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Review

Stem cells in dentistry – Review of literature

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Abstract

Stem cells have been successfully isolated from a variety of human and animal tissues, including dental pulp. This achievement marks progress in regenerative dentistry. This article reviews the latest improvements made in regenerative dental medicine with the involvement of stem cells. Although, various types of multipotent somatic cells can be applied in dentistry, two types of cells have been investigated in this review. Dental pulp cells are classified as: DPSCs, SCAPs and SHEDs.The third group includes two types of cell associated with the periodontium: PDL and DFPC. This review aims to systematize basic knowledge about cellular engineering in dentistry.

Key words: regenerative medicine, stem cell, stem cell banking, regenerative dentistry

Introduction

Stem cells are biological cells that possess two properties: self-renewal, i.e. the ability to go through unlimited cycles of cell division for the purpose of replenishing the cell pool, and potency, i.e. the capacity to differentiate into other cell types. Owing to the cells' proliferative capacity, the available pool of stem cells is not reduced when cells are transformed into other tissues and participate in the renewal of vital structures such as the bone marrow.

A zygote is the initial, ideal stem cell. A zygote is a totipotent cell which has the ability to develop into any mature cell. Large numbers of stem cells are observed during fetal development. As the embryo develops, stem cells are gradually deprived of their capacity to transform into other cells, and differentiation may take place only in a given germ layer. The embryo's capacity for unlimited division is preserved until stem cells differentiate into three germ layers. Cells that are transformed solely into endoderm, ectoderm and mesoderm layer cells are known as multipotent stem cells. Unipotent stem cells have the capacity to develop into only one type of cell.

Stem cells found in an embryo during fetal development as well as placental stem cells are known as embryonic stem cells (ESC). Stem cells in the peripheral blood of adult individuals are referred to as somatic stem cells (SSC). The number of undifferentiated somatic stem cells remains constant in the bloodstream of adult mammals, including humans (Prescott et al. 2008). This cell pool is required for the renewal of biological structures, and it has to be regularly replenished throughout life. To ensure cell renewal, stem cells undergo asymmetric division. One of the resulting daughter cells retains the properties of the mother stem cell and undergoes further asymmetric division, whereas the other daughter cell is transformed into a specialized cell. The cell's self-renewal potential becomes limited upon specialization. Asym-

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metric division generates vast numbers of stem cells that form tissues and organs throughout an organism's life and guarantee its self-renewal capacity.
In adult humans, stem cells are present in tissues such as bone marrow, dental pulp, nervous tissue and skin, as well as organs, including the liver, heart, pancreas, bones, kidneys and retina. Stem cell research offers great hope for medicine. Attempts are made to use stem cells in the repair of damaged heart muscle and pancreatic islets, in the treatment of Alzheimer's disease (Casagrande et al. 2011), Parkinson's disease, infertility, and the regeneration of damaged limb tendons in valuable race horses. Stem cells are also a promising tool for dental reconstruction and regeneration (Unno et al. 2009).

Stem cells of dental origin

The fast, spontaneous and fully physiological process of dentin regeneration prompted the observation that the tooth contains stem cells (Yamashiro et al. 2006). Researchers discovered that stem cells can be used to develop a physiological adhesive for fixing implants in the dental sockets, and that the patient's somatic stem cells can be applied in dental reconstruction (Young et al. 2005). In dentistry, the use of somatic cells is the optimal solution. The patient's own somatic cells are easy to acquire without raising ethical concerns.

Various types of multipotent somatic cells can be used in dentistry. There are two types of cell of non-dental origin: bone mesenchymal stem cells (BMSCs) and epithelial stem cells. Ectomesenchymal dental cell types include dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAPs) and stem cells from human exfoliated deciduous teeth (SHEDs). The third group of cells is related to the periodontium and comprises periodontal ligament stem cells (PDL) and dental follicle precursor cells (DFPCs).

In pigs, enamel matrix proteins stimulate the differentiation of bone marrow stromal cells into porcine cementoblasts (Song et al. 2007). In humans, dental epithelial stem cells are lost after teething, but they are present in mouse and rat incisors throughout life, which is why mice or rats are the key animal model for studying dental stem cells (Matsumoto et al. 2011).

Dental pulp stem cells are not completely lost after teething in humans. Interestingly, they possess identical properties to mesenchymal stem cells (Shi et al. 2001), so they can differentiate into fat cells – adipocytes, and cartilage cells – chondrocytes and cementoblasts. Dental follicle precursor cells have the properties of mesenchymal stem cells as well, and in humans, DFPCs can be isolated during the extraction of molar teeth (Kemoun et al. 2007).

Periodontal ligament stem cells are present on the root surface of extracted permanent teeth, and they develop into tissues that are very similar to the periodontium. They have a high capacity for tissue regeneration and periodontal repair (Sonoyama et al. 2006).

Stem cells from the apical papilla can be retrieved only at initial stages of tooth development. A combination of SCAPs and PDL stem cells supported the attachment of an artificial tooth crown to the alveolar process by newly-formed dental connective tissue (Sonoyama et al. 2006).

Stem cells from human exfoliated deciduous teeth (SHEDs) are multipotent cells with a high proliferative potential. They can differentiate into dentin-forming cells, tubular dentin (Sakai et al. 2010),bones, adipocytes and even nerve cells (Miura et al. 2003). SHEDs are easy to acquire without raising ethical concerns. They have a very high capacity for tissue regeneration, they easily proliferate and harbor a wide variety of precursor cells.

The presence of the described cell types in teeth and periodontal tissues creates great potential for regenerative dental medicine. Further research efforts are needed to fully harness this potential.

Regenerative dentistry with the use of dental pulp stem cells (DPSCs)

The complete reconstruction of lost crowns raises the highest hopes in regenerative dentistry (Shi et al. 2005). Attempts are made to use DPSCs to induce the response of mesenchymal stem cells. The dental epithelium first forms a tooth bud (germ) which induces tooth formation. Next, the dental epithelium proliferates intensely to form a structure with a cap-like appearance. The enamel knot, which comprises the outer and inner enamel epithelium, stratum intermedium and stellate reticulum cells of the enamel organ, does not proliferate during the above process. Tooth buds are clusters of dense, proliferating tissue in the oral epithelium. Ectomesenchymal cells of the dental papilla aggregate below the enamel organ. The dental follicle is formed outside the enamel organ and the dental papilla, and it is eventually transformed into periodontal tissue (Morsczeck et al. 2009).

In physiologically developed teeth, the enamel formed by the epithelium is the only fully mineralized tissue. Epithelial tissues do not possess regenerative abilities. Tooth sections formed from the mesenchyma have a certain capacity for self-renewal, probably due to the presence of stem cells (Karaöz et al. 2010).

Cultures of pulp cells derived from early developing dental root tissue and pulp tissue can differentiate into odontoblasts (Couble et al. 2000, Okiji et al. 2009). The above observation invalidates the previous belief that dentin-forming cells develop from osteoblasts. Dental pulp cells have stem cell properties, and they can give rise to, for example, new pulp-like tissues (Casagrande et al. 2011). Dental pulp stem cells contribute to the development of connective tissue needed for tooth recovery (Gronthos et al. 2000, 2002). Dental pulp is the source of mesenchymal stem cells (Zhang et al. 2006). In 2011, dental pulp stem cells were isolated from transgenic mice to enhance our understanding of these cells' biological properties. Cell cultures revealed the presence of diverse cell populations with mesenchymal cell markers characteristic of embryos. After two weeks of in vitro culture, the cells began to differentiate towards adipocytes, chondrocytes and bone cells (Yu et al. 2010, Guimarães et al. 2011). The latest research findings (2011) suggest that adipose tissue-derived stem cells (ADSCs) are a more efficient source of stem cells for dentin regeneration. Rabbit ADSCs are also characterized by more intense growth and higher resistance than DPSCs (Hung et al. 2011).

In 2011, two types of stem cells retrieved from the dental root were compared: immature root papilla stem cells (iRPSCs) and mature dental pulp stem cells (mDPSC). Although dental papilla stem cells have lower bone-forming capacity, they have a higher dentin-forming potential than dental pulp cells. Dental papilla cells originating from the tooth root could have a superior dental regenerative capacity (Lei et al. 2011).

Research into stem cells from the apical papilla (SCAPs) and dental follicle precursor cells (DFPCs)

Dental follicle precursor cells (DFPC) were isolated from bovine tooth buds with the use of collagenase (Handa et al. 2002). DFPCs became the precursors of cementum. Dental follicle precursor cells can be retrieved from molars (Morsczeck et al. 2005). These cells resemble fibroblasts which form mineralizing nodules in the presence of dexamethasone, a short-acting steroid. They colonize the periodontium during teething or directly after tooth formation, and they can differentiate into periodontal tissues.

In 2011, dental follicle precursor cells were isolated from human molars. The sampling procedure produces at least three DFPC populations with varied morphology, differentiation potential and gene expression. Osteogenesis, chondrogenesis and adipogenesis can be induced inthese cell cultures. Despite differences in morphology and differentiation potential, all three cell populations have been shown to possess the same bone forming capacity in rats under in vivo conditions (Honda et al. 2011).

Stem cells of human exfoliated deciduous teeth (SHEDs)

Neural crest cells could give rise to dental pulp stem cells. Neural crests are multipotent cells with a high regenerative capacity (Rinon et al. 2011).They play a vital role in tooth development by inducing the growth of the mesenchymal component, including odontoblasts, dental pulp, apical vessels and periodontal ligaments (Dangaria et al. 2011). SHEDs have the same molecular properties as neural crests and stem cells. SHEDs have similar effects of wound-healing promotion as hFibro (Nishino et al. 2011). Proteins on the surface of dental pulp cells support their differentiation into bone, periodontal, dental pulp, nerve cells and adipocytes. SHEDs are quickly transformed into nerve cells (Seo et al. 2004). Cells from human exfoliated deciduous teeth may differentiate *in vitro* into nerve cells through the expression of combined gene and protein sets. SHEDs may be used in autologous transplants in the treatment of various neurological diseases and neural traumas (Nourbakhsh et al. 2011).

Periodontal ligament stem cells (PDL)

The tooth is bound to the socket by two types of ligaments that hold it in place: periodontal ligaments and gingival ligaments. Periodontal ligament stem cells (PDL) and dental follicle precursor cells (DFPC) are precursor cells that develop into periodontal ligaments. Periodontal ligaments have many functions. They hold the tooth in the socket and act as prioreceptive sensors which provide the brain with information about the type of forces acting on teeth and jaw bones. Ligaments also play a regenerative role is replenishing not only own cells (Boyko et al. 1981), but alveolar process cells, cementoblasts (Isaka et al. 2001),and collagen-like tissue as well. The first study demonstrating that stem cells can be retrieved from solid-frozen periodontal ligament was a milestone discovery (Seo et al. 2004). Interestingly, ligament stem cells were found in both healthy and diseased periodontal ligaments (Chen et al. 2006). Mesenchymal stem cells (MSC) capable of regenerating the periodontium were isolated from the dental pulp of deciduous and permanent teeth (Lin et al. 2008).Mesen-

chymal stem cell markers Stro-1 (Mrozik et al. 2010) and CD 146 are found on the surface of periodontal ligament cells. In *in vitro* cultures, these cells form alizarin-red-positive nodules indicative of calcium absorption. The above observation clearly suggests that PDL can be used in periodontal regeneration. Periodontal ligament stem cells are responsible for the osseointegration of titanium implants. It has been demonstrated that stem cells proliferate more efficiently on rough surfaces (Heo et al. 2011).

Tooth regeneration and dental prostheses held by the patient's own ligaments

Intensive research efforts have been undertaken to examine the role of stem cells in the regeneration of immature permanent teeth (Thibodeau et al. 2007, Huang et al. 2008, Friedlander et al. 2009) and tooth regeneration through the reconstruction of dental crowns (Yamashiro et al. 2006). In the natural crown forming process, the crown's ultimate appearance is determined by epithelial precursor cells and mesenchymal precursor cells. Dental reconstruction research has continued for several decades (Yamada et al. 1980, Yoshikawa et al. 1981).

Two novel dental reconstruction methods were proposed in 2008. The first involves the growth of dissociated tooth germs and the development of small dental structures on a tooth-like scaffold (Roberts-Clark et al. 2000, Koyama et al. 2009). The scaffold structure remains at the development stage, giving rise to numerous research studies around the world. In 2006 scientists investigated 3-dimensional scaffold materials such as a porous ceramic, a spongeous collagen, and a fibrous titanium mesh (Zhang et al. 2006). In July 2011, the use of treated dentin matrix (TDM) for dentin regeneration in human patients was investigated. To date, TDM has been used exclusively in rat experiments, and a recent study demonstrated that it is also a suitable scaffold for human dentin regeneration (human treated dentin matrix, hTDM) (Li et al. 2011). In June 2011, nanofibrous (NF) poly-L-lactide (PLLA) scaffolds were showed to deliver superior mineralization and differentiation of dental pulp stem cells than non-porous PLLA scaffolds (Wang et al. 2011). In the same month, scientists compared the use of adipose tissue-derived stem cells and dental pulp stem cells in a non-engineering dental implantation method. Their results clearly demonstrate that both DPSC and ADSC implants grow to form new teeth, and both cell types are characterized by similar proliferation capacity (Hung et al. 2011).The other method involves the proliferation of mesenchymal and epithelial stem cells which interact to form new teeth (Yamashiro et al. 2006).

The effort to develop porcelain crowns with the involvement of stem cells is a completely different concept that focuses on the development of the most ideal prosthesis rather than tooth reconstruction. A pioneer study into the above was carried out with the involvement of pigs in 2006 (Sonoyama et al. 2006). Post-natal SCAPs and PDLSCs were combined to form the bio-root periodontal complex. Stem cells from the apical papilla have dentin regenerative capacity. SCAPs are multipotent stem cells with a high self-renewal potential. The pulp contains DPSCs which regenerate dentin. Although, in theory, DPSCs should be characterized by higher regenerative capacity, this is not the case. Owing to high levels of telomerase (Shi et al. 2002), PDL stem cells have the highest renewal potential, and they form the base of the bio-root periodontal complex. PDL stem cells are easily acquired and they proliferate rapidly *ex vivo*.

The latest research studies completed in 2011 indicate that an implant's long-term stability in the socket is determined by the degree of integrity between the bioimplant and tissue cells. Osseointegration between mature mesenchymal stem cells and biomaterial is regulated by the intercellular matrix and growth factors (Tuan et al. 2011).

Dental stem cell banking

It is reported that not all stem cells can be freely accessed throughout the patient's life, so there is a preference to retrieve the apical papilla stem cells and the dental follicle precursor cells with wisdom teeth extraction. The stem cells obtained may be banked for future dental treatment. Dogs do not develop wisdom teeth and stem cells should be obtained from canine patients during the formation of permanent teeth, which begins in the fourth month and ends in the middle of the sixth month of life.

Exfoliated deciduous teeth are quickly formed and equally quickly lost in animals. SHEDs are easy to obtain, and they are a generally acceptable source of multipotent stem cells transforming into specialized tissues (Miura et al. 2003). Banks of human and animal deciduous teeth have been created in the United States as a source of autologous stem cells for future transplants (Arora et al. 2009).

PDLs have a growing clinical potential. They can be isolated from frozen ligaments to provide a readily available source of MSCs for various types of treatments (Seo et al. 2004). The possibility of banking natural, frozen ligaments is thus becoming a real-

ity. Ligaments obtained during tooth extraction can be freeze-stored and used for regenerative purposes in the same patient.

The first study of dental pulp stem cells isolated from canine premolars was carried out in 2011. DPSCs were retrieved from a 10-month-old Beagle. The results indicate that canine dental pulp stem cells (cDPSCs) have similar properties to human cells. This suggests that dogs can be used as models for regenerative dental research, while the results of human research can be deployed in veterinary medicine (Dissanayaka et al. 2011).

Conclusions

The broad spectrum of mesenchymal stromal stem cells creates significant prospects for dental reconstruction research. MSCs are somatic cells that may be acquired from deciduous teeth and they constitute widely available research material which does not raise social controversy. Dental patients often forget that the loss of teeth has not only esthetic and hygienic consequences, but it also negatively affects nutrition and health. Teeth reconstruction raises hope for dental patients worldwide and research work should be continued. The progress made so far proves that stem cell-based therapy is a realistic option. Stem cell banking could offer an effective cure in the future when the use of stem cells in medicine becomes as widespread as roentgenography is today.

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