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TOOTH BANKING OR DENTAL STEM CELL BANKING & ITS ROLE IN PEDIATRIC DENTISTRY; LITERATURE REVIEW

Paediatric Dentistry

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ABSTRACT

Stem cell biology has become an integral part of regenerative medicine and dentistry. Since the identification of mesenchymal stem cells, stem cell biology has been a heavily explored area of regenerative medicine and tissue engineered therapies, and has become an integral part of dentistry. Stem cells from deciduous teeth are those obtained with least trauma as deciduous tooth undergoes physiologic exfoliation. Dental stem cell preservation services, "tooth banking," focus on harvesting a child's baby teeth when they fall out naturally and preserving the stem cells from the pulp for future therapeutic use when the child needs them. The purpose of this review is to focus only on role of stem cells in paediatric dentistry and their banking.

KEYWORDS

INTRODUCTION

Our body perform a broad list of functions for its survival and maintenance, one of which is to rebuild or regenerate itself after trauma or disease. This is possible due to the presence of a unique group of unspecialized cells called stem cells.[1] The collection of stem cells for long-term storage for therapeutic purposes is now a service offered by dentists. More specifically, the dentist collects the teeth and "TOOTH BANK" services extract and preserve the stem cells in the pulp for the patient's future benefit.[2] However, the discovery of postnatal stem cell populations in dental pulp by Gronthos and Shi about two decades ago opened up new horizons for stem cell research and propelled dentistry into the exciting field of regenerative medicine. Postnatal stem cells are present in the pulp of deciduous teeth that are lost or exfoliated by all children during the first 6 to 12 years of development, that demonstrates the important role of paediatric dentist in this field.

This review will primarily focus on the practical aspects and application of "tooth banking or dental stem cells banking" in paediatric dentistry.

Oral tissue sources of stem cells

Dental stem cells come from a number of sources that can be obtained at different points throughout an individual's life. Dental pulp from both adult dental pulp stem cells (DPSC) and human exfoliated deciduous stem cells (SHED) includes most the studied populations in regenerative medicine and with periodontal ligament stem cells (PDLSC), alveolar bone most stem cells (ABSC), apical papilla stem cells (SCAP) are harvested from tissue in and around the tooth itself. Tooth germ progenitor cells (TGPC), and dental follicle stem cells (DFSC) present in the tooth bud which mainly involves in development of tooth and are not easily accessible for stem cell banking. Associated oral tissues such as the epithelium, gingiva (gums), and salivary gland also harbor unique populations of stem cells. However, the least invasive source of dental stem cells are clearly those naturally released as part of development - SHED which are contained in the pulp of deciduous teeth and DPSC which are present in pulp.[2]

DPSC

In 2000 Gronthos et al. were the first to identify MSCs in the dental pulp of teeth[3], now known as dental pulp stem cells (DPSCs). These cells were examined based on their putative clonogenic and proliferative properties. Gronthos et al. proposed that DPSC have the necessary progenitors to have cellular properties similar to BMMSC. Gronthos et al. concluded that DPSCs can be considered as a source of stem cells due to their profound regenerative, differentiation, and proliferative abilities. DPSC can be extracted from a pulp cavity and used for dentin regeneration in many teeth.[3]

SHED

In 2003 Miura et al. identified human exfoliated deciduous teeth (SHED) as a deep source of MSCs to be considered for use in autologous regenerative therapies. An advantage of SHED as a source of stem cells is that they can be easily obtained from a child at a relatively young age that makes importance of these stems cell in paediatric dentistry. SHEDs are found in the dental pulp that remains in deciduous teeth that are lost and replaced by adult permanent teeth during adolescence in a person's life. This makes SHED an ideal candidate for preservation by stem cell banks.[4]

In vivo characterization –

Dental tissue regeneration - SHED introduced into immunocom promised mice produced human-specific odontoblast-like cells with a dentin-like architecture expressing dentin sialophospho protein.[4] They also noted the differentiation of SHED into blood vessels that anastomosed with the host vasculature.[5]

Osteogenic potential - 40% of the SHED colonies showed a dramatic amount of new bone formation when injected into immunocompromised mice . When transplanted in vivo, SHED was able to transform recipient mouse cells into osteoblasts, which was not observed in DPSCs.[5]

Neurogenic potential - The neural developmental potential was examined by injecting SHED into the hippocampal dentate gyrus of immunocompromised mice, it was found that SHED expresses neural markers such as neurofilament M (NFM). Some studies also reported that SHED expresses neuronal and glial cell markers that may be related to the origin of neural crest cells from dental pulp.

Therapeutic Applications

Dental tissue engineering:

Studies demonstrated SHED differentiation into functional odontoblasts (which express dentin sialoprotein and generate tubular dentin) when implanted into mice. Positive B-galactosidase staining in cells lining the walls of blood vessels within dental frameworks/sections resembled unstained (host) blood vessels. This research confirmed that SHED can regenerate pulp tissue in vivo with properties similar to natural teeth.

Medicine

Currently, SHED are being used for treating bone fractures, cancer (bone marrow transplants), spinal fusion surgery and immune-related diseases like lupus erythematosus

DPSC vs SHED

proliferative ability of DPSC compared to bone marrow stem cells. Indeed, repeated studies have found that SHED has even greater proliferative properties and osteogenic differentiation in SHED along with increased expression of CD73 when compared than DPSC and may have a higher propensity for survival than its adult counterparts. DNA microarray analysis revealed higher expression of some genes related to pluripotency, cell proliferation and extracellular matrix, including several cytokines such as fibroblast growth factor and tumor

growth factor B, in SHED than in DPSC, where an outstanding improvement in expression was observed by collagens (Col I, III, VII and XIII) and proteoglycans (glypican and versican).[6]

APPLICATIONS OF DENTAL STEM CELLS IN PEDIATRIC DENTISTRY

Apexification and apexogenesis

Tissue regeneration at the apex of an immature permanent tooth may derive from stem cells already present in vital pulp tissue, the apical papilla, the PDL, or the alveolar bone; Alternatively, stem cells and growth factors seeded onto scaffolds can be used to regenerate tissues in vitro or in vivo. Stem cells already exist in vital pulp tissue, apical papilla, PDL or alveolar bone. In addition to these other potential sites, they may include perivascular regions, areas adjacent to blood vessels, and peripheral nerve endings. Hertwig's epithelial root sheath (HERS) also plays an important role in apical development and regeneration by stimulating the SCAP to produce new dentin deposits and rest of the apex.[7]

Mooney et al. (1996) first described an in vitro technique to engineer new pulp-like tissues from cultured human pulpal fibroblasts.[8] Regeneration of pulp or periodontal tissues relies on the provision of appropriate biodegradable scaffolds which are capable of containing or being seeded with growth factors and bioactive signalling molecules, supporting cell organization and growth of a vascular supply. Natural scaffolds like collagen offer good biocompatibility and bioactivity; however, synthetic scaffolds such as poly- lactic acid, polyglycolic acid, foams and hydrogels have more predictable mechanical properties and offer greater control of degradation time.

Cordeiro et al. (2008) seeded SHED and endothelial cells on biodegradable scaffolds into human tooth sections and then implanted them into immunocompromised mice.[9] The cells were observed to differentiate in vivo into odontoblast-like cells and endothelium-like cells, with the resulting tissue closely resembling dental pulp with a viable blood supply. Gomez Flores et al. (2008) developed a novel approach for in vivo periodontal regeneration using a multilayer technique of human PDL cell layers, which resulted in the formation of immature cementitious tissue and PDL with an orientation perpendicular to dentin surfaces.[10] When an open apex is present, a similar scaffold design alongside vascularization can aid in apexification by thickening and enclosing the apical portion of the root with hard tissue Tissue banking of one's own cells can overcome the immunological and ethical considerations associated with the use of allogeneic cells. In particular, given the highly proliferative nature of these cells and the high incidence of traumatic tooth injury in the early permanent dentition, encapsulation of SHED or immature third molar stem cells would be beneficial.[7]

Tooth banking – the process

Although stem cell banks collecting bone marrow and placental cord blood have been in operation for decades, banks specializing in stem cells isolated from teeth are relatively new. The number of dental stem cell banks is growing, especially in North America, India and Great Britain.

Few tooth banks are listed in Table 1 by searching in key words like dental stem cell bank or tooth banks. While this is not an exhaustive search, and other tooth banks function locally, many of these companies, the USA-based ones in particular, extend their banking facilities continentally and globally.

Table 1 Tooth Banking services examined in this review:-

Tooth banking service	Location	Website	Collection by (per web site)
BioEden	USA	https://www.bioeden.com/us/	patient or dentist
Future Health Biobank	UK	https://futurehealthbiobank.com/	Patient
Mothercell	India	https://www.mothercell.com	Dentist
ReeLabs	India	https://reelabs.com	Dentist
Oothy	USA	https://www.oothy.com/	patient or dentist
Stemade	India	http://www.stemade.com	Dentist
Stemodontics	USA	https://stemodontics.com/	Dentist
Stem Protect	UK	https://www.stemprotect.co.uk/	Patient
Stem Save	USA	https://www.stemsave.com	Dentist
Store-A-Tooth/Provia Labs	USA	http://www.store-a-tooth.com/	Dentist
Store Your Cells	India	https://www.storeyourcells.com	Dentist

Role of paediatric dentist

A. Selection of right tooth

i Primary incisors and canines with no pathology and with at least one-third of root remaining. Studies have proved that the characteristics of stem cells from dental pulp depend on root resorption. The researchers failed to isolate stem cells from the dental pulp which did not show any visible root resorption.

ii. Apart from primary teeth, extracted third molars, permanent teeth removed for orthodontic purposes.

iii. The tooth exfoliated should have pulp red in color (Pulp vital).

b). Patient Education and Registration

In general, parents/patients interested in embanking stem cells from teeth should register with one of the nearest commercially available stem cell embankment services or have the dentist provide information and educate patients about tooth embankment. It is important to note that obtaining stem cells from close relatives with a positive history of genetic diseases, cancer or other diseases should be avoided. The dentist then makes an appointment for the extraction. In addition, the organization works directly with the dental office to provide all the necessary materials and instructions. For example, the company StoreAToth offers a tooth extraction kit. It is always recommended that a dentist register well in advance of the patient's arrival.[11]

Step 1 – tooth collection –

Many collection protocols for dental stem cell storage are similar, but there are some notable and important differences in both sample requirements and sample processing. Most services recommend that a dentist remove the baby tooth once it's loose. In contrast, BioEden (www.Bioeden.com) claims to use an optimized collection and transport process for naturally exfoliated teeth (Table 1).

The sample is transferred into a container whose usual capacity is up to four teeth. The contents of the container include a sterile saline solution in order to supply nutrients and prevent dehydration during shipment. The container is carefully sealed and placed in thermette (Temperature change phase carrier). The thermette is then shifted to the insulated metal box . This process maintains the sample in a hypothermic phase and is referred as sustentation. The maximum time span time from collection to arrive at the processing storage facility should not exceed 40 hours.[11]

Stem cells are typically extracted from the pulp by mechanical and enzymatic preparation of single cell populations, or alternatively by tissue engineering, allowing the cells to migrate naturally from the extracted pulp onto plastic culture surfaces. In early studies on the isolation and characterization of dental pulp stem cells, Songtao Shi and Stan Gronthos enzymatically digested and ablated pulp tissue with collagenase type 1 to detach the cells from the extracellular matrix and then passed them through a 70 μm sieve. Thereafter, individual cells were allowed to grow in culture. keep it simple The cells migrate out of the tissue and form colonies on the plastic culture surface.[2] Flow cytometry is a common analysis technique that requires only a few thousand cells from the entire sample.

Cryo preservation

It is the process of preserving whole cells or tissues by cooling them to sub-zero temperatures. Liquid nitrogen vapor is commonly used for this purpose to keep the cells at < -150ºC to keep. The basic idea of this technique is that at these temperatures the biological activity of the cells persists for a period of time to maintain vitality and then thaws when needed. Cells removed towards the end of the logarithmic growth phase are ideal for cryopreservation. The optimal cell number for successful recovery would be 1 to 2 x 106 cells in 1.5 mL of freezing medium.[11]

Magnetic Freezing

This is an alternative freezing technique first proposed by Hiroshima University and called the live cell system (CAS); is known. Here a weak magnetic field is applied to the tissue, which lowers the freezing point by up to 6-7 °C. As soon as the body cools down evenly, the

magnetic field switches off. Unlike other systems, CAS does not damage the cell wall, cell survival rate in teeth increased by up to 83%, and it is cheaper than cryogenics.

In addition, the application of magnetic fields during freezing has been shown to increase the viability of frozen cells.

Recent Innovative Method of Banking SHED

Dental stem cells such as SHED eventually enter an irreversible state of proliferation arrest known as replicative senescence after long-term in vitro culture under culture stresses such as hyperoxia and elevated temperatures. Cell aging and lifespan depend on the rate of telomere loss during each cell division and primary telomere length. It has been shown that reconstitution of telomerase by TERT expression can lengthen telomeres, extend cell lifespan, and even immortalize cells. To reverse this effect, restored ectopic expression of TERT in SHEDs by lentiviral transduction with a puromycin selection marker. The results showed that TERTSHED exhibited strong proliferation ability, showing that TERT has immortalized SHED as a potential source for stem cell therapy.[14]

CONCLUSION

With the discovery and research of dental stem cells, there are great opportunities to use these cells in regenerative medicine and in the repair of dental tissue. Aspects of each stem cell source need to be analyzed so that the best candidate can be used for the stem cell bank and specific regenerative treatment in personalized medicine. Given the ease and convenience of collecting stem cells from the tooth, it would be desirable if more dentists, clinicians and dental clinics residing in middle- and high-income countries became part of banking services. Ultimately, it will be the patient or parents who decide the fate of stem cell banking as a business; However, aside from the cost and the tooth fairy, there may be little reason not to store dental stem cells.

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