International Journal of Dentistry and Oral Science (IJDOS)
ISSN: 2377-8075

Cell Reprogramming Technology Advances and Exploration of Human Teeth Renewal Capacity

Research Article

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Abstract

Having a third dentition is a major goal of dental regenerative medicine. However, the development of new teeth does indeed require dental epithelium, which can permit genesis of organized temporal rhythms necessary for spatial form events. Nonetheless, the current advances in cell fate engineering both in vitro and in vivo are now quite numerous, enriching the research and promising us to begin to explore how dental regenerative medicine can be of valuable benefit. Our threefold aim is to first update research of the literature, then explore new theories and eventually experiment with the developmental origin of relationships between oral mucosa and dental tissues. In part two of our research, we will start by analyzing the feasibility of in situ recruitment and conversion of oral mucosa to odontogenic tissues and then proceed to reviewing the multifunctional microsystems and/or nanosystems as innovative dental devices that can permit local in vivo direct cell reprogramming of oral mucosa to acquire odontogenic properties, which will allow us to assess the orchestrating reactivation of odontogenesis events for an episodic whole tooth renewal. A final aim of this review is to explore recent advances in ideas and progress towards the approach of possible and feasible use of in situ reactivation of human odontogenesis processes like that of early development, which can be achieved safely, and efficiently and be applied to clinical practice. This approach is supported by the inductive capacity of the oral mucosa for building up functional dental cells and tissue like that of early dental development. Adopting a scrupulous evaluation of the challenges and limits of this approach, this work aspires to underline the imperative that the in vivo genesis of germs with all odontogenesis steps could dictate a third dentition wherever possible.

Keywords: Whole Tooth Regeneration; Oral Mucosa Reprogramming; Multifunctional Micro/Nanodevices.

Introduction

Within the framework of human dentition development, odontogenesis is a highly complex temporal and spatial event. The structural and functional changes during human dentition from the undifferentiated state to a highly organized and specialized state is a long and complex process. Biological studies of tooth replacement have demonstrated that humans have lost the capacity for life-long tooth renewal and have only two generations of teeth. Hence, third dentition remains the major goal of dental regenerative medicine. In order toprovide a better insight into this area, the development of new teeth requires dental epithelium and odontogenic tissues that have competence for triggering tooth germ formation, which can be initiated at each related site. Tooth germ is a specific dental organ that produces a whole tooth. Previous studies reveal that tooth germ bioengineering was approached in vitro, followed by *in vivo* transplantation, and was more deeply studied with advanced results [1][2]. The oral cavity is extensively explored for progenitor cells reserve with the potential to give rise to various differentiated tissue. In addition, the dental epithelium is derived from oral epithelium during the early development and the odontogenic potential of oral mucosa and was reported [3, 4]. On the other hand, human dental lamina rests might offer a potential source of odontogenic progenitor cells for tooth renewal [5], and the *in vitro* induction of odontogenesis process similar to those of early human tooth development was demonstrated [6]. However, adult progenitor cells can change epigenetically their identity with rejuvenated capacity by in vivo direct reprogramming [7, 8]. More importantly, direct reprogramming technology

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Received: December 23, 2020
Accepted: January 29, 2021
Published: February 13, 2021

Citation: Hassan LBOUTOUNNE. Cell Reprogramming Technology Advances and Exploration of Human Teeth Renewal Capacity. *Int J Dentistry Oral Sci.* 2021;8(2):1583-1588.
doi: http://dx.doi.org/10.19070/2377-8075-21000314

might lead to rejuvenation of a cell to their embryonic stage, by controlling and resetting the aging clock at different time levels [9, 10]. The advances in cell fat engineering are now quite numerous, enriching and promising us to begin to explore how dental regenerative medicine can benefit from.

The initial aim of this review is to explore the recent advances in ideas towards the in-situ induction of human tooth germ formation for third dentition. Therefore, the challenge is to highlight the possibility and to assess the feasibility of restarting odontogenesis processeslike that of early development, safety, and convenience for tooth replacement. We will then assess the possibility of in situ recruitment of oral mucosa and define/determine its inductive capacity for building up odontogenic tissues, by adopting a direct epigenetically reprogramming strategy. Eventually our research aspires to prescribe multifunctional systems as innovative dental devices, which may allow access to odontogenic temporal structural systems and functional information memory and then, orchestrating reactivation of odontogenesis events. Finally, we will set the process, trace clearsteps, and define accurate pathways for achievement of possible in vivo tooth germ genesis safely and efficiently.

Evolution Of Dental Clinical Approaches

The evolution of clinical approaches to repair whole tooth loss always continue to bring new and more effective results[11].Despite the difficulties, the progress in ideas and advances in existing technologies converges and supports the possibility of human third dentition. Though tooth regrowing both in vitro and in vivohave been extensively approached, the feasibility of an episodic renewal of human teeth has only recentlybecome a reality in dental practice [12]. More interestingly, in situ whole tooth renewal was demonstrated [2], and that, by in vivo allogenic transplantation of minipigs tooth germs at an early stage in jawbone of adult pigs. A brief overview of these clinical approaches is illustrated in Table 1.

Potential Source Of Odontogenic Tissues

Our review of the literature has clearly shown that the histophysiology and biological dynamics of oral mucosa has been enough explored. It is characterized by a high turnover and permanent self-instructed adaptation to external stimuli [13, 14]. Likewise, it is considered as a model system to explore the characteristics of any cell quiescent state [15]. In this respect, its proximity to teeth, oral mucosa may offer unique opportunities to enrich cells and tissues suitable for tooth renewal thanks to its odontogenic capacity [16]. On the other hand, oral mucosa can strongly be a stimulus to obtain a dental epithelium, and cab respond dynamically to a variety of stimuli of different natures. The histological ultrastructure of oral mucosa is shown in Figure 1.

Temporal Structural Systems Of Odontogenesis

One of the major challenges our research is likely to face is to diagnose an easy access to odontogenesis temporal structural systems and save its coding information memory. This systemwould allow us to adapt rhythms and draftforms of odontogenesis, like those of the gestation phase as show as in Figure 2. The natural renewal of tissues integrates positional identity cues with preexisting body structures, as far as the epigenetic modulation

Table 1. Evolution of dental clinical approaches for partial or whole tooth repair.

Engineering	Substrat	Technique	Approach	Product	Practice
Biomatertal	Biomaterials	Design	Manufacturing	Prothesis/ Biomaterial implant	In1plai1tation
				Preparation	Anolication
Craning	Organ	Presrevation and consenation	Donation	Tooth/ Natural imolant	Grafting
Tissue	Stem/Progenitor cells	In virro cell manipulation	Cell	Tooth/ BioloQ-ic-al imolant	Transplantatio11
				Suspension	Injection
				Cell sheets	Grafting
			Biomaterial scaffold	Germ	Transplantation
			Biolo1tical scaffold	Tissue	GraftinR
Cell Fate	Progenitor/ Diffe rentiated oells		Indirect reprogramming	Tooth/ Biologic-al ilnplant	Transplantation
				Germ	
			Direct reprogramming	Tissue	Grafting
				Suspension	Injection
		Ex·vivo cell and tissue manipulation	Organ and direct reproArammin	Germ	Transplantatio11
			In situ Direct reprogrammmg	Tissue/Young state	Induction
		In vivo cell and tissue 1nanipulatio n		Germ	

Figure 1. Histological ultrastructure of human oral mucosa which is depending on its location.

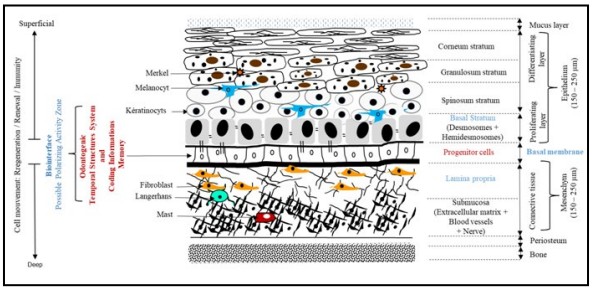


Figure 2. Main stages of the targeted gestation phase for possible induction of odontogenesis events.

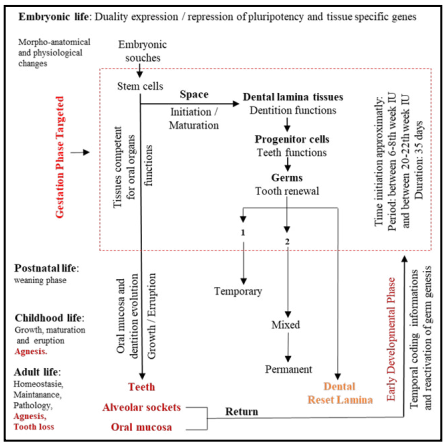
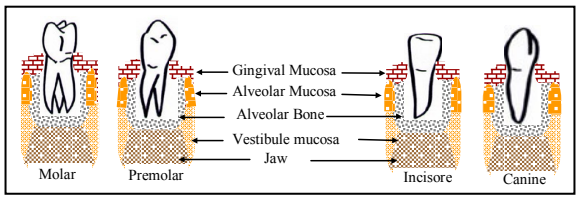


Figure 3. Teeth identities and morphogenetic positions.



remains sufficient to govern genetic stability and tissue integrity [17]. However, a dental organ identity is established regionally as four morphogenetic positional information as shown in Figure 3. Abrief overview of the human dentitionautopoiesis system is illustrated in Figure 4. On the other hand, lamina propria of human oral mucosa harbors a robust progenitor cell population, with a distinct primitive origin. Despite the negative effects of ageing, its reprogramming was demonstrated [18]. Accordingly, lamina propria, basal membrane and basal stratum as an excitable interface competent for genesis,could order and organize odontogenesis events by in situ direct reprogramming. A brief overview of the structure and composition of this interface, which is necessary to induce the tooth primordia initiation,is illustrated in Figure 5. However, cytoskeletal and DNA nodes, which are found in chromatin, are a potential pathway to access the genetic circuit system [19, 20], and advise their possible epigenetic modeling and remodeling by in situ direct cell reprogramming.

Direct Cellular Reprogramming Strategy

Human teeth have few or no niche resident stem cells to support renewal. However, human cells retain the reprogramming potential, and new cell identities could be generated by epigenetic reconfiguration of gene circuits system [21]. Recently, direct cellular reprogramming strategy for regenerative medicine applications has beenrepeatedly approached, and more advanced studies on the chemical cell reprogramming with small molecules have been made [22, 23]. Therefore, it is conceivable that an oral mucosa cell population can be reprogrammed and re-directed to determine odontogenic fate with tooth-inducing capability like that in a human embryonic stage. A case in point, an in vitro model of human segmentation clock, which controlled somitogenesis, was suggested [24, 25]. In order to achieve successfullyan in situ direct reprogramming, it is essential to identify types and numbers of cells to recruit as well as a tissue suitable for induction of odontogenesis events without anomalies as shown as in Figure 5.

Reprogramming Potential Of Oral Mucosa

The progenitor cells population in epithelium and lamina propriaof oral mucosa have exceptionally induced broad differentiation capacity into othercells including dental cells [25, 32], and their odontogenic potential was demonstrated *in vitro* [15]. Nevertheless, it is possible that the instructing of an epithelial cell population, which has neural crest development origin, will be directed to acquire odontogenic properties. Then, their interaction with cell population of lamina propria, which have mesenchymal development origins at basal membrane may be considered as a physical support of odontogenesis temporal structural system and its coding information related to the gestation phase of early development. These multicellular systems can be considered as a bio-interface for possible polarizing activity zone, which is neces-

sary for odontogenesis process induction as shown as in Figure 5. Alveolar sockets as a natural site fortooth germ reconstruction. During tooth development, the jawbone interacts with tooth germ and provides the development of microenvironment. However, after tooth extraction, the empty alveolar sockets undergoes a large remodeling of the architecture of tissues and cell populations [33, 34]. Interestingly, empty alveolar socket linked to the agenesis or extraction and the surrounding oral mucosa offers an opportunity to create possible zones for in vivocell and tissues recruitment and their in situ direct reprogramming as illustrated in Figure 6.

Tooth Germ Genesis: Processes, Paths, And Steps

At the early development stage, the beginning of epithelial thickening to grow followed by the process of tissue invagination and stratification is key for tooth germ formation [35, 36]. This process depends on force and tension repartition in apical, basal, lateral sides of the cells. As craniofacial development is part of various general integrative process in the head, in the absence of the nervous system, the local neurogenic placodes as a local signal center orchestrates early development events [37]. It is worth noting that during organogenesis and morphogenesis, the formation and building of signaling centers event were derived by mechano-chemical patterning [38]. In addition, the activation of tissue system interaction depends on communication signals within the microenvironment, dictating whether the cells undergo epithelial-mesenchymal transition states and coordinated reprogramming processes or not [39]. Importantly, the coordination of cellular system dynamics contributes to epithelium tissue deformations, which are determined by density, and supported by the contribution of single or collective cell migration without proliferation [40-43]. That is what led us to conclude thatthe anisotropy of cell adhesive microenvironment and a coordinated change of shape and/or position of a population of cells govern cell internal organization and orientation of polarity. On the other hand, the apical constriction resulted in response to external stimulation, is sufficient to drive tissue invagination [44, 45]. Interestingly, the modulation of immune cell systems can be achieved by cell reprograming [46]. Note the diagramming of invagination processes with possible interface of coding information memory of odontogenesis temporal structures as illustratedin Figure 7.

Multifunctional Systems As Dental Innovative Devices

The methods to manipulate the spatial patterning and temporal dynamics of biological activities were developed as multifunctional devices, and classified in chemically, optically, and magnetically induced tools [47]. Fascinating progress was made in the engineering of biological signal and communication systems based on delivered in vivo stimulation at single or collective cells to modulate their processes and/or functionalities [48, 49]. More importantly, the chemical and physical techniques allow direct manipulation of mechanical and chemical signals that permit control of direct cell reprogramming and therefore determine cell fate [50, 51]. Recent advances in patchable micro/nanosystems or implantable wirelessly controlled systems as microchipwithout external connections which interacting with human tegument was well documented [52, 53]. On the other hand, the dynamic cell stimulation technology for controlling gene networks dynamics and cellular information processing was developed [54]. These multifunctional devices may allow an instructed, induced, controlled, directed, and guided stimulation at a cellular resolution and then switched cell fate and activate biological functions and/or processes [55]. In addition, they can offeropportunities for rationally modifying the resulting multicellular structure as spatial and temporal genesis of biological rhythms and forms, like those

Figure 4. Human dentition Autopoiesis system.

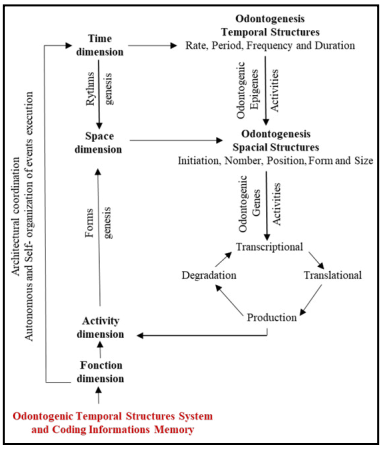


Figure 5. Excitable interface system as a potential coding information memory of odontogenesis.

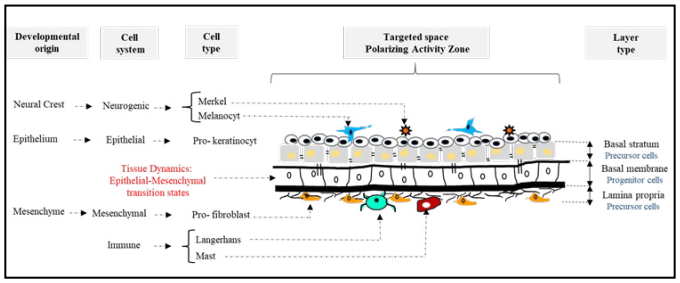


Figure 6. Possible zones for cell and tissue recruitment for in situ induction of tooth germ genesis.

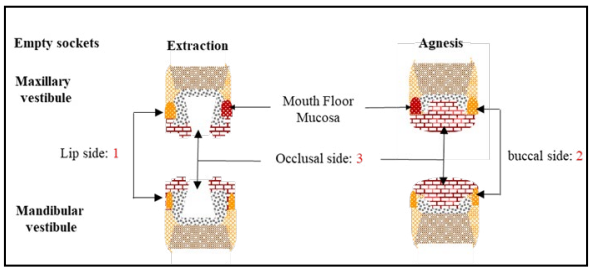


Figure 7. Process, pathways, steps for in vivo induction of germ formation events.

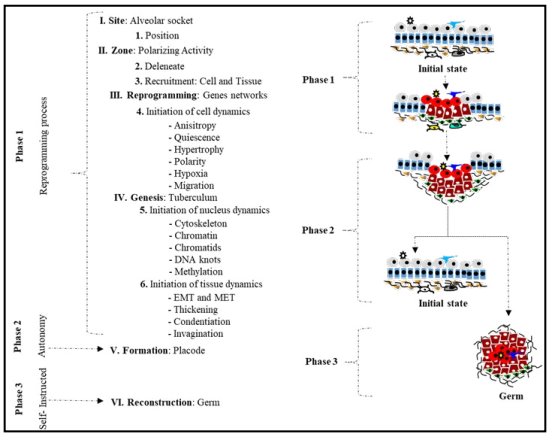
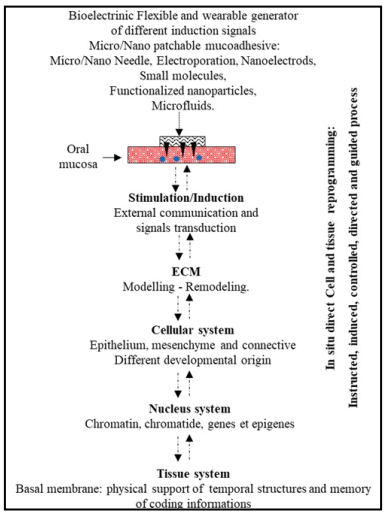


Figure 8. Multifunctional micro/nanodevices for cell and tissue direct reprogramming.



of natural systems [56]. Finally, it is interesting to explore and to adapt these multifunctional systems as innovative devices for regenerative dental applications, as shown as in Figure 8.

Conclusion

Despite the complicated appearance on human teeth renewal and possible human third dentition, this review is expected to highlight the possibility and feasibility of in situ direct oral mucosa reprogramming for in vivo human tooth genesis. This approach is supported by of inductive capacity of the oral mucosa for building up functional dental cell and tissue, similar to that of early dental development. In order to confirm its achievement, it is of great interest to develop clinical protocols and adaptation of multifunctional devices safely and more favorably for clinical practice of human tooth replacement.

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