STEM CELLS: THE CHANGING FACE OF DENTISTRY

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Introduction

Stem cell research is making giant leaps that could revolutionize the way we treat diseases and test drugs. The subject of stem cells is one of the most interesting and upcoming fields in medical research with vast areas yet to be discovered. The pluripotent nature of the stem cells has been studied and used in various scientific fields for curing the disease and regeneration of a body part. Some cells are more specialized than others. Stem cells since they are not specialized can be differentiated to any tissue of choice. But the availability of stem cells was impossibility until recent times. Now researchers have found an abundant source of stem cells with the potential to treat a number of diseases in dentistry including craniofacial disorders, deficient jaws, cleft lip and palate, traumatized teeth etc. The purpose of this article is to provide an understanding of the basic biology and sources of stem cells and review the clinical applications of dental stem cells in particular.

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financial patrons. The purpose of this article is to provide an understanding of the basic biology and sources of stem cells and review the clinical applications of dental stem cells in particular.

The Changing Role of Dentists:

Medicine and dentistry are on the cusp of a new treatment modality. For both physicians and dentists to take advantage of this new modality, not only do the clinical applications need to be further developed, but sources of stem cells from teeth will be necessary. Similar to umbilical cord blood, teeth are one of the few tissues in the body that are naturally shed (or extracted during the normal course of dental care) that contain potent stem cells, creating an opportunity to save this tissue for when it is needed. Dentists and patients need to be aware that the option exists to preserve the stem cells from healthy extracted or exfoliating teeth as a resource for these future clinical applications (Figure 1).

Patients increasingly want to know more information about dental stem cell banking and procedures using dental stem cells. The dentist will have a dual role to play in dental stem cell cryopreservation: educating patients and/or their parents about the existence and use of dental stem cells, and helping them select an appropriate approach to collecting and preserving these stem cells. In addition, oral surgeons and pediatric dentists indeed, any dentist involved in extracting teeth may also be called on to assist with the collection of the teeth for cryopreservation. Patients now have a new choice for the use of these teeth to preserve their own stem cells in the anticipation that these cryopreserved stem cells may prove valuable for their dental or medical health in the future.

Biology of Stem Cells:

The term “stem cell” has roots as far back as 1868 [17]. Stem cells are generally defined as clonogenic cells with the capacity to both self-renew and give rise to differentiated cells [18]. Stem cells can be thought of as the “building blocks” of the body. Whereas most cells in the body, e.g., muscle cells or red blood cells, are specialized cells that can form only the exact same type of cell and only perform narrow biological functions, stem cells are versatile and can develop into a number of different cell types. The layperson often associates the term “stem cells” with the ability to both self-renew and 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 [11].

Unique Properties of Stem Cells:

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

1. Proliferation: 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 [11].

2. Blank cells: 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 [11].

3. Differentiation: 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 [11].

Types of Stem Cells:

1. Embryonic stem cells
2. Adult stem cells
3. Embryonic stem cells:

Embryonic stem cells are derived from embryos that develop from eggs fertilized in-vitro in fertilization clinics donated for research purpose with informed consent of the donors. They have a new choice for the use of these teeth to preserve their own stem cells in the anticipation that these cryopreserved stem cells may prove valuable for their dental or medical health in the future.

In 1998, James Thompson of the University of Wisconsin-Madison proved that embryonic stem cells can be sustained indefinitely in the laboratory, creating hundreds of generations of identical stem cells [19].

In spite of its various advantages, embryonic stem cells have certain disadvantages:

1. It is hard to control its growth.
2. It is ethically controversial to use human embryos.
3. It may be rejected by the immune system of the human body.

2. Adult Stem Cells:

Adult stem cells are undifferentiated cells found amongst the differentiated cells of a specific tissue or an organ. These stem cells can renew themselves and can differentiate to yield the major specialized cell types of the tissue or organ. They are mostly multipotent cells [19]. The primary role of the adult stem cell is to maintain and repair the tissues in which they are primarily found. They are also known as “Somatic stem cell”. The regenerative property of the adult stem cell has been reported 40 years ago. As hematopoietic stem cells forms all types of blood cells in the body, similarly the regenerative property of the bone marrow stroma help in repairing fractured bone and is thus likely to be responsible for repairing microfractures that occur on a daily basis.
They can divide for a long period and can give rise to mature cell types that have characteristic shapes, specialized structures and functions of a particular tissue like neural cells, cardiac muscles etc [21].

**Advantages of Adult Stem Cells:**

1. They are immune to immunological attack.
2. They are partly specialized.
3. They are flexible in their nature as they may form other types of tissues [21].

**Disadvantages of Adult Stem Cells:**

1. They are very scarce in nature because all types have not been found
2. They are vanishing in nature, as they don't live long.
3. They are very rare.

**Sources of Stem Cells:**

As reviewed in this section, adult stem cells are typically characterized as either hematopoietic (capable of forming all types of white blood cells and red cells) or mesenchymal (capable of forming a wide variety of connective tissues such as bone, muscle, cartilage, fat, tendons but not internal organs or skin). Hematopoietic stem cells have been routinely used to treat blood cancers such as leukemia and other blood disorders. Bone marrow contains both types of stem cells and has been most extensively researched. Umbilical cord blood is another source of hematopoietic stem cells. Both deciduous teeth and wisdom teeth contain MSCs but not hematopoietic stem cells, as does adipose (fat) tissue.

**Bone Marrow Stem Cells**

The most commonly known procedure involving stem cells is the bone marrow transplant, first used by Dr. E. Donnall Thomas in the late 1950s to treat humans; early studies involved using bone marrow from one identical twin to attempt treatment of the other twin who had leukemia [22]. By the late 1960s, further research involving how to address graft versus host disease and other clinical advancements led to successful transplants between non-twins. In 1990, Dr Thomas was awarded the Nobel Prize in Medicine for his pioneering work in bone marrow transplantation. A study specific to dentistry involved MSCs from bone marrow aspirate concentrate plus scaffold to regenerate hard tissue enabling dental implants [23].

**Cord Blood Stem Cells**

In the mid-1980s, scientists proposed that hematopoietic stem cells in umbilical cord blood, resembling those in bone marrow, could be used when a bone marrow transplant was not available; in 1988 the first cord blood stem cell transplant was used to treat a young boy with Fanconi’s anemia [24]. The properties of cord blood stem cells to treat blood related diseases and also to be readily collected and cryopreserved for future use formed the basis for the umbilical cord blood banking industry.

**Adipose Tissue Stem Cells**

MSCs can be isolated from adipose tissue obtained from liposuction aspirates or abdominoplasty procedures, and are being studied for repairing tissue defects resulting from traumatic injury, tumor resection, and congenital defects [25], calvarial defects following severe head injury, and in dentistry for repair of jaw bone.

**Embryonic Stem Cells**

In 1998, scientists derived cells from frozen human embryos to generate human embryonic stem cells for the first time [21]. Many scientists and clinicians were enthusiastic that embryonic stem cells would provide a way to cure most, if not all, diseases due to their pluripotent nature (the ability to form most if not all cell types). However, this has proven difficult in practice for many reasons.

**Induced Pluripotent Stem Cells**

In 2006, it was discovered that by using genetic engineering techniques, unipotent cells could be reprogrammed back into cells that resemble pluripotent embryonic stem cells. While this technology avoids the ethical issues of embryonic stem cells and uses the patient's own tissues, thus reducing immunologic incompatibility, induced pluripotent stem cells have also been shown to cause teratomas and are expensive to generate [24].

**Dental Stem Cells**

A new source of readily available MSCs teeth was discovered in 2000 by scientists at the NIH [4]. Stem cells can be collected from deciduous teeth when they naturally exfoliate from approximately age 6 to 11 years, and also from teeth that are surgically removed, such as premolars for orthodontia and third molars during wisdom teeth extraction. 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. (Fig.2)

**Dental Stem Cells in Current Practice and Research:**

**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 in human clinical studies [16]. 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.

**Periodontal Ligament:**

Following research showing that human periodontal ligament stem cells contribute to periodontal tissue repair in both rat and swine [26], Feng, et al 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[27]. (Fig.3)
Regenerative Dentistry:

Regenerative dentistry is based in part on the concept that stem cells will become increasingly useful in dentistry; strategies include using the patient’s stem cells in situ to stimulate healing, or the use of laboratory cultured stem cells with or without tissue engineering scaffolds. A recent survey of practicing endodontists found that more than half of those surveyed thought that “stem cell banking would be useful to regenerate dental tissues,” and almost 90% “would be willing to save teeth and dental tissues for banking.” Promising examples of using stem cells in dentistry include the conservative endodontic treatments of immature teeth[28], pulp regeneration[2], evaluation of bone formation on dental implants, evaluation of cytotoxicity of resin based sealers, and for drug screening. Clearly, the phenomenon of dental stem cells is already starting to affect the practice of dentistry.

Potential Role of Stem Cells in Replantation and Transplantation:

Andreasen et al and Krog et al, showed excellent radiographic images of the ingrowth of bone an periodontal ligament (PDL) (next to the inner dential 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/or HERS[29]. 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[30].

Bioengineered teeth (Third dentition):

A method has been developed to regenerate tooth buds in a single procedure by combining dental pulp and bone marrow on a scaffold and implanting this into surgically created defects. After a number of months, the construct led to organized dentin, enamel, pulp, cementum, and periodontal ligament surrounded by regenerated alveolar bone, suggesting a method that could translate directly to humans[31]. Since periodontal disease is the primary cause of tooth loss in adults age 35 years and older and approximately 25% of those more than age 65 years have lost all of their teeth[7], dental applications alone may justify the banking and use of dental stem cells for future uses by millions of people.

Orthodontic Implications:

Adult stem cells have been identified in craniofacial bone, dental Pulp, periodontal ligament, and developing tooth buds recently from the wisdom teeth also. In orthodontics we can utilize this technology for the following purposes:

Repair of Alveolar Bone Defect:

Unwanted alveolar bone defects are often created after orthodontic extractions. Repair of these defects is needed to avoid the risk of dehiscence and other periodontal insults at a later stage after the teeth have been retracted into the extraction site. Often an accidental loss of the buccal plate has occurred during extraction of a buccally placed premolar for orthodontic purposes. This type defect can be repaired with the help of stem cells[21].

Remodeling and Regenerating Oral Tissues:

Bone remodeling of the craniofacial complex during orthodontic and orthopedic treatment is a complicated process in which bone formation and bone resorption are closely coupled. Alveolar bone within the maxilla and mandible is one of the most actively remodeled during orthodontic/orthopedic treatment. The proliferation and differentiation of osteoblastic and osteoclastic stem cells are important in the remodeling process being controlled by local signaling/growth factors and systemic hormones[32]. (Fig. 4)

Distraction Osteogenesis:

Distraction osteogenesis is done frequently for generating new bone in cases requiring orthognathic surgery. This is done by progressively distracting bone surfaces. It is essentially a bone remodeling procedure which includes mobilization of the osteoblastic/osteoclastic cells. Hence stem cells which can regenerate bone can play active role in this procedure.[25,32]

Bioroot Engineering:

Presently, individually created tissues seem to be a more tangible promise within a reasonable time frame[33]. Teeth that underwent external root resorption for orthodontic reasons, for instance, are not likely to recover the tissue loss. That would seem to positively change research evolvement. The apical papilla differs from the dental pulp for containing less cellular and vascular components[7]. However, apical papilla stem cells have shown to have both high repair and differentiation potential. Proof of that may be found in some situations when traumatized and incomplete root formation permanent teeth underwent pulpectomy and subsequent endodontic therapy, and were still able to keep on with the apexification process. These findings open the possibility of using steam cells from apical papilla (SCAP) as well as other types of stem cells for pulp and dentin repair, together with the association between SCAP and periodontal ligament stem cells. This possibility has been called the ‘Bioroot Engineering’.

Stem Cell Banks

“Dental stem cells are a valuable source of stem cells and are found in teeth with healthy pulp,” StemSave’s Chotkowski explained. “These teeth could be deciduous teeth, wisdom teeth and other permanent teeth. Presently, these teeth are being discarded as medical waste. A stem cell bank allows an individual the opportunity to preserve their biomaterial for future regenerative therapies.”

Chotkowski cited the banking of umbilical cord blood as a source of stem cells, which has been advocated for the past 15 years to parents of newborns. “To date, there have been many lives saved through the transplantation of these stem cells,” he said. “Cryopreservation or banking of stem cells maintains the viability of these cells indefinitely[34].

“During cryopreservation, the cells are put to sleep through a process called vitrification, in which the tissue is placed in liquid nitrogen at a temperature of -196 degrees Celsius. The cryopreservation process stops all cellular metabolism involving both cell growth and cell death. The cells preserved today can be applied to future regenerative therapies. There are many parents who did not have the opportunity to bank their children’s cord blood. StemSave allows these parents another chance to bank their children’s accessible and valuable stem cells when they are undergoing a routine dental procedure.”
**Future Prospects of Stem cells in Dentistry:**

Although there is great excitement in scientific community about stem cells and regenerative medicines, it is yet to be known about the clinical applications of stem cells. Therapies based upon cell replacement and tissue engineering, underpinned by stem cell biology is emerging as potentially powerful strategies in modern regenerative medicines. Additional research to coordinate advances in various fields, such as clinical medicine, biology, materials science, nanotechnology, and chemistry will increase the advancement of regenerative therapies. The bioengineering technologies developed for tooth regeneration will make substantial contributions to understanding the developmental process and will encourage future organ replacement by regenerative therapies in a wide variety of organs, such as the liver, kidney, and heart.

**Fig. 1.** Teeth commonly removed in the course of normal dental care that contains stem cells.

**Fig. 2.** Dental and other tissue generated by stem cells from baby teeth and wisdom teeth.

**Conclusion:**

Research has shown that teeth are a source of high quality stem cells that may be used for the treatment of medical and dental disease. The discovery that odontogenic tissues are a source of adult stem cells has opened up a new role for dentists in the field of medicine. Dentists 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.

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