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Deciduous teeth stem cells, promising source of stem cells: narrative literature review

Células-tronco de dentes decíduos, fonte promissora de células-tronco: revisão de literatura narrativa

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ABSTRACT

Among the most progressive types of medical-scientific research, the study with stem cells stands out. Stem cell therapy has emerged as an innovative model in the treatment of diseases and injuries, presenting numerous advantages, which guarantee it will reach the population in the future. The pulp of deciduous teeth, because it is a tissue rich in stem cells, is capable of producing different cell types and offers an easy and minimally invasive way to obtain stem cells. These cells can be isolated, cultured, and expanded *in vitro*, differentiated *in vitro* and *in vivo* into odontoblasts, chondrocytes, adipocytes, endothelial cells, and neural cells. In addition, they have low reactions or rejection after transplantation and may remain undifferentiated and stable after long-term cryopreservation. This study aimed to review the literature on stem cells from human exfoliated deciduous teeth (SHED) and their possible applications in clinical practice. A bibliographic survey was carried out considering full texts published between 2000 and 2021 in the PUBMED database. In this review, current knowledge about stem cells obtained from human exfoliated deciduous teeth, tissue engineering approaches that use SHED, and possible applications in clinical practice were addressed. When comparing SHED with stem cells from other sources, such as stem cells from permanent teeth (DPSC), bone marrow stem cells, and stem cells from the umbilical cord, it is concluded that SHED has a higher rate of proliferation and multiplication, without ethical or legal implications, representing a new approach in regenerative therapy, being a promising alternative treatment.

Keywords: Deciduous tooth. Dental pulp. Mesenchymal stem cells. Stem cells.

RESUMO

Entre os tipos mais progressistas de pesquisa médico-científica, destaca-se o estudo com células-tronco. A terapia com células-tronco emergiu como um modelo inovador no tratamento para doenças e lesões, apresentando inúmeras vantagens, o qual garante ter alcance futuramente sobre a população. A polpa de dentes decíduos, por se tratar de um tecido rico em células-tronco, é capaz de produzir diferentes tipos celulares e oferecer uma forma fácil e minimamente invasiva de obter células-tronco. Essas células podem ser isoladas, cultivadas e expandidas *in vitro*, diferenciadas *in vitro* e *in vivo* em odontoblastos, condrócitos, adipócitos, células endoteliais e células neurais. Além disso, apresentam baixas reações ou rejeição após transplante, podendo permanecer indiferenciadas e estáveis após a criopreservação a longo prazo. O objetivo deste estudo foi fazer uma revisão de literatura das células-tronco de dentes decíduos esfoliados humanos (SHED) e suas possíveis aplicações nas práticas clínicas. Realizou-se um levantamento bibliográfico considerando textos completos publicados entre 2000 e 2021 no banco de dados PUBMED. Nesta revisão, foi abordado o conhecimento atual sobre células-tronco obtidas de dentes decíduos esfoliados humanos, as abordagens de engenharia de tecidos que usam SHED e possíveis aplicações nas práticas clínicas. Ao se comparar SHED com células-tronco provenientes de outras fontes, tais como: células-tronco de dentes permanentes (DPSC), células-tronco da medula óssea e células-tronco do cordão umbilical, conclui-se que SHED possui uma maior taxa de proliferação e multiplicação, sem implicações éticas ou legais, representando uma nova abordagem em terapia regenerativa, sendo uma alternativa promissora de tratamento.

Palavras-chave: Células-tronco. Célula-troncomesenquimal. Dente decíduo. Polpa dentária.

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INTRODUCTION

The evolution of science in search of improving the quality of dental treatments is happening quickly. Stem cell therapies consist of an alternative treatment based on regenerative medicine, in which every loss can be repaired. This evolution has created in dentistry professionals the interest in bringing stem cell-based therapy to dental treatments (Anoop & Datta, 2021).

Stem cells are clonogenic, non-specialized cells found in all multicellular organisms capable of self-renewal, differentiating into numerous types of specialized cells (Saez, Sasaki, Costa Neves & Silva, 2016; Popuri, 2018). In addition to being important in the field of medicine, such as for the expansion of therapies based on stem cells, they can also be used in dentistry, in order to repair damaged teeth or mandibular defects, for example (Xiaoxia, Shi, Yuming, 2017; Popuri, 2018).

The oral cavity has become an important source of mesenchymal stem cells (MSC) due to the easy access and removal of these cells (Saez et al., 2016). The dental pulp presents several clusters of stem cells, which are responsible for the formation of reparative dentin and renewal of pulp tissue. In addition, they have the ability to differentiate into multicellular lineages, such as adipocytes, chondrocytes, osteoblasts, odontoblasts and neural cells (Xiaoxia et al., 2017). Among the different populations of stem cells available in the dental pulp, we can name stem cells from permanent teeth (DPSC) and stem cells from human exfoliated deciduous teeth (SHED), with SHED being the candidate to play a leading role in engineering tissue and regenerative medicine (Rosa, Dubey, Islam, Min & Nör, 2016; Saez et al., 2016).

SHEDs are found in deciduous teeth, they are immature and unspecialized stem cells, with the ability to differentiate into several types of specialized cells (V. Arora, Arora & Munshi, 2009). They appear in the 6th week of the embryonic phase of human development, they express surface markers of mesenchymal stem cells, in addition to having a high proliferation and self-renewal capacity (Arora et al., 2009; Xiaoxia et al., 2017).

In view of the above, the objective of this review was to describe the current knowledge about SHED, its use for tissue engineering and cell-based regenerative medicine therapies and its applicability in the dental field, understanding its advantages over other stem cell populations in terms of its proliferative potential, minimally invasive procurement, and ethical concerns.

MATERIAL AND METHODS

This is a literature review study considering full-text scientific articles published between 2000 and 2021 in the PUBMED database, based on the keyword and/or abbreviations: stem cells from human exfoliated deciduous teeth (SHED), mesenchymal stem cells, deciduous teeth, and dental pulp.

It was 38 articles selected for analysis and review. We included 33 articles published in English that addressed stem cells from deciduous teeth, their possible clinical applications, and advantages over stem cells collected from another source. Articles that did not refer to stem cells from deciduous teeth and those published before the year 2000 were excluded.

RESULTS AND DISCUSSION

Stem cells

Stem cells are undifferentiated, unspecialized cells capable of continuous self-renewal and differentiation, having the potential to become different types of specialized cells (Telles et al., 2011; Aydin & Şahin, 2019). Their main function is to repair injured tissues, they are being researched as a new therapeutic option for the treatment of several diseases, including neurodegenerative diseases, autoimmune diseases, liver disease, diabetes, cardiovascular diseases and musculoskeletal disorders (Arora et al., 2009; Telles et al., 2011). The use of own stem cells excludes the potential to acquire

diseases from the donor cells, in addition to presenting little risk for the development of immune responses after transplantation (Saez et al., 2016). These cells can be isolated from different tissues, such as bone marrow, hair follicles, brain, umbilical cord and dental pulp (Miura et al., 2003; Daltoé, Mendonça, Mantesso & Deboni, 2014).

In the oral cavity, a variety of mesenchymal stem cells (MSC) have been identified that help in the repair and homeostasis of various tissues of the body (Saez et al., 2016; Sharpe, 2016). Oral MSCs can be classified into dental stem cells, including dental pulp stem cells (DPSC) (Gronthos, Mankani, Brahim, Robey & Shi, 2000); stem cells from human exfoliated primary teeth (SHED) (Miura et al., 2003); apical papilla stem cells (SCAP) (Sonoyama et al, 2006); as well as non-dental stem cells, including periodontal ligament stem cells (PDLSCs) (Seo et al., 2004); dental follicle stem cells (DFSC) (Morsczeck et al., 2005); gingival mesenchymal stem cells (GMSCs) (Zhang et al., 2009); oral periosteal stem cells (Cicconetti et al., 2007), and, recently, MSC from human periapical cysts (Marrelli, Paduano & Tatullo, 2013). SHEDs are the cells that show better results in multipotential and proliferative capacity (Saez et al., 2016).

Dental pulp is a highly vascularized connective tissue, responsible for the homeostasis of the dental organ, capable of providing cells with characteristics of mesenchymal stem cells (Gronthos et al., 2000; Telles et al., 2011; Rosa et al., 2016). It is possible to identify different samples of stem cells in dental pulp, such as dental pulp stem cells (DPSC) in permanent teeth and stem cells from human exfoliated primary teeth (SHED) (Gronthos et al., 2000). The SHEDs are isolated from deciduous teeth, which are discarded naturally, easily and safely, thus the collection avoids any kind of ethical considerations about the use of these cells (Gronthos et al., 2000).

The replacement of the primary by permanent dentition is a physiological phenomenon, in which the development and eruption of permanent teeth are synchronized with the resorption of the roots of their predecessors (Telles et al., 2011; Baniebrahimi, Khanmohammadi & Mir, 2019). Thus, deciduous teeth, in addition to providing guidance for the eruption of permanent teeth, induce bone formation during the eruption of permanent teeth (Wang et al., 2010). However, deciduous teeth differ from permanent teeth in relation to their tissue structure, function, and development (Huang, Gronthos & Shi, 2009). Likewise, SHEDs are different from DPSCs in terms of their higher proliferation rate, increased cell population doubling, formation of sphere-shaped cell clusters, and osteoinductive capacity *in vivo* (Wang et al., 2010; Kerkis & Caplan, 2012; Xiaoxia et al., 2017).

According to Rosa et al. (2016), SHEDs were isolated for the first time from exfoliated human primary incisors, which showed positive expression for embryonic stem cell markers, mesenchymal stem cell markers, stage-specific embryonic antigens, tumor recognition antigens, and negative for the expression of hematopoietic markers (Rosa et al., 2016). Furthermore, SHEDs are able to differentiate into adipocytes (Arora et al., 2009); neural cells (Arora et al., 2009); endothelial cells (Gronthos et al., 2000); dental pulp (Arora et al., 2009); as well as in osteoblasts and odontoblasts (Saez et al., 2016). This ability makes these cells interesting for bone tissue repair after appropriate stimulation (Kerkis & Caplan, 2012).

SHEDs are classified as adult stem cells, and offer attractive advantages such as: providing a safe, compatible donor (autologous transplant) for life, with no risk of rejection and lower risk of communicable diseases; the source is readily available and non-invasive; lower storage cost compared to cord blood storage; can be used by family members such as parents and grandparents; if parents have not chosen to store umbilical cord stem cells, SHED will be taken as a second chance (Arora et al., 2009; Kerkis & Caplan, 2012; Yu, Volponi, Babb, An & Sharpe, 2015).

Osteogenic Potential

SHED can undergo osteogenic differentiation and form bone *in vivo*, transforming these cells into an attractive model for bone tissue regeneration. This was evidenced by a study in which SHED mixed with β-tricalcium phosphate scaffolds promoted bone regeneration in swine mandibular defects (Gronthos et al., 2000). Likewise, SHED combined with platelet-rich plasma (PRP) was able

to develop the formation of mature vascularized bone tissue in defects in the mandible of dogs (Kerkis & Caplan, 2012). Furthermore, Seo et al. (2008) explain that SHED may be a promising model for the reconstruction of large human cranial/skeletal defects in craniofacial surgery, through a study using these cells to repair critical-sized skullcap defects in rats (Seo et al., 2008).

Another study aiming to evaluate the ability of SHED to reconstruct cranial bone defects found bone formation one month after surgery, the results suggested that SHED is a complementary cellular device to repair large cranial defects in rats (Mendonça Costa et al., 2008). Zheng et al. (2009) used SHED to regenerate orofacial bone defects in pigs. The results indicated that SHEDs are a source of autologous stem cells that are capable of regenerating bone to repair mandibular defects.

The following year, Yamada et al. (2010) pointed out that SHED combined with platelet-rich plasma (PRP) has the ability to form bone tissue, and this bone-forming action may be usable for dental implants coated with osseointegrated hydroxyapatite with adequate degrees of bone-implant contact. Through these studies, it is possible to affirm that SHED is a suitable model for the reconstruction of large human cranial defects in craniofacial surgery (Costa et al., 2008).

Neurological Potential

To elucidate the neurogenic potential, SHED was injected into the brain of immunocompromised mice (Miura et al., 2003). Histopathological examination showed that SHED survived for more than 10 days in the mouse brain, and expressed neural markers (Miura et al., 2003). These results related to the neuronal differentiation potential of SHED increase the interest in using these cells as an option for the treatment of neurological injuries and diseases (Gronthos et al., 2000).

Differentiation in hormone-secreting cells

In addition, the differentiation potential of SHED in hormonal cells has been studied. These studies provide evidence that SHED is able to differentiate into liver cells, that is, under appropriate stimulation SHED expresses liver markers (Yu et al., 2015). Transplantation of SHED into the liver of rats with carbon tetrachloride-induced fibrosis revealed that the cells can participate in liver recovery (Yu et al., 2015). Likewise, SHED is able to differentiate *in vitro* into islet-like cell aggregates, and can reverse the symptoms of diabetes disease and provide the recovery of normal blood glucose levels in rats (Gronthos et al., 2000; Kerkis & Caplan, 2012).

Having presented these wide therapeutic applications and with the technology for the cryopreservation of SHEDs currently available, it is possible to affirm that stem cell therapy has emerged as a revolutionary type of treatment for diseases and injuries, with great benefits, and promises to have immense effect on the future of the population (Arora et al., 2009; Popuri, 2018). The results obtained in research with SHED exemplified its clinical utility in Regenerative Dentistry, with therapies offering regeneration of damaged oral tissues replacing conventional approaches (Bakopoulou & About, 2016). It is known, therefore, that more *in vitro* and *in vivo* trials and clinical studies are needed to prove its effectiveness in regenerative therapy (Arora et al., 2009; Saez et al., 2016). However, dentists must be aware of the use of stem cells to perform therapeutic procedures, and thus, explain this possibility to their patients and guardians, emphasizing the ease and convenience of collecting the SHED (Popuri, 2018).

Regeneration of dental pulp and dentin

Tissue engineering is a multidisciplinary science that develops new tissues and organs and can be a new method to repair teeth (Telles et al., 2011). Dental pulp tissue engineering aims to replace the inflamed or necrotic pulp with healthy and functional tissue, capable of forming new dentin (Telles et al., 2011). Dental pulp engineering is considered the first step towards dentin

regeneration in teeth with necrosis, and a possibility beyond conventional endodontic treatment, offering the advantage of restoring pulp vitality.

Several studies have shown that SHED has the potential to regenerate the dentin-pulp complex. Gronthos et al. (2000) and Miura et al. (2003) mixed DPSC (Dental Pulp Stem Cell) and SHED, respectively, with hydroxyapatite/tricalcium phosphate and transplanted them into immunocompromised mice. The results showed a dentin-like structure coated with odontoblast-like cells.

The *in vitro* assay found several types of tissues related to the dentin-pulp complex, neural tissue, endothelium, bone and smooth muscle. Furthermore, transplants of DPSC or SHED with hydroxyapatite/tricalcium phosphate were evaluated and it was possible to observe tissues with different layers of odontoblasts and a mineralized dentin matrix structure was formed (Shi et al., 2005). According to the authors, it was concluded that it is possible to regenerate dental structures with the presence of different populations of dental stem cells associated with scaffolds.

Two studies have linked SHED to tissue engineering of the dental pulp. In one study, we analyzed the morphological characteristics of the tissues produced when biodegradable scaffolds seeded with SHEDs in tooth slices were transplanted into immunosuppressed mice. The resulting tissues have been observed to express architecture and cellularity analogous to pulp tissue (Kaneko et al., 2018). Furthermore, SHED was found to differentiate into odontoblast-like cells *in vivo*. Thus, the study suggested that exfoliated primary teeth are a usual source of stem cells for tissue engineering of the dental pulp, sparing the need for endodontic treatment (Cordeiro et al., 2008; Arora et al., 2009).

In light of this, the identification of appropriate stem cells, the development of scaffolds, and the use of various growth factors are essential (Telles et al., 2011). Rosa, Zhang, Grande e Nör (2013) showed that SHED was able to survive and differentiate when transplanted into full-length human root canals with scaffolds. Functional odontoblasts capable of promoting the regeneration of tubular dentin were formed. SHEDs, therefore, can repair damaged dental structures, induce bone regeneration, and possibly to treat neuronal tissue injuries or degenerative diseases (Miura et al., 2003).

Obtaining SHED and its clinical application

Mesenchymal stem cells can be obtained from the primary dentition, also known as baby teeth, and have the ability to differentiate into multicellular lineages, such as adipocytes, chondrocytes, osteoblasts, odontoblasts and neural cells (Miura et al., 2003; Xiaoxia et al., 2017). Among the various sources of oral mesenchymal stem cells, pulp stem cells from deciduous teeth (SHED) are the cells that present the best results in terms of proliferative and multipotential capacity, hence the importance of more advanced studies in this area (Saez et al., 2016).

Miura et al. (2003) showed that the deciduous tooth that is naturally exfoliated harbors a population of clonogenic cells completely distinct from the previously identified stem cells, capable of differentiating into different cell types, and providing sufficient cells for clinical practice (Miura et al., 2003).

The application of SHED in clinical practice is mainly given to its isolation, which is done easily and safely, and can replace stem cells obtained from other tissue sources (Gronthos et al., 2000; Baniebrahimi et al., 2019). In view of this, these cells are interesting for the stem cell bank, which collects, processes, and preserves stem cells (Baniebrahimi et al., 2019).

Angiogenic Potential

Another study investigated the possibility of SHED to differentiate into angiogenic endothelial cells and odontoblasts capable of generating tubular dentin. SHED seeded on slices of dental elements (cellular scaffold) were implanted in immunocompromised mice. It was concluded

that SHED differentiates into odontoblasts, which have the ability to originate tubular dentin, and endothelial cells, providing the process of angiogenesis (Sakai et al., 2010).

In addition, Bergamo, Zhang, Oliveira e Nör (2021) showed through flow cytometry analysis that SHED has high levels of VEGFR-1 (Vascular Endothelial Growth Factor Receptor 1) when compared to DPSCs, that is, SHED can induce greater vascularization (Bergamo et al., 2021). Both studies show that SHED have important potential in tissue engineering and dental pulp regeneration, however it is necessary to explore the ability of SHED further to mediate dentin-pulp regeneration in the oral environment.

It is already known that SHED is extremely important in the regeneration process within Dentistry with numerous clinical applications. There is still a lot of study to be done, but existing studies have clearly shown that deciduous teeth are an advantageous source of stem cells.

CONCLUSION

Stem cells from human exfoliated deciduous teeth have the ability to differentiate into different tissues of the human body, as they are young and immature cells. They are obtained naturally and with limited ethical concerns, presenting themselves as an opportunity for Dentistry to contribute to the development of tissue engineering and becoming a viable alternative to other sources. In addition, they have a higher proliferation rate compared to DPSCs. When compared to stem cells from the umbilical cord, it has a high degree of analogy and a higher multiplication rate in relation to stem cells from the bone marrow. However, for SHED-based therapies to become a clinical reality and provide quality of life, further studies are needed to obtain information about the characteristics of these stem cells and to examine their developmental potential.

REFERENCES

Anoop, M., & Datta, I. (2021). Stem cells derived from human exfoliated deciduous teeth (SHED) in neuronal disorders: a review. *Current Stem Cell Research & Therapy*, *16*(5), pp. 535–550. doi: 10.2174/1574888X16666201221151512

Arora, V., Arora, P., & Munshi, A. (2009). Banking stem cells from human exfoliated deciduous teeth (SHED): saving for the future. *Journal of Clinical Pediatric Dentistry*, *33*(4), pp. 289–294. doi: 10.17796/jcpd.33.4.y887672r0j703654

Aydin, S., & Şahin, F. (2019). Stem cells derived from dental tissues. *Advances in Experimental Medicine and Biology*, *1144*, pp. 123–132. doi: 10.1007/5584_2018_333

Bakopoulou, A., & About, I. (2016). Stem cells of dental origin: Current research trends and key milestones towards clinical application. *Stem Cells International*. doi: 10.1155/2016/4209891

Baniebrahimi, G., Khanmohammadi, R., & Mir, F. (2019). Teeth-derived stem cells: A source for cell therapy. *Journal of Cellular Physiology*, *234*(3), pp. 2426–2435. doi: 10.1002/jcp.27270

Bergamo, M. T., Zhang, Z., Oliveira, T. M., & Nör, J. E. (2021). Vegfr1 primes a unique cohort of dental pulp stem cells for vasculogenic differentiation. *European Cells and Materials*, *41*, pp. 332–344. doi: 10.22203/eCM.v041a21

Cicconetti, A., Sacchetti, B., Bartoli, A., Michienzi, S., Corsi, A., Funari, A.,… Riminucci, M. (2007). Human maxillary tuberosity and jaw periosteum as sources of osteoprogenitor cells for tissue engineering. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology*, *104*(5), 618.e1-618.e12. doi: 10.1016/j.tripleo.2007.02.022

Cordeiro, M. M., Dong, Z., Kaneko, T., Zhang, Z., Miyazawa, M., Shi, S., … Nör, J. E. (2008). Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. *Journal of Endodontics*, *34*(8), pp. 962–969. doi: 10.1016/j.joen.2008.04.009

Daltoé, F. P., Mendonça, P. P., Mantesso, A., & Deboni, M. C. Z. (2014). Can SHED or DPSCs be used to repair/regenerate non-dental tissues? A systematic review of *in vivo* studies. *Brazilian Oral Research*, *28*(1), pp. 1–7. doi: 10.1590/1807-3107bor-2014.vol28.0037

Gronthos, S., Mankani, M., Brahim, J., Robey, P. G., & Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(25), 13625–13630. doi: 10.1073/pnas.240309797

Huang, G. T. J., Gronthos, S., & Shi, S. (2009). Critical reviews in oral biology & medicine: Mesenchymal stem cells derived from dental tissues vs. those from other sources: Their biology and role in Regenerative Medicine. *Journal of Dental Research*, *88*(9), 792–806. doi: 10.1177/0022034509340867

Kaneko, T., Gu, B., Sone, P. P., Zaw, S. Y. M., Murano, H., Zaw, Z. C. T., & Okiji, T. (2018). Dental pulp tissue engineering using mesenchymal stem cells: a Review with a protocol. *Stem Cell Reviews and Reports*, *14*(5), 668–676. doi: 10.1007/s12015-018-9826-9

Kerkis, I., & Caplan, A. I. (2012). Stem cells in dental pulp of deciduous teeth. *Tissue Engineering - Part B: Reviews*, *18*(2), 129–138. doi: 10.1089/ten.teb.2011.0327

Marrelli, M., Paduano, F., & Tatullo, M. (2013). Cells isolated from human periapical cysts express mesenchymal stem cell-like properties. *International Journal of Biological Sciences*, *9*(10), 1070–1078. doi: 10.7150/ijbs.6662

Miura, M., Gronthos, S., Zhao, M., Lu, B., Fisher, L. W., Robey, P. G., & Shi, S. (2003). SHED: Stem cells from human exfoliated deciduous teeth. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(10), 5807–5812. doi: 10.1073/pnas.0937635100

Mendonça Costa, A., Bueno, D. F., Martins, M. T., Kerkis, I., Kerkis, A., Fanganiello, R. D., ... Passos-Bueno, M. R. (2008). Reconstruction of large cranial defects in nonimmunosuppressed experimental design with human dental pulp stem cells. *Journal of Craniofacial Surgery*, *19*(1), 204–210. doi: 10.1097/scs.0b013e31815c8a54

Morsczeck, C., Götz, W., Schierholz, J., Zeilhofer, F., Kühn, U., Möhl, C., … Hoffmann, K. H. (2005). Isolation of precursor cells (PCs) from human dental follicle of wisdom teeth. *Matrix Biology*, *24*(2), 155–165. doi: 10.1016/j.matbio.2004.12.004

Popuri, S. K. (2018). Concerns of a pediatric dentist in dental stem cells: An overview. *The Open Dentistry Journal*, *12*(1), 596–604. doi: 10.2174/1745017901814010596

Rosa, V., Zhang, Z., Grande, R. H. M., & Nör, J. E. (2013). Dental pulp tissue engineering in full-length human root canals. *Journal of Dental Research*, *92*(11), 970–975. doi: 10.1177/0022034513505772

Rosa, V., Dubey, N., Islam, I., Min, K. S., & Nör, J. E. (2016). Pluripotency of stem cells from human exfoliated deciduous teeth for tissue engineering. *Stem Cells International*, *2016*. doi: 10.1155/2016/5957806

Saez, D. M., Sasaki, R. T., Costa Neves, A., & Silva, M. C. P. (2016). Stem cells from human exfoliated deciduous teeth: A growing literature. *Cells Tissues Organs*, *202*(5–6), 269–280. doi: 10.1159/000447055

Sakai, V. T., Zhang, Z., Dong, Z., Neiva, K. G., Machado, M. A. A. M., Shi, S., … Nör, J. E. (2010). SHED differentiate into functional odontoblasts and endothelium. *Journal of Dental Research*, *89*(8), 791–796. doi: 10.1177/0022034510368647

Seo, B. M., Sonoyama, W., Yamaza, T., Coppe, C., Kikuiri, T., Akiyama, K., … Shi, S. (2008). SHED repair critical-size calvarial defects in mice. *Oral Diseases*, *14*(5), 428–434. doi: 10.1111/j.1601-0825.2007.01396.x

Seo, B. M., Miura, M., Gronthos, S., Bartold, P. M., Batouli, S., Brahim, J., … Shi, S. (2004). Investigation of multipotent postnatal stem cells from human periodontal ligament. *Lancet*, *364*(9429), 149–155. doi: 10.1016/S0140-6736(04)16627-0

Sharpe, P. T. (2016). Dental mesenchymal stem cells. *Development (Cambridge)*, *143*(13), 2273–2280. doi: 10.1242/dev.134189

Shi, S., Miura, M., Seo, B. M., Robey, P. G., Bartold, P. M., & Gronthos, S. (2005). The efficacy of mesenchymal stem cells to regenerate and repair dental structures. *Orthodontics and Craniofacial Research*, *8*(3), 191–199. doi: 10.1111/j.1601-6343.2005.00331.x

Sonoyama, W., Liu, Y., Fang, D., Yamaza, T., Seo, B. M., Zhang, C., … Wang, S. (2006). Mesenchymal stem cell-mediated functional tooth regeneration in Swine. *PLoS ONE*, *1*(1), 1–8. doi: 10.1371/journal.pone.0000079

Telles, P. D., Machado, M. A. de A. M., Sakai, V. T., & Nör, J. E. (2011). Pulp tissue from primary teeth: New source of stem cells. *Journal of Applied Oral Science*, *19*(3), 189–194. doi: 10.1590/S1678-77572011000300002

Wang, J., Wei, X., Ling, J., Huang, Y., Huo, Y., & Zhou, Y. (2010). The presence of a side population and its marker ABCG2 in human deciduous dental pulp cells. *Biochemical and Biophysical Research Communications*, *400*(3), 334–339. doi: 10.1016/j.bbrc.2010.08.058

Xiaoxia, L., Jiaozi, F., Shi, Y., Yuming, Z., & Lihong, G. (2017). Hua xi kou qiang yi xue za zhi = Huaxi kouqiang yixue zazhi. *West China Journal of Stomatology*, *35*(5), pp. 533–537. doi: 10.7518/hxkq.2017.05.017

Yamada, Y., Nakamura, S., Ito, K., Sugito, T., Yoshimi, R., Nagasaka, T., & Ueda, M. (2010). A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow-derived. *Materials Engineering*, *16*(6). doi: 10.1089/ten.TEA.2009.0732

Yu, T., Volponi, A. A., Babb, R., An, Z., & Sharpe, P. T. (2015). Stem cells in tooth development, growth, repair, and regeneration. *Current Topics in Developmental Biology*, *115*, pp. 187-212. doi: 10.1016/bs.ctdb.2015.07.010

Zhang, Q., Shi, S., Liu, Y., Uyanne, J., Shi, Y., Shi, S., & Le, A. D. (2009). Mesenchymal stem cells derived from human gingiva are capable of immunomodulatory functions and ameliorate inflammation-related tissue destruction in experimental colitis. *The Journal of Immunology*, *183*(12), 7787–7798. doi: 10.4049/jimmunol.0902318

Zheng, Y., Liu, Y., Zhang, C. M., Zhang, H. Y., Li, W. H., Shi, S., … Wang, S. L. (2009). Stem cells from deciduous tooth repair mandibular defect in swine. *Journal of Dental Research*, *88*(3), 249–254. doi: 10.1177/0022034509333804