Future perspective of new tooth creation

Mouetaz Kheirallah*

Maxillofacial Surgery Department, College of Dentistry, Alanados University for Medical Sciences, Al-Qadmous, Syria

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ABSTRACT

Currently, outcomes of dental stem cells studies indicate that the tooth is an available source for clinical application. Finding a universal cell that can morph into many several types of oral tissues is a key for new tooth creation. If dental stem cells are isolated to form new tooth buds, with creation of an imitative condition to the embryonic jaw, this will be a revolutionary new way to replace a missing tooth. Although investigators have created tooth-like structures in studies, so far, later dental stem cells investigations will be able to create a workable vascularized implant in the human body. This review study discusses current challenges in creating a biological environment that mimics the condition of teeth as they form in an embryo.

KEY WORDS: Dental stem cells, Tooth creation, Tooth development, Tooth-like structures

Introduction

The therapeutic philosophy is the crucial factor that determines tooth prognosis [1]. Missing tooth require solving a problem in the form of implants or dentures. Effective, workable implant with blood vessels in the jaw might be the best choice than synthetic implants. Consequently, there is a clinical desire to regenerate tooth root with periodontal ligament. Tooth development is a common interactional labour among ectodermal oral epithelial cells, and neural crest-derived mesenchymal cells [2]. The dentin, cementum and dental pulp originate from neural crest-derived mesenchyme whereas tooth enamel derives from oral epithelium [3]. Stem cells from adult tooth pulp can be isolated and converted into teeth buds; then the tiny tissue clusters may finally grow into a natural tooth. For that reason, exploitation of dental stem cells has preponderance above available tooth replacement therapies. It is renowned that embryonic stem cells are giving rise to any

cell type (totipotent) while adult stem cells could differentiate into a limited amount of cell patterns. Furthermore, embryonic stem cells might have the capacity to distinguished for any cell type that arises from ectoderm, endoderm and mesoderm. Finding universal cell that can morph into many several types of oral tissue is a key for growing a new tooth. The current understanding of tooth development and eruption is undoubtedly a series of actions, not possible to separate. The presence of dental follicle is required for tooth eruption and becomes apparent that it regulate the osteogenesis and osteoclastogenesis needed for tooth eruption [4,5]. If the dental stem cells are isolated to form new tooth buds, with the creation of an imitative condition to the embryonic jaw, where tooth begin to take shape, this will be a revolutionary new way to replace the missing tooth. Although investigators have lucky to create tooth like structures in brute studies, so far, later dental stem cells investigations will be able to create a workable vascularized implant in a human body. This review article will discuss the current challenges to create a biological environment that mimics the condition of teeth as they form in an embryo.

Human tooth development

Usually, tooth growth could be divided into three stages, pre-eruptive stage, eruptive stage and post-eruptive stage.

*Corresponding author: **Mouetaz Kheirallah**

Maxillofacial Surgery Department, College of Dentistry, Alanados University for Medical Sciences, Al-Qadmous, Syrian Arab Republic. Temporarily a visitor at College of Dental Medicine, Majma'ah University, KSA
Tel.: +963-43-657600, Fax: +963-43-656174
E-mail: moutazkheirallah@gmail.com, mk@au.edu.sy, m.kheirallah@mu.edu.sa

During the pre-eruptive stage, the enamel grows from ectoderm of the oral cavity, whereas all other tissues come from the connected mesenchyme [6]. Tooth buds originate from growing the dental laminae into the mesenchyme. The dental papilla (mesenchyme) folded back on itself inside the deep surface of each ectodermal bud to form the dentin and dental pulp [7]. The ectoderm above the papilla forms the enamel organ which contains external cellular stratum and internal enamel epithelium. The zone among these two strata constitutes the bulk of the cap (enamel reticulum) [8]. The periodontal ligament and the cementum are formed by the surrounding mesenchyme, after the figuration of the dental papilla and enamel organ. The mesenchymal cells of dental papilla closed to the internal enamel epithelium, produce pre-dentin by differentiation into odontoblasts. When the dentin deposit, the odontoblasts regress toward the centre of the dental papilla and odontoblastic processes, remain in the dentin (dental fibers) [8]. Cells of the internal enamel epithelium close to the dentin shape ameloblasts to produce the enamel above the dentin stratum. The inner and external enamel epithelia connect to grow into the mesenchyme to start the root formation. Dentin growth leads to smaller pulp cavity which begins to be a narrow canal for the nerves and vessels. Cementoblasts from the internal cells of the dental sac produce the cementum. The outer cells of the dental sac begin to be active after the bone and the periodontal ligament formation [6]. Accordingly, the tooth gathered.

Provenance of dental stem cells

Postnatal autologous tooth germ cells (third molars) or autologous dental stem cells are of limit obtainable, for that reason, it's hard to be applied clinically. However, adult stem cells show multipotency and self-renewal capacity and have separated from various parts of the tooth. These sources are dental follicle, apical root papilla, periodontal ligament and exfoliated primary teeth. Otherwise, bone marrow stromal cells can differentiate into enamel and dentin structures [9]. Moreover, to produce tooth tissues, researchers have used combined suspension of single cell embryonic tooth germ with scaffold through regulation of certain signalling pathways, they found that individual cells can reorganise themselves and differentiate into odontoblasts and ameloblasts. However, the limit of embryonic germ confined these methods for clinical application [10].

From dental follicle (DFSCs)

During tooth development, the dental papilla and the

enamel organ ringed by ectomesenchyme tissue which is called dental follicle [11]. It is believed that it may be the progenitor of other cells of the periodontium, including osteoblasts and cementoblasts [12]. DFSCs differentiate into periodontal ligament fibroblasts which excrete the collagen to react with the fibres on the surface of closed cementum and bone. When DFSCs were transplanted into severe combined immunodeficiency mice, they formed cementoblast-like cells [13]. However, other reports indicated little cementum or bone formation when human adult stem cells used for periodontal regeneration [14]. Moreover, there have been several studies subscribe the angiogenic, and neurotrophic effects of DFSCs. All these studies confirmed the neurogenic potential of DFSCs because they originate from the embryonic neural crest [15]. Kanao *et al.* [16] have investigated the capacity of human DFSCs to differentiate into neural cells, they concluded that DFSCs were undergoing neuronal differentiation via neurospheres, while expression of nestin and β -III-tubulin was downregulated. Also, Heng *et al.* [17] have inspected whether culture can enhance neural differentiation of DFSCs on decellularised matrix substrata derived from neurogenesis of human embryonic stem cells. This study concluded that decellularised matrix substrata derived from neurogenesis of embryonic stem cells could enhance the neurogenic potential of DFSCs.

From apical papilla (SCAP) or dental pulp (DPSCs)

Extracted third molars in dental practice are a reliable source to obtain active stem cells with embryonic-like properties. During root growth, before root eruption, the root apical papilla is presented, and the dental pulp is a useful source of dental pulp stem cells [18]. DPSCs showed elevated frequency of colony formation and propagation. Furthermore, embedded DPSCs were differentiated into active neurons [19], and SCAPs have the capability to differentiate into odontoblasts and other mesenchymal cells such as adipocytes, chondrocytes and osteoblasts [20-22]. Transplantation of these cells into an impaired immune system of mice demonstrated their efficiency to create dentin and pulp structures [23]. Sonoyama *et al.* [24] have transplanted both human SCAP and PDLSCs to generate a root/periodontal complex capable of supporting a porcelain crown, resulting in normal tooth function. Although, demonstrated results, more investigations are needed on the properties of these cells. The author with coworkers, in another study, have discovered SCAP which showed a different population of stem cells than DPSCs. They applied

SCAP to engineer bio-roots using minipigs, and they concluded that these cells are a promising cell source to regenerate bio-roots for future clinical applications [25]. The evidence is collecting to support the assumption that SCAP appears the origin of essential odontoblasts for root dentin formation, whereas DPSCs are likely the source of replacement odontoblasts [18].

From human periodontal ligament (PDLSCs)

Impacted third molars are a reliable source to obtain PDLSCs that are multipotent postnatal stem cells [26], possess characteristics of mesenchymal stem cells, but there is incomparability among different studies for their culture and consistency. It notified that periodontal tissues originate from migrated neural crest cells during tooth development [27], whatever, PDLSCs obtained from ripe periodontal ligaments instead of the neural crest, showed stem cell properties such as the mesenchymal stem cells [28]. Several studies have reported a population of stem cells from human periodontal ligaments capable of differentiating into cementoblasts and connective tissue rich in collagen I in vitro and in vivo [26,29]. Furthermore, periodontal ligaments are under forces of mastication; therefore, they may have an internal origin to enable periodontal ligament cells number, for that reason, may they be preferable than dental stem cells isolated during the formulation of periodontal ligament structures [30]. Several studies have reported that stem cells transplantation has a propensity to form tumours. Amariglio *et al.* [31] reported that transplantation of human foetal neural stem cells might lead to multifocal brain tumour if the transplanted cells were from two donors at least. Although there is no evidence that transplantation of mesenchymal stem cells may lead to tumours, there is riskiness, wherefore this aspect should be inspected before PDLSCs transplantation. Furthermore, the study provided by Xie and Tang [32] concluded that undifferentiated PDLSCs triggered several immune responses with high lymphocytic infiltration and elevated IFN- γ secretion, they suggested that in vitro differentiation may alter stem cell immune properties. Regardless of the fact that PDLSCs suppressed the immune response before and after osteogenic induction before transplantation the immune properties of PDLSCs should be investigated [33].

From human exfoliated deciduous teeth (SHED)

Human exfoliated deciduous teeth could be a useful source to isolate several types of stem cells such as osteoblast, odontoblast, adipocytes, chondrocytes and neural

cells [34]. The primary task of these cells is the formulation of hard tissues and could be applied to increase bone regeneration [35,36]. Stem cells from human exfoliated deciduous teeth can differentiate into osteoblasts but cannot regenerate entire dentinal and pulpal structures in vivo [37]. Furthermore, it secretes neurotrophic factor to regenerate the motor neurons after dental trauma, and so on, SHED can be applied for neurodegenerative diseases treatment. The principal advantage of these cells is that the immunosuppressive therapy is not required when autologous transplantation is used [38]. Consequently, exfoliated teeth may be an excellent unique resource for stem cells therapy including autologous stem cells transplantation and tissue engineering [34].

Odontogenic reacting epithelial cells

Many biological factors have been used to enable interactions between epithelial and mesenchymal stem cells [39], for example fibroblast growth factor and bone morphogenetic protein combined with these cells may induce them [40]. The oral epithelium of murine embryos showed creation of tooth formation in non-dental mesenchyme [41]. Furthermore, epithelial cells from mouse embryos have been showed to result in the tooth like frameworks if joined with embryonic dental mesenchyme, however, not whole functional teeth [42-44]. Yajima-Himuro *et al.* [45] have transplanted bioengineered tooth germ into the alveolar bone with an epithelial component, and concluded that epithelium from the bioengineered tooth fused with the oral epithelium, and the junctional epithelium was apparently formed around the bioengineered tooth 50 days after transplantation.

From nondental origin

Studies reported that odontogenic epithelial signals could stimulate non-dental mesenchymal cells. The combination of inductive embryonic oral epithelium with bone marrow-derived cells or neural stem cells can form tooth structures in vitro [46]. Ikeda *et al.* [47] have demonstrated that transplantation of embryonic tooth primordia into alveolar bone in the lost tooth alveolus for sufficient time could grow to form whole tooth. Furthermore, when tooth germs are separated and admitted reconnecting in a scaffold, they re-aggregate to reform the tooth germs [48]. The advent of pluripotent stem cells should speed up the application of regenerative tissues or organ such as the tooth in the clinic [49]. Researchers have used the human urine to obtain pluripotent stem cells and to create tooth structures in mice with a success rate of up to 30% [50].

They have concluded that these cells are capable of tooth creation using odontogenic signals from embryonic dental mesenchyme and pre-differentiating them into epithelial sheets [50]. Furthermore, the created teeth had comparable properties to regular human teeth excluding the hardness; they also resulted that these cells do not form tumours when transplanted into the body conversely other stem cells [50]. Anyway, many defiances still need to be overcome, and more knowledge is required before to become a routine clinical approach to the treatment of diseases [51].

Conclusion

Currently, outcomes of dental stem cells studies indicate that tooth is a useable source for clinical application of adult mesenchymal stem cells. Although investigators have successes to generate tooth like structures, they cannot replace actual teeth, and there remain several determinations, such as limitation to animal models. However, their clinical applications still to investigate. Functional human tooth creation may need many months or even many years, while production of mouse tooth may take a few weeks only. Investigations on blood and nerve supply in human teeth are required to move forward the dental regenerative therapy. Furthermore, there are other barriers in identification, isolation, cleaning and growing stem cells consistently in labs. Many problems and risks still need to be resolved. Up to date, it is premature to consider stem cells as an efficient procedure for tooth replacement.

Conflict of Interest

The authors declare that they have no competing interests.

ORCID

Mouetaz Kheirallah 0000-0002-3094-3195

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