Review Article

A review on oral mesenchymal stem cells and tissue engineering, prospects of stem cell-based regenerative dentistry

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Abstract

Regeneration of the damaged organs and tissues is an important physiological mechanism of the human body. Embryological research has shown that the pluripotent stem cells are responsible for the development and growth of an organism. The mesenchymal stem cells (MSCs) are present in various adult tissues including those of dental origin. Recently a lot of attention has been laid on the unique features of stem cells like replacing, repairing, maintenance and augmenting tissue function. Oral dental MSCs are able to not only regenerate dental pulp and other dental structures but also other parts of the body, especially those, which have almost, have lost their ability to regenerate.

Key words

Oral mesenchymal stem cell, Tissue engineering, Stem cell-based regenerative dentistry.

Introduction

Repair and regeneration of the damaged organs and tissues is an important physiological homeostatic mechanism. Comprehending the intricacies of the normal growth and development of a particular tissue or structure is crucial. In this regard past few decades have witnessed tremendous research on the most critical drivers of the regenerative processes of the human body, the stem cells. Stem cells are non-specialized cells that can continuously divide, have the ability of self-renewal, and are capable of synthesizing complex tissues and organs [1]. They are broadly categorised as either embryonic or postnatal.

Embryological research has shown that the pluripotent stem cells are responsible for the development and growth of an organism [2]. These pluripotent stem cells segregate into multipotent stem cells like epithelial, parenchymal, mesenchymal and many other stem cells unique to each tissue [3, 4]. As the organs grow and mature, these embryonic stem cells gradually vanish, leaving some of them to persist in some of the human tissues like bone marrow [5], dental pulp [6], adipose tissue [7], dermis [8] and umbilical cord [9], which are responsible for the human body repair [10].

The mesenchymal stem cells are present in various adult tissues including those of dental origin. Recently a lot of attention has been laid on the unique features of stem cells like replacing, repairing, maintenance and augmenting tissue function [11]. The transplantation of cells for the purpose of tissue regeneration with or without a scaffold for growth of the cells is called tissue engineering, first coined by Langer and Vacanti in 1993 [12]. The two special characters of mesenchymal stem cells is their ability of automatic renewal and their propensity to differentiate into numerous cell lineages like bone cells, cartilage cells and cardiac cells [13].

One of the readily accessible and newer sources of mesenchymal stem cells is dental tissue. Stem cells have been successfully isolated from the dental pulp, periodontal ligament, dental follicle, the apical papilla and from the deciduous teeth [14, 15]. In the past few years, dentistry has been exploring the utilities of stem cells and tissue engineering towards the repair and regeneration of dental structures. The majorly focused tissue regeneration techniques in dental medicine mainly are the process of formation of tertiary dentin and the guided tissue regeneration of the periodontium. The ambitious aim of harnessing the multi-potent stem cells in the development of a whole new tooth in all its complexity has been recently explored [16, 17].

Objectives

This review discusses the state-of-the-science on the role of dental stem cells in tissue engineering, and offers a prospectus for the field of stem cell-based regenerative dentistry.

Materials and methods

The current study was a narrative review of the role of the stem cells based on recently published evidence on the subject. The authors had conducted organized search for the relevant studies published on the subject in two major data bases i.e. PUBMED and EMBASE using a structured search strategy.

Inclusion criteria

- Studies predominantly discussing about the role of stem cells in dental practice
- Published in last two decades i.e. between 1997 to 2017

A narrative review of the identified articles was done to provide a perspective on current status of stem cell research, with relevance to dental practice. The study has not employed any statistical methods to provide pooled estimates, as wide range of study designs including case studies to experimental designs were included in the review.

Discussion

Classifying oral mesenchymal stem cells

Oral mesenchymal stem cells (MSCs) are mainly classified into two types: dental MSCs, that have the capacity to produce dentin-pulp organ in-vivo and non-dental MSCs, that cannot form the dentin-pulp complex. The dental MSCs include DPSCs [6], stem cells from exfoliated deciduous teeth (SHED) [18], and stem cells from apical papilla (SCAP) [19]. Non dental oral MSCs include periodontal ligament stem cells (PDLSCs) [20] and MSCs from gingiva

(GMSCs) [21].

Dental pulp stem cells

Dental pulp is a connective tissue, the cellular components comprising of endothelial cells, neurons, fibroblasts, and odontoblasts. One of the first tooth-related stem cell types was found in the pulp of permanent teeth and was named dental pulp stem cells (DPSCs) and are characterized by a high proliferation rate and cellular differentiation depending on the medium culture [13]. They were first isolated by Gronthos, et al. [6] from dental pulp in impacted third molars.

The microenvironment of dental pulp offers an unique place for maintaining stem cells as it lacks oxygen and nutrition mainly due the very narrow apical foramen (250 microns) [22]. DPSCs express mainly the mesenchymal and bone marrow stem cell markers (CD146, STRO-1) and the embryonic stem cell marker (Oct4).

Batouli et al observed that DPSCs were able to form a reparative dentin-like structure on the human dentin surface loaded DPSCs in immunocompromised mice [23]. On ethylenediaminetetraacetic acid (EDTA)-treated dentin scaffolds, DPSCs formed a vascularized soft connective tissue similar to dental pulp [24].

Stem cells from exfoliated deciduous teeth

The first identification and isolation of stem cell in deciduous teeth [18] heralded an fascinating opportunity of using oral MSCs for tissue engineering. Evidence suggests that SHEDs have distinctive advantages owing to their higher rate of multiplication, ease of in-vitro handling, greater plasticity as they can differentiate into neurons, adipocytes, osteoblasts and odontoblasts [18]. SHEDs were shown to express early mesenchymal stem cell markers (Stro-1) and embryonic stem cell markers (Oct4, Nanog) suggesting a neural crest origin of these cells [18].

SHEDs are unique with the osteo-inductive ability and also can form odontoblasts. An experiment by Cordeiro showed that SHEDs could form odontoblasts like cells when they were seeded into porous poly L-lactic acid treated scaffolds of human teeth in immunodeficient mice [25]. It was also noted that SHEDs had induced formation blood vessels that anastomosed with the host vasculature. The evidence is promising in revealing the utility of SHEDs in repairing the damaged tooth or stimulate bone regeneration [25].

Stem cells from apical papilla

The apical papilla is a specialized connective tissue located at the apex of the tooth and has been recently discovered to harbor stem cells having a higher rate of proliferation. The SCAPs have the potential to form odontoblasts type of cells and there by the ability to form dentin like material [19]. Like other oral MSCs, SCAPs express early mesenchymal surface markers like STRO-1. The major markers expressed by these stem cells are CD146 and CD24, a unique marker for this cell lineage [26].

Stem cells from dental follicle

Dental follicle is a mesenchymal tissue surrounding tooth germ that is responsible for formation of cementum, periodontal ligament (PDL), and alveolar bone [27]. Stem cells from dental follicle (DFSCs) have been isolated from human third molars. They are found to express markers like Notch1, STRO-1 and nestin [28] and can form osteoblasts/cementoblasts, adipocytes, and neurons [29]. Wu showed that dNCPs (dentin non-collagenous proteins) extracted from dentin could stimulate DFSCs to differentiate into cementoblast lineages [30]. Kémoun, et al. confirmed that that enamel matrix derivatives induced human dental follicle stem cells to differentiate into cementoblastic phenotype. These stem cells acquired cementoblast features under stimulation of BMP-2/-7DFSCs. Overall DFSCs are heterogeneous type of stem cells and may be a useful research tool for studying PDL formation and for developing regeneration therapies.

Periodontal ligament stem cells

The periodontal ligament is a special form of connective tissue, has its origin from neural crest cells. Research suggests that PDLSCs multipotent type like DPSCs that can form tooth and bone related tissues making it a major source of stem cells for bone tissue engineering in regenerative dentistry [31]. Orciani, et al. revealed that osteogenic potential of PDLSCs could be due to increase in the production of Ca^{2+} and nitric oxide and hence it can be efficient method for managing periodontal defects [32]. Also PDLSCs can induce cementogenesis through the initiation of cementoblasts in immunocompromised mice [33].

Oral MSCs derived from human gingiva (GMSCs) also have been investigated as a potential substitute cell source for periodontal regeneration [34]. In one study on a dog model, GMSCs considerably increased the periodontal regeneration in class III furcation defects [35].

Systemic applications of Oral MSCs

Some research groups have looked into the muscle- and tendon-forming properties of oral stem cells. DPSCs have been shown to differentiate into cardiomyocyte-like cells in in-vitro neonatal rats' cardiomyocytes (36). Also they can form muscle cells that in turn can synthesize dystrophin in mouse model, which can have implications in the treatment of muscular dystrophy [34].

Tendons have inadequate ability for self-repair after injuries. As periodontal ligaments are similar to tendons in their ability of absorbing mechanical stress and strain, PDLSCs have been used for tendon regeneration. Gronthos, et al. found that ovine PDLSCs express scleraxis, a tendon-specific transcription factor in vitro [37].

Oral MSCs both dental and nondental types share common origin with neuronal cells as all of them are derived from neural crest stem cells. Hence, these cells also express markers of neural progenitors, such as nestin, p75/NGFR, Pax6, and Tuj1 [38]. Some in-vitro studies have revealed the differentiation of oral MSCs to neuronal cells [39].

A major challenge for stem cell-based tissue regeneration is to ensure rapid establishment of efficient blood vessel networks that allow for the survival of transplanted cells and provide adequate supply of oxygen and nutrients required to maintain the high metabolic demands of cells involved in tissue regeneration.

On the whole, the existing research reveal that oral dental MSCs are able to not only regenerate dental pulp and other dental structures but also other parts of the body, especially those, which have almost, have lost their ability to regenerate. However, in most cases, transplanted stem cells survive only in vascularized places (such as subcutaneous tissue). Without an abundant blood supply, most transplanted stem cells will undergo necrotic or apoptotic cell death [40].

Conclusion

The usefulness of stem cells in clinical applications depends on their proliferation rate, differentiation potential, and accessibility. It is becoming increasingly clearer that this conceptual approach to therapy will have its place in the clinical practice of dentistry and medicine in the future.

Limitations

The study was only a narrative review of the selected articles published on the subject at the discretion of the reviewers. Hence even though attempts were made to provide a balanced view on the subject, the role of bias can't be completely ruled out.

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