human stem cell derivatives upon transplantation. Generally, the immunogenicity of a human cell depends on its expression of class I and II major histocompatibility (MHC) antigens, which allow the body to distinguish its own cells from foreign cells.
- The use of patient-specific (autologous) adult stem cells from redundant third molar teeth should overcome potential immune rejection.
- However, this approach may be redundant if recent reports are considered which indicate that MSC can suppress the immune system and thus allows the use of either autologous or allogenic MSC preparations.
- It is likely that the more specific and extensive the therapeutic application, the longer the stem cells may have to remain in vitro to obtain sufficient numbers for therapeutic use.
- Thus during this extended period in the culture there could be a greater likelihood that genetic or epigenetic changes will accumulate. If such changes are not accompanied by an overt phenotypic transformation, they may go undetected and harm the patient.
- Therefore, it is critical to have a thorough understanding of the rate of genetic change and the type of selective pressures that allows this change to dominate a culture.\(^{[33,34]}\)
- Thirdly, it is unclear whether human stem cell derivatives can integrate into the recipient tissue and Delivery of appropriate cells and molecules to the target site without inducing ectopic tissue formation is of paramount importance for the safety and effectiveness of tissue engineering-based tooth regeneration.
RISK FACTORS OF STEM CELL THERAPY

1. Tumor formation
Stem cell resembles some of the features of cancer cells, such as long life span, relative apoptosis resistance and ability to replicate for an extended period. There for, stem cell may be considered potential candidate for malignant transformation.\(^{[35]}\)

2. Immune responses
Administration of stem cells may affect the host immune system. The administered cells may directly induce an immune response or may have a modulating effect on the immune system.\(^{[35]}\)

3. Human pathogen transmission and adventitious agents
Mesenchymal stem cells have been reported to be immune privileged and have a low immunogenic potential.

4. Unwanted dedifferentiation\(^{[35]}\)
Adventitious agents: manufacturing of cell-based medicinal products inevitably does not include terminal sterilization, purification, viral removal and inactivation. Therefore, viral and microbial safety is a pivotal risk factor associated with the use of non autologous cells including stem cells. Donor history is of particular importance for stem cell lines. The risk of a donor to recipient transmission of bacterial, viral and fungal or prion pathogens may lead to life-threatening reactions.\(^{[36]}\)

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