

Review Article

Therapeutic applications of stem cells from human exfoliated deciduous teeth: a review

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ABSTRACT

Dental stem cells have been found to have the ability to differentiate into nerve cells, adipose cells, chondrocytes, osteoblasts, myocytes, hepatocytes, and odontoblasts. They can be derived from permanent teeth or deciduous teeth. Stem cells from human exfoliated deciduous teeth (SHED) have a higher proliferation rate and higher osteogenic and neurogenic potential than dental pulp stem cells (DPSC). Therefore, SHEDs are an attractive cell source for tissue regeneration. A large plethora of *in vitro* and animal studies have been conducted in the last few decades that has demonstrated the potential uses of these cells for the treatment of oral and non-oral diseases. The aim of this article was to review the potential therapeutic applications of stem cells derived from human exfoliated deciduous teeth. A Medline search was done, including international literature, published in English between 2003 and 2020. In this area, further research is needed to ensure the applicability of SHED in the treatment of diseases in humans.

Keywords: Human deciduous teeth dental pulp cell, Human exfoliated deciduous teeth, Stem cell

INTRODUCTION

The uses of stem cells from various sources such as bone marrow, umbilical cord, and adipose tissue have been long known. Numerous research studies have documented stem cells derived from human teeth as a promising novel source for the treatment of oral and non-oral diseases. These cells possess certain characteristics which make them an excellent alternative to the current population of stem cells. Some of these characteristics are:

1. Pulp tissue contains a huge number of undifferentiated stem cells.
2. It is relatively easier to extract stem cells from permanent and deciduous teeth compared to other sources of stem cells.
3. Extirpation of dental stem cells is non-invasive and is not related to any morbidity.

4. Dental stem cells are capable of multi-lineage differentiation. They can differentiate not only into cells of bone and dentin but also to fat, muscle, nerve and cartilage.¹
5. Stem cells derived from teeth are less likely to cause immune reactions.²
6. Cryopreservation of these cells has good results because these cells remain undifferentiated and stable.³

The stem cells from teeth are neural crest in origin, which may be responsible for their applicability in the regeneration of tissues of ectodermal as well as mesenchymal origin. Both dental pulp stem cells (DPSC) obtained from permanent teeth and stem cells from human exfoliated teeth (SHED) possess all these characteristics. Nevertheless, SHEDs are different in several ways. SHEDs are more immature, have a higher proliferation rate, forms in sphere-like cell-cluster, shows osteoinductive capacity *in vivo*, do not reconstitute

dentin–pulp-like complex, and have fewer considerations with regard to ethics. They have shown higher osteogenic and neurogenic potential as compared to DPSC.^{4,5}

SHEDs are essentially mesenchymal stem cells, and they are an ideal cell source for regenerative medicine that uses stem-cell transplantation and tissue engineering techniques.⁴ The purpose of this review is to describe the therapeutic applications of stem cells from human exfoliated deciduous teeth.

THERAPEUTIC APPLICATIONS OF SHED

Oral diseases

Periapical lesions

Periapical lesions are defined as the destruction of bone around the apex of teeth. These lesions are identified on radiographs as a radiolucency attached to apex with/without defined borders. Prasad et al found the resolution of radiolucency area and healing of the periapical tissues 30 days after the implantation of SHED in the root canals.⁶ They also had noted the continuation of the growth of root in teeth with open apices. The healing of periapical tissues was much faster when stem cells were used as compared to conventional treatment methods.

Entire tooth regeneration and bio-root regeneration

SHED is considered an appropriate source for bio-root regeneration because it has shown angiogenesis, odontogenic, and neurotization potential in several studies. In a study by Yang et al, these cells (complexed with treated dentin matrix: acts as scaffold) were transplanted subcutaneously into nude mice, which led to the formation of dentin and periodontal ligament-like fibrous tissues.⁷ Stem cells from exfoliated deciduous teeth also showed excellent neurogenesis and angiogenesis potential. Regeneration of the entire periodontal ligament-alveolar bone complex was also seen. In particular, root regeneration seems a more viable and practical option for tooth restoration when compared with the entire tooth regeneration.

Cleft lip and palate

The management of this condition is closing the bone defect with autogenous iliac bone graft. Essentially, this involves extensive surgeries and has a negative psychological impact on the child. In a study, Nakajima et al found that SHED has the capability to produce osteoid and a rich network of collagen fibers that exceeded one produced by human dental pulp stem cells (HDPCs) and human bone marrow stem cells (HBMSCs).⁸ Higher bone regeneration ability of SHED makes it the richest source of stem cells for the reconstruction of the alveolar cleft. Furthermore, researchers have found that the addition of fibroblast

growth factor-2 mediates intra-membranous bone formation at a much faster rate.^{9,10}

Orofacial skeletal defects

Maxillary and mandibular defects can be caused by trauma, severe infections such as osteomyelitis, or cancer. Prosthetic replacement of teeth on missing portions of jaws is not only challenging but also has not shown very positive outcomes. SHED implantation has been found to have a success rate in the reconstruction of mandibular defects in some studies. For example, Zheng et al engrafted stem cells from pig deciduous teeth into the bony defects in swine mandible models.¹¹ In their study, they found the regeneration of bone at 6 months post-surgery.

Periodontitis

Periodontitis is the inflammation of supporting structures of teeth namely periodontal ligament and alveolar bone. It is a very common disease of the oral cavity with several treatment options. Scientists have proposed stem cells as a viable alternative to the available options. In a study by Gao, a multi-dose delivery of SHEDs caused periodontal tissue regeneration.¹² They found that SHED application in a rat model altered the cytokine expression profile in gingival crevicular fluid, increased new attachment of periodontal ligament, and decreased osteoclast differentiation. In another study, SHED administration suppressed expression of inflammatory factors, inhibited the production of osteoclasts, and promoted regeneration of periodontal tissues.¹³

Non-oral diseases

Temporomandibular joint osteoarthritis (TMJOA)

It is an inflammatory disease of temporomandibular joints. The exosomes of stem cells from human exfoliated deciduous teeth have demonstrated a reduction in TMJ inflammation.¹⁴ SHED-Exosomes treatment suppressed the expression of interleukin-6 (IL-6), IL-8, matrix metalloproteinase 1 (MMP1) and other inflammatory mediators.

Post-traumatic lesions with transection of the facial nerve

In a study, the mandibular branch of rat facial nerve after neurotmesis was repaired by autograft and SHED in a polyglycolic acid tube (PGAT).¹⁵ The results of the study confirmed that the stem cells integrated and remained viable in the neural tissue after transplantation and initiated in vivo differentiation.

Diabetes mellitus type II

The disease is characterized by insulin resistance due to defective pancreatic β -cell secretory function. Rao et al

injected SHEDs in rats via the tail vein.¹⁶ After 8 weeks, the disease was dramatically attenuated. Histological analysis showed that the injection decreased pancreatic islet and liver damage. In addition, real-time PCR analysis and western blotting demonstrated that SHED significantly reversed the diabetic-induced increase or decrease in the glucose-6-phosphatase and reversed the diabetic-induced effects.

Diabetic nephropathy (DN)

Diabetic nephropathy (DN) is one of the major causes of chronic kidney disease. It had been shown that SHED administered by the tail vein in rats inhibited AGE-induced EMT in HK-2 cells, and therefore can be used as a novel method for improving the symptoms of diabetic neuropathy.¹⁷ The transplantation of SHED relieved neuropathic pain in diabetic patients, caused functional recovery of the peripheral nerves, and increased capillary to muscle fiber ratio and intra-epidermal nerve fiber density.¹⁸

Hypoxic-ischemic encephalopathy (HIE)

Perinatal HIE is a neurological disorder that can cause death. SHED was injected into the right external jugular vein in HIE neonatal rats to find out the usefulness of these cells for HIE in a study by Kitase et al. There was a significant improvement with elongation of the endurance time in a treadmill test.¹⁹

Multiple sclerosis (MS)

It is an autoimmune disease characterized by neuro-inflammatory demyelination in the CNS. Studies have been conducted to investigate the efficacy of SHED in conditioned medium (SHED-CM) in the treatment of MS. In a study by Shimojima et al, one injection of SHED-CM in an experimental autoimmune encephalomyelitis (EAE) mouse resulted in a decrease in demyelination and axonal injury, decrease in inflammatory cell infiltration and pro-inflammatory cytokine expression in the spinal cord, and an overall improvement in disease scores.²⁰

Traumatic brain injuries (TBI) and focal cerebral ischemia

Li et al studied the effects of SHED and SHED-Exosomes (Ex) in TBI rat models.²¹ SHED-Ex reduced neuro-inflammation by shifting microglia polarization. This improved rat motor functional recovery and reduced cortical lesion post-TBI. Inoue et al tested the effects of SHED administered intranasally on middle cerebral artery occlusion in rats. Results of the study confirmed that SHED induced vasculogenesis and neurogenesis in the rat brain.²²

Spinal cord injuries (SCIs)

The effects of SHED transplantation on glial scar formation and astrocytic reaction after SCI were studied

by Nicola et al.²³ The results of the study suggested that SHED acts as a neuroprotector agent. They function mainly through paracrine signalling to reduce glial scar formation, induce tissue plasticity, and causes functional recovery.

Parkinson's disease (PD)

In parkinson disease, the dopamine nerve cells of the substantia nigra degenerate. Zhang et al transplanted neural-primed SHED to the striatum of 6-hydroxydopamine (6-OHDA)-induced rats with PD.²⁴ They found significant improvement in the recovery of the motor deficits. After transplantation, SHED was differentiated into dopamine neurons and integrated into the rat brain by forming synaptic connections.

Allergic rhinitis (AR)

It is an allergic disease related to immune imbalance. SHEDs have been found to correct CD4+ T cell immune imbalance in a study by Dai et al.²⁵ In their findings, nasal symptoms and inflammatory infiltration were reduced significantly in response to SHED exposure. They inhibited the Th2 (helper T cells) immune response *in vivo* suggesting their potential use to treat allergic rhinitis.

Retinitis pigmentosa (RP)

Retinitis pigmentosa (RP) is a hereditary disease with degeneration and loss of photoreceptors. SHEDs can be differentiated into retinal photoreceptor-like cells.²⁶ This was confirmed in a study where cells having neuron-like morphology with specific genes and proteins expression like retinal precursors, and mature photoreceptors were formed by SHED differentiation *in vitro*. These newly formed cells remained viable *in vivo* after transplantation into mice. In another study, they found that SHEDs improved electroretinogram responses, reduced photoreceptor degeneration, and maintained the structure of photoreceptors in a mouse model with RP.²⁷

Chronic liver fibrosis, acute liver failure, and hemophilia A

SHED can be a promising source for treating pediatric refractory diseases such as chronic liver fibrosis and hemophilia A. Takahashi et al investigated the therapeutic effects of SHED in mouse models.²⁸ The SHED converted to hepatocyte-like cells spheroids were transplanted into the liver of mice with chronic liver fibrosis and hemophilia A. This improved the liver dysfunction and increases bleeding time in mice with hemophilia A. Yamaza et al also seen liver regeneration capabilities of SHED after transplantation in carbon tetrachloride-induced liver fibrosis model mice.²⁹ Matsushita et al found a marked improvement in the acute liver failure condition in a rat model after a single infusion of SHED.³⁰ It improved pro-inflammatory

response caused by acute liver failure, and in addition, created a tissue-regenerating environment.

Dysphagia related to superior laryngeal nerve injury

The superior laryngeal nerve (SLN) has a central role in swallowing. An injury to the nerve following trauma and surgery can be a cause of dysphagia. In a study by Tsuruta, the administration of SHED-conditioned media (SHED-CM) caused functional recovery of the SLN and axonal regeneration.³¹ This also improved new blood vessel formation at the injury site.

CONCLUSION

The clinical applications of SHED demonstrated in animal models so far seem promising. SHED can be a novel treatment modality for a wide variety of diseases in humans. Ongoing research in this area might pave the way for treating oral and non-oral diseases to tissue regeneration using stem cells as the first line of treatment. However, before we establish their therapeutic effects in humans, randomized clinical trials need to be conducted in adherence to standardized procedures and safety protocols.

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