TOOTH REGENERATION- A REVIEW

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ABSTRACT

Tooth loss is quite common worldwide. For treating a lost tooth, treatments such as dental implants (most common worldwide), fillings (made up of inert dental material), dentures, etc. These techniques can restore all the functions of a normal tooth. But using dental tissues and other dental related materials are still a mystery to the dental world. Pubmed research revealed 117 relevant articles. Out of which a total of '33' systematic reviews and their original citations were included in this review. Tooth regeneration is a very complicated process and needs more depth study on this topic. From many of the researches that were reviewed in this article it was seen that there were many new methods developed but none were approved for applying in real life. Tooth regeneration is a vast topic and requires a lot of knowledge to be understood. This study can be used as reference for future research.

KEYWORD: Biomaterials, stem cells, tooth regeneration.

INTRODUCTION

Tooth comprises mineralised tissue (includes enamel, cementum, and dentin) and soft tissues [includes dental pulp and periodontal ligaments (Balic, 2018)]. Tooth loss can occur due to various factors such as different oral diseases, injury, accidents. It has also been noted that the presence of teeth can also prevent dementia which occurs in elderly people as mastication stimulates the brain (Dadu, 2009). Loss of tooth affects chewing of food, biting, smiling, speech, etc. Tooth loss is also very common worldwide. For treating a lost tooth, treatments such as dental implants, fillings, dentures are provided. These techniques can restore all the functions of a normal tooth. But using dental tissues and other dental related materials for regenerating a lost tooth is still a mystery to the dental world (Ahad and Gheena, 2016; Angelova Volponi *et al*., 2018)

A previous research article written by Balic, has given a very clear and precise explanation on the topic tooth development, and then the various changes seen in teeth with relation to age, such as life span of a tooth, and its related factors. The author has also explained about the different stem cells such as epithelial and mesenchymal stem cells are present. A method called the 'Nakao method' (i.e., generating a tooth de nova from a postnatal animal) was very impressive but unfortunately cannot be done in humans as there are many complications which follow while executing this method (Balic, 2018).

Volponi *et al.* have explained about the various stem cells present such as its function, about its various uses that can be used in the clinic or for therapeutic purposes. Root regeneration has also been performed but has not been included in clinical practices. Development of the human root includes formation of

dentin, generating the cementum, epithelium instruction and eruption of a tooth. But this process is quite hard as there must be more advanced instruments for full generation of a tooth according to the article written by Dadu (Dadu, 2009; Angelova Volponi *et al.*, 2018). With this background, the main aim of this review article is to explore and collect various detailed information on the tooth regeneration process, as it is a complicated process to decode.

METHODOLOGY

This research is seen as a scoping literature review. In seeking to identify the relevant literature from the past twenty years, we used common databases such as Pubmed, Google Scholars. Searches of the reference list from relevant review articles were also employed to identify further relevant studies. The obtained articles were later thoroughly read through and understood. A total of '33' articles have been selected and reviewed in this article. The level of evidence of the reviewed articles were categorized as per the criteria of Centre for Evidence- Based Medicine, Oxford, UK (Jeremy *et al.*, 2011).

Stem cells

Dental stem cells are a small group of mesenchymal cells present in dental tissues such as dental pulp, dental follicle, periodontium. While isolating or identifying a stem cell, it showed promising functions and uses for tooth repair. These cells can self renew, multipotency, and also have tissue specific determination potential. But the exact and precise mechanism of these stem cells are not known up to date. But if this mechanism is, then tooth regeneration is possible (Shuai e*t al.*, 2018; Palati *et al.*, 2020). Transitional studies such as clinical trials and stem cell banking must be performed to increase various strategies for tooth and periodontal repair and other related studies (Hu *et al.*, 2018; Shree *et al.*, 2019). There are various dental stem cells present such as dental pulp stem cells, stem isolated from human pulp of exfoliated deciduous teeth, periodontal ligament stem cells, stem cells from apical papilla and also dental follicle cells. All these stem cells can help regenerate a tooth. The exact role of these stem cells is still not known ((Yu *et al.*, 2015; Zhai *et al.*, 2019). Regeneration of lost or damaged tissue in the periodontium also uses stem cells, but is still undergoing a lot of studies and investigations (Guru and Gheena, 2016; Xu *et al.*, 2019).

Techniques

Odontogenesis is a natural but complicated process. The side of epigenetic regulation includes DNA methylation, histone modification and also non- coding RNAs, in odontogenesis gives a theoretical base in tooth regeneration ((Sarbeen and Gheena, 2016; Lin *et al., 2*018). In situ revitalising, *in vivo* repair of damaged teeth, and *in vitro* techniques has also been used in generation of lost teeth. But many challenges have been found while regenerating a tooth using these various techniques (Li *et al.*, 2019). Various advances in osteogenic differentiation have been developed especially for tooth repair and regeneration (Abdel Meguid *et al.*, 2018; Abitha and Santhanam, 2019). The discovery of methods to repair and regenerate a tooth can become a major revolution in stomatology (Yildirim *et al.*, 2011; Uma *et al.*, 2020).

Biomaterials

Biomaterials are synthetic polymers that act as transport- carriers for drugs or even scaffolds (provide chemical stability and physical properties, cell compatibility) in tissue or in our case tooth regeneration. Selection of appropriate biomaterial, scaffold fabrication, stem cell transplant and homing, this knowledge is necessary for tooth regeneration (Yuan e*t al.*, 2011) (Krishnan *et al.*, 2018). The various biomaterials being developed must have great potential in tissue engineering and regenerative applications of a tooth (Du and Moradian-Oldak, 2006) (Palati *et al.*, 2019).

Success models

Methods such as the 'organ germ method' (regeneration of a tooth in vitro) and 'Nakao method' (generating a tooth de nova from a postnatal animal) have been developed but a lot of complications followed. Hence has not been implemented in human practice. The organ germ method can regenerate a tooth in vitro and when transplanted into the oral cavity, it can erupt successfully. This tooth can perform physiological functions of a normal tooth such as mastication. The Nakao method helps generate a tooth de nova from a postnatal animal. This method was also very impressive but unfortunately both 'Organ germ method' and 'Nakao method' cannot be performed in humans as there are many complications which follow while executing this method (Oshima and Tsuji, 2015) (Balic, 2018).

Future Scope

Deeper study on stem cells biology, functions and mechanism) can help pave the pathway for treatment based on repair and regeneration of a lost tooth by optimising patient tailored treatments (Morsczeck and Reichert, 2018) (Hannah *et al.*, 2018). A three dimensional method called the 'organ germ method' had been developed. This method can regenerate a tooth in vitro and can erupt successfully when transplanted into the oral cavity. This bioengineered tooth can perform physiological functions such as mastication (Oshima and Tsuji, 2015). Generation of teeth using functional tooth modules is also being experimented. The construction of a functional tooth module is still yet to be clearly defined (Tian, 2017) (Harrita and Santhanam, 2019). Solving the real mystery of generating a tooth while understanding its various mechanisms is still unknown and hopes to be discovered in the near future (Inanç and Murat Elçin, 2011) (Gunasekaran and Abilasha, 2016).

Challenges

Many challenges such as decoding the tooth regeneration process as it is a very complicated process, finding the suitable materials for regeneration, even after a new method is introduced, it must be suitable for performing it on humans. People don't understand the basic knowledge of mesenchymal stem cells and other stem cells too (Inanç and Murat Elçin, 2011) (Du and Moradian-Oldak, 2006).

RESULTS AND DISCUSSION

From the articles collected and reviewed on tooth regeneration, a method called 'Orgam Gem method' [a three dimensional cell manipulation method] helps in generating a tooth in vitro. It erupts successfully when placed in the oral cavity. This bio- engineered tooth is generated ectopically which compares a mature tooth, periodontal ligament (PDL and alveolar bone. This tooth performs all the physiological functions of a tooth (Oshima and Tsuji, 2015) (Padavala and Sukumaran, 2018).

The knowledge on epigenetic regulation in tooth regeneration during the odontogenesis process gives a stable theoretical base which helps improve regeneration of teeth (Lin *et al.*, 2018) (Sheriff and Santhanam, 2018). In many of the advanced techniques and researches, the basic knowledge of mesenchymal stem cells has been poorly understood. This can be very dangerous during therapeutic use or clinical use. Maximum knowledge on stem cells [functions, uses, mechanisms] must be understood by all who wish to experiment in tooth regeneration (Yu *et al.*, 2015) (Manohar and Abilasha, 2019). A wide range study on this topic must be done for maximum results. And in case of future scope, many new different techniques must be developed.

CONCLUSION

Tooth regeneration is a vast topic and requires a lot of knowledge to be understood. This study can be used as reference for future research.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Hemaanhini Tamilmani: literature search, data collection, analysis, manuscript writing. Dr. Gifrina Jayaraj: Data verification, manuscript drafting. Dr. R. Gayathri: Data verification, manuscript drafting.

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Table 1: Description Of Included Studies

Sl.No	Author	Year	Type Of Study	Sample Size	Key Findings	Level Of Evidence
1.	Balic (Balic, 2018)	2018	Systematic review	nil	Tooth development process	Level 2
2.	Hu *et al* (Hu *et al.*, 2018)	2018	Systematic review	nil	Strategies present in tissue engineering	Level 1
3.	Volponi *et al* (Angelova Volponi *et al.*, 2018)	2018	Systematic review	nil	Analyse various approaches in tooth regeneration	Level 1
4.	Morsczeck and Reichert (Morsczeck and Reichert, 2018)	2018	Systematic review	nil	Dental stem cell properties explained	Level 5
5.	Lin *et al* (Lin *et al.*, 2018)	2018	Systematic review	nil	Epigenetic regulation provides base for tooth regeneration	Level 1
6.	Oshima and Tsuji (Oshima and Tsuji, 2015)	2015	Systematic review	nil	Organ germ method Future treatments	Level 2
7.	Shuai *et al* (Shuai *et al*., 2018)	2018	Systematic review	nil	Dental stem cells-improve formation of dental structures and healing	Level 3
8.	Zhai *et al* (Zhai *et al*., 2019)	2019	Systematic review	nil	Stem cell's outline and various strategies	Level 2
9.	Yu *et al* (Yu *et al*., 2015)	2015	Systematic review	nil	Stem cell's clinical uses	Level 2
10.	Xu *et al* (Xu *et al*., 2019)	2019	Systematic review	nil	Endogenous regenerative techniques	Level 2
11.	Meguid *et al* (Abdel Meguid *et al*., 2018)	2018	Systematic review	nil	Summary of recent researches and progress	Level 2

12.	Yildirim *et al* (Yildirim *et al*., 2011)	2011	Systematic review	nil	Stomatology- evolution	Level 2
13.	Dadu (Dadu, 2009)	2009	Systematic review	nil	Summary of evolution	Level 3
14.	Li *et al* (Li *et al*., 2019)	2019	Systematic review	nil	In- vitro approach In- vivo approach	Level 2
15.	Tian (Tian, 2017)	2017	Systematic review	nil	Functional tooth modules	Level 2
16.	Yuan *et al* (Yuan *et al*., 2011)	2011	Systematic review	nil	Selection of biomaterial	Level 3
17.	Du *et al* (Du and Moradian-Oldak, 2006)	2006	Systematic review	nil	Challenges and various opportunities in tooth regeneration	Level 2
18.	Inanç *et al* (Inanç and Murat Elçin, 2011)	2011	Systematic review	nil	Stem cells- challenges seen in tooth regeneration	Level 2