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Review Article

Stem Cells: Biological Solution for Biological Problems

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ABSTRACT

In recent years, there has been an increasing interest and research in developmental biology that has led to the discovery of human stem cell system. The isolation of human embryonic stem cells has been considered the biggest breakthrough of the 21st century. These pluripotent stem cell populations can proliferate and differentiate into various connective tissue lineages. Stem cells have been successfully isolated from variety of human tissues including dentofacial tissues. In fact dental stem cells (DSCs) are easily accessible, require non invasive procedure for isolation, are efficient source of mesenchymal stem cells (MSCs) and have different differentiation potentialities. They have more striking odontogenic capability than bone marrow stromal stem cells and have the ability to regenerate a dentin-pulp-like complex. The rapid proliferative capacity of dental pulp-MSCs may prompt future studies aimed at allogeneic tissue transplantation.

Based on its wide applications and future implications in tissue engineering, dental stem cell research and development will, over time, transform dental practice in a magnitude far greater than any other recent advancement in the field. The purpose of this article is to review the body of knowledge relating to stem cells, their tremendous prospects in dentistry and the role of dentists in the field.

Keywords: stem cells, dental, odontogenic, mesenchymal.

INTRODUCTION

Stem cells are defined as "Clonogenic cells with the capacity to both self-renew and give rise to differentiated cells". [1] The term "stem cell" has roots as far as 1868, [2] and originated from old botanical monographs as the stems of plants, that were responsible for the regenerative competence of plants.

Stem cells can be thought of as the "building blocks" or "blank slate" of the body. [1]Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, they serve as internal repair system, dividing essentially without limit, to replenish other cells. Stem cells divide to produce one stem cell and one cell capable of differentiation. In addition to this asymmetrical division, they can also divide symmetrically into further stem cells or into differentiated cells, as necessity demands. [3]

Stem cells have two key properties. 1) The ability to SELF RENEW, dividing in a way that makes copies of themselves; and 2) The ability to DIFFERENTIATE, giving rise to the mature cell types with special functions. [4] (Fig 1)

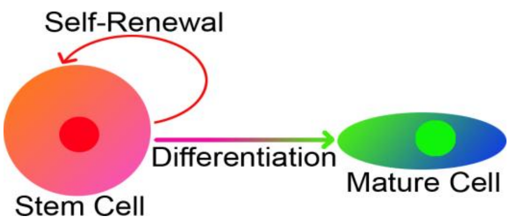

Fig.1: Key properties of stem cells

BIOLOGY OF STEM CELLS:

A layperson often associates the term “stem cells” with “embryonic” stem cells, but there are also noncontroversial “adult” stem cells that can be collected from various tissue niches within the body and which retain important stem cell properties.

1. **Embryonic stem cells (ESC)**

In 1998, for the first time, scientists derived cells from frozen human embryos to generate stem cells. [5]

- They are pluripotent in nature and have the potential to generate every cell type found in the body. They are best derived from embryos of 2-11 days old called blastocyst that consists of approx 150-200 cells. [6] (Fig 2)
- The fertilized egg and the cells that immediately arise in the first few divisions are
- “TOTIPOTENT” i.e. they can generate a viable embryo including placenta. Within a matter of days, however these cells undergo further transitions to become “PLURIPOTENT”. [6]
- ESCs are considered immortal as they can be propagated and maintained in an undifferentiated state indefinitely. [6]
- Despite their enormous potential, they are difficult in practical approach as there are ethical, legal, moral, and social issues associated with embryonic stem cells as extracting stem cells from embryo destroys the embryo itself.
- Owing to their nature there are also significant medical and engineering challenges in using pluriopotent stem cells such as immunorejection, and tumorigenesis. [7]

Because of these shortfalls, ESCs remained only as platform for laboratory research…

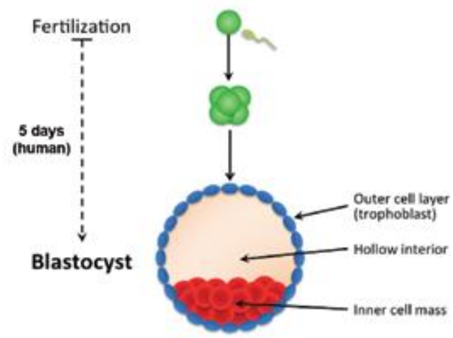

Fig.2: Blastocyst- Embryonic stem cells niche.

2. **Adult Stem Cells** [6,7]

- Also known as postnatal / somatic or tissue specific Stem Cells
- They are multipotent, capable of differentiating in to more than one cell type but not all cell types.
- Have plasticity that is ‘its ability to expand beyond its potential irrespective of the parent cell from which it is derived’.
- Adult stem cells are typically characterized as either:
    1. Hematopoietic (capable of forming all types of white blood cells and red cells)
    2. Mesenchymal (capable of forming a wide variety of connective tissues such as bone, muscle, cartilage, fat,

tendons—but not internal organs or skin).

- They represent a very small population and are buried deep within a given tissue,
- making them difficult to identify, isolate and grow in laboratory settings.
- Adult stem cells can be collected from various tissue niches within the body.
- Hematopoietic - Bone marrow
  Umbilical cord blood
- Mesenchymal - Bone marrow
  Deciduous teeth and wisdom teeth
  Adipose tissue.

3. Induced Pluripotent Stem Cells

In 2006, it was discovered that by using genetic engineering techniques, unipotent adult cells could be reprogrammed back into cells that resemble pluripotent embryonic stem cells. [8] (Fig.3) This technology avoids the ethical issues of embryonic stem cells and uses the patient's own tissues, thus reducing immunologic incompatibility, but these induced pluripotent stem cells have also been shown to cause teratomas and are expensive to generate. [9]

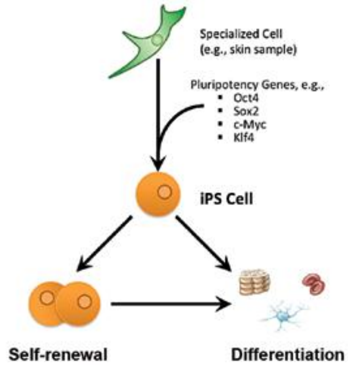

Fig. 3: Induced Pluripotent Stem Cells - Unipotent adult cells reprogrammed into pluripotent embryonic stem cells.

REVIEW OF BASIC RESEARCH OF DENTAL STEM CELLS:

Among the various adult tissues, dental pulp, the soft connective tissue entrapped within the dental crown, a sort of 'sealed niche'; is an extremely rich site for stem cell collection. Owing to its peculiar formation, [10] i.e. made of both ectodermic and mesenchymal components containing neural crest cells, it display plasticity and multipotential capability. Dental pulp stem cells were isolated for the first time in 2000 by Gronthos et al. [11] Since then the field is advancing quickly as many tools and techniques have developed during the past half century.

Niches of Dental Stem Cells

The first conclusive study demonstrating the presence of stem cells in teeth was published in 2000 by dental scientists at the NIDCR. (National institute of dental and craniofacial research)

-Dental stem cells reside in multiple niches of deciduous and permanent teeth. [12]

-The first one to be identified was from pulp, subsequently other sources were also identified.

- dental pulp stem cells (DPSC)
- Stem cells from human exfoliated deciduous teeth (SHED)
- periodontal ligament stem cells (PDLSC)
- Stem cells from apical papilla (SCAP)
- dental follicle stem cells (DFSC)

Collectively, these dental stem cells are currently being investigated for numerous scientific and clinical uses.

Characteristics of Dental Stem Cells

All of these sources of dental stem cells display typical mesenchymal stem cell characteristics. [13] They have the capacity to generate a broad range of mesenchymal tissue or cell types including dentin producing odontoblasts, adipocytes, osteoblasts, bone, cartilage, smooth and skeletal muscle. [14] They can even give rise to cells of the endodermal lineage, such as endothelial cells, hepatocytes, [15] and insulin-producing cells. [16] Additionally, dental stem cells can switch lineage to form ectodermal tissues such as neurons or epithelial-like stem cells. Dental stem cells allow for autologous use, meaning the adult stem cells can be collected from and used on the same person, so there are no issues of immunological incompatibility

Taken together, it suggests that the dental stem cells contain a hierarchy of highly potent pluripotent, multipotent mesenchymal, endodermal and ectodermal stem cells. Teeth have now been proven to contain stem cells with similar capabilities to, but without many of the challenges of, embryonic stem cells - and this has important implications for clinical use and tissue banking. [14]

Advantages of DPSCs over other MSCs: [4,17]

- ✓ Collecting stem cells from dental pulp is a noninvasive practice that can be performed in the adult during life and in the young after surgical extraction of wisdom teeth, a common surgical practice.
- ✓ Tissue sacrifice is very low when collecting dental pulp stem cells.
- ✓ Several cytotypes can be obtained from dental pulp stem cells owing to their multipotency.
- ✓ Transplantation of new-formed bone tissue obtained from dental pulp stem cells leads to the formation of vascularized adult bone and integration between the graft and the surrounding host blood supply.
- ✓ Dental pulp stem cells can be cryopreserved and stored for long periods.
- ✓ Dental pulp is ideal for tissue engineering and for clinical use in several pathologies requiring bone tissue growth and repair.

CLINICAL APPLICATIONS FOR DENTAL STEM CELLS:

Continued research and the property of stem cells have opened a new era of cell based therapy with tremendous potential in clinical dentistry and medicine. Apart from that they are also used in various genomic and biological studies. [17] (Table 1)

Current therapies	Potential therapies
Dental bone regeneration Periodontal disease Regenerative dentistry	Craniofacial defects Whole tooth regeneration

Table.1: Applications of Dental Stem Cells.

CURRENT USES OF DENTAL STEM CELLS:

Alveolar Bone Regeneration

Only 9 years after the first published literature involving dental pulp stem cells, dental stem cells were used in humans to regenerate dental bone. [18] Abukawa et al used a novel scaffold design to generate an autologous tissue engineered construct which was used to repair a segmental mandibular defect. [19] (Fig.4) The technique promoted osteogenesis enhanced penetration of bone with blood vessels thereby accelerating tissue regeneration. This development of new scaffold fabrication technology has facilitated a successful repair of three dimensionally complex cranial defects. Defects of at least 1.5 cm in the alveolar ridge of 17 human volunteers were filled with a construct of stem cells collected from third molars and seeded onto a collagen matrix. One year later in many cases, the gap was filled with bone. [20]

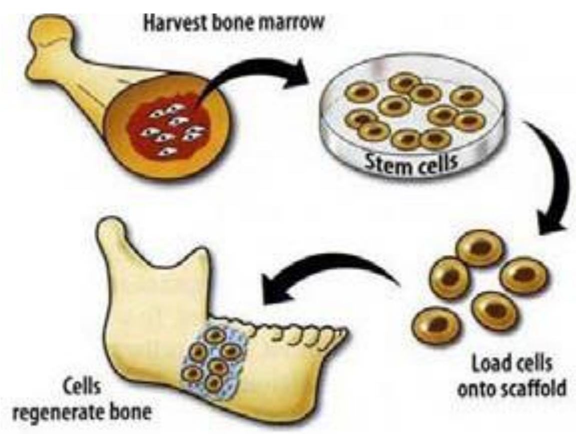

Fig.4: Alveolar Bone Regeneration using stem cell scaffold.

Periodontal Ligament

Periodontal regeneration has always remained a challenge as it consists of hard and soft tissues. It is evident, that the ligament complex contains stem cells that can commit to a number of pathways (bone, cementum and ligament). In an exciting recent study, Kawaguchi et al (2004) used autologous bone marrow MSC in combination with allocollagen to regenerate periodontal ligament in an experimental grade III defects in animals. One month after implantation, there was regeneration of cementum, periodontal ligament, and alveolar bone. [6] Following this research Feng, et.al [21] demonstrated clinical and experimental evidence supporting the safe and efficacious use of autologous PDL cells to treat periodontitis in 3 humans in a multiyear study.

This study provided firm evidence that MSC embedded in the appropriate environmental niche, can be used to regenerate a tissue as complex as the periodontium.

Regenerative Dentistry

Granthos et.al, demonstrated both in vitro and in vivo in animals that dental pulp stem cells (DPSCs) were capable of forming ectopic dentin and associated pulp tissue. [22] Later Batouli et al used an in vivo stem cell transplantation system to investigate differential regulation mechanisms of bone marrow stromal stem cells and DPSCs. DPSCs were found to be able to generate a reparative dentine like tissue on the surface of human dentin in vivo. This study provided direct evidence to suggest that osteogenesis and dentinogenesis mediated by BMSCs and DPSCs, respectively, may be regulated by distinct mechanisms, leading to the different organization of the mineralized and nonmineralized tissues. [6]

Pulp tissue regeneration involves either delivery of autologous/ Allogenic stem cells in to the root canals or implantation of the pulp that is grown in the laboratory using stem cells. [6]

FUTURE:

Third dentition (bioengineered teeth)/ (bio-tooth)

Replacing a missing tooth has always been a challenge in the field of dentistry. Although implants have solved the problem to an extent but they rely on direct integration of bone and implant surface which is indeed an unnatural relationship as compared to natural tooth. A method has been developed to regenerate tooth buds in animals in a single procedure by combining dental pulp and bone marrow on a scaffold and implanting this into surgically created defects. These scaffolds should be biodegradable and rate of degradation should coincide with the rate of tissue formation. They should be porous and allow appropriate differentiation of cells without affecting their progeny. After few months, the construct led to formation of organized dentin, enamel, pulp, cementum, and periodontal ligament surrounded by regenerated alveolar bone; suggesting a method that could be translated directly to humans. Recently some researchers have developed a bioroot in to which post and crown can be placed, this would develop a natural relationship with bone. [23]

So, dental applications alone may justify the banking and use of dental stem cells for future uses by millions of people.

However, apart from its dental applications, dental stem cells have been successfully used as a medical therapeutic modality as well. Such as, for treatment of diabetes. The use of stem cells to treat diabetes is focused on 2 fronts: developing cells that secrete insulin in a glucose-responsive manner, and using MSCs to regulate the immune response by inducing tolerance to pancreatic antigens. [24] Dental stem cells have been shown to produce insulin and to modulate the immune system by suppressing T-cell response in laboratory and animal testing. [25] Dental stem cells therefore represent an easily available source of stem cells for therapeutic approaches to diabetes.

Hence, new developments in stem cell research have created an environment in which dentists will be in the position to assume a leading role in the treatment chain of medical disease with broad range of clinical applications that could potentially benefit a majority of the population. Therefore, dentists may become a critical first link in the chain of collecting dental stem cells, to be used not just for the treatment of dental pathoses, but also for medical disease.

THE SCIENCE OF STEM CELL BANKING:

The Process of Banking Dental Stem Cells

After the tooth or teeth sample is collected by the dentist, the sample is transported from the dentist office to the laboratory. Cells should be transported in a sterile, isotonic solution, shipped chilled to reduce the growth of contaminating microbes, and delivered to the laboratory as quickly as possible. The laboratory must have validated processes with appropriate quality control metrics in place, verifying its ability to remove contaminating oral flora from the tooth and to recover viable stem cells. [26]

Stem Cell Cryopreservation

The practice of cryopreserving and later using cells for clinical use is well established. Bone marrow, cord blood, and fertilized embryos have been routinely preserved for decades. For example, cord blood began being preserved for clinical use immediately after its potential for therapeutic use was reported and has successfully been recovered from long term storage. [27] Therefore; the cryopreservation of dental stem cells simply represents the application of existing technology to a new source of stem cells. Cryopreservation of cells typically involves equilibrating the cells with a cryoprotectant solution- a solvent that protects the cells from the formation of ice crystals and that helps preserve the integrity of cell membranes upon thawing. The temperature is typically slowly brought down to freezing using programmable controlled-rate freezers. Frozen cells are then transferred to vapor-phase liquid nitrogen freezers for long-term storage at ultra-low temperatures, typically at about -150°C. [17]

CHALLENGES IN STEM CELL RESEARCH:

Stem cells obtained from any source are less in number. Isolation, culture and storage are technique sensitive. Their immunomodulatory characteristics are still questionable. They are expensive and require time consuming procedures which limit their use. [6]

CONCLUSION

Stem cell therapies have virtually unlimited applications. All the challenges must be overcome before this novel therapy can be translated from labs to clinics. Collaboration between basic scientists and clinicians is required to achieve this goal. The discovery that odontogenic tissues as a source of adult stem cells has opened up a new role for dentists. They are positioned to become one of the key providers of stem cells, and as a result, their linkage with the medical field will become very intimate. Stem cell research is one of the most fascinating areas of contemporary biology, but, like many other expanding fields of scientific knowledge, research on stem cells also raises scientific questions as rapidly as it generates new discoveries.

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