

The Prospects of Using Perinatal Stem Cells in Tooth Engineering – A Review

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ABSTRACT

In the recent years, there has been dramatic progress in the field of stem cell research. These remarkable cells promise potential therapies for numerous diseases.

Human embryonic stem cells (hESCs) remain the most versatile with hopes for treatment of many incurable diseases but their hurdles of tumorigenesis and immunorejection have deferred their use in clinical settings. Attempts to bypass the problem of immunorejection by personalising tissues to patients have led to the development of induced pluripotent stem cells (IPSCs) but the problem of tumorigenesis still exists. Adult mesenchymal stem cells (aMSCs) are painful to harvest. Owing to these limitations, perinatal stem cells prove to be uncomplicated in terms of harvest and have gained considerable attention for therapeutic purposes such as treatment of hematologic and metabolic diseases.

We explore the different perinatal sources of stem cells and their potential use in regenerating teeth in this review.

Keywords: Stem cells, Tissue engineering, Perinatal stem cells

INTRODUCTION

Tooth loss due to diseases and trauma has become a global concern which affects the health and quality of life of an individual. Replacement of lost tooth by whole tooth regeneration is one of the major goals of dental technology [1].

How do we engineer a whole tooth, a part of it or the periodontium? Since the tooth is not a necessary tissue for survival, its regeneration has not been the main concern for research in all these years [2]. It has been estimated that around 150 million adults currently suffer from tooth loss. Tissue engineering is a promising science in regenerating damaged or lost teeth.

Tissue engineering has 3 main components - scaffolds, stem cells (SC) and growth factors (GF). Significant progress towards successful tooth regeneration has been achieved by Young et al., using porcine postnatal tooth cells and cell-scaffold constructs. In their study, tooth buds were harvested and dispersed as cell suspensions onto scaffolds, and grown in immunodeficient rats. Although their technique produced all tooth structures except periodontium, regeneration of a complete tooth was not achieved.

The tooth is a complex structure consisting of hard tissue (enamel and dentin), connected to bone with periodontal ligament. Teeth are highly mineralized organs, resulting from sequential and reciprocal interactions between the oral epithelium and the underlying cranial neural crest-derived mesenchyme [3].

Two major cell types are involved in dental hard tissue formation: the mesenchyme-originated odontoblasts that are responsible for the production of dentin, and the epithelium-derived ameloblasts that form the enamel [4]. Shortly after enamel deposition, the formation of the root starts as a consequence of cell proliferation in the inner and outer dental epithelia at the cervical loop area. Cells from the dental follicle give rise to cementoblasts (forming the cementum that covers the dentin of the root), fibroblasts (generating the periodontal ligament) and osteoblasts (elaborating the alveolar bone). Cementum, periodontal ligament and alveolar bone are the periodontal tissues that support teeth in the oral cavity [5].

TISSUE ENGINEERING

The term tissue engineering was coined at a national science workshop in 1988 to mean “the application of principles and methods of engineering and life sciences towards the fundamental understanding of structure - function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore,

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maintain or improve tissue function". Although the field of tissue engineering is new, the idea of replacing damaged tissues dates back to the 16th century when Gasparo Tagliacozzi, Professor of Surgery and Anatomy at a university in Italy, described a nose replacement that he had constructed from a flap from forearm [6].

The field of tissue engineering is multidisciplinary involving experts from the fields of genetics, mechanical engineering, clinical medicine and other related disciplines [7]. Tissue engineering relies on the use of porous 3D scaffolds to provide the appropriate environment for the regeneration of tissues and organs. The scaffolds are seeded with stem cells and growth factors and are used as templates for tissue formation. These cells seeded scaffolds are then cultured in-vitro to either synthesize tissues that can be implanted into the injured site or are directly implanted onto the injured site relying on the body's own mechanism to regenerate the lost tissues [8].

Scaffolds: Their requirements and types

The nature of a scaffold is a key concern since it will provide cell support and allow exchange of oxygen, nutrients, growth factors, and cytokines [9]. In order to reproduce the extracellular matrix conditions, such biomimetic scaffolds need to display a series of characteristics. They should:

1. Be easy to handle.
2. Allow matrix deposition.
3. Allow vascular supply, hence a porous structure is needed.
4. Allow diffusion of growth factors.
5. Allow transport of nutrients to take place.
6. Not produce toxic degradation products.
7. Be biodegradable.

Scaffold materials commonly used

Natural polymers, synthetic polymers and ceramics are the three different groups of scaffolds typically used in tissue engineering (Table 1).

Table 1. Scaffold materials.

Natural polymers	Collagen Proteoglycans Alginate based substrates Chitosan
Synthetic polymers	Polystyrene Poly-L-lactic acid (PLLA) Polyglycolic acid (PGA) Poly-DL-lactic-co-glycolic acid (PLGA)
Ceramics	Hydroxyapatite (HA) Tricalcium phosphate (TCP)

Growth factors (GFs)

They are polypeptides that stimulate cell proliferation and are major growth regulating molecules for cells in-vitro and in-vivo. They are extra-cellularly secreted signals governing morphogenesis during epithelial-mesenchymal interactions. They are of five major classes:

- Bone morphogenetic proteins (BMPs)
- Fibroblast growth factors (FGFs)
- Wingless- and int- related proteins (Wnts)
- Hedgehog proteins (Hhs)
- Tumor necrotic factor (TNF)

BMPs have been implicated in mammalian tooth development from the very beginning. Although studies report the expression of several BMPs, BMP4 has been suggested to play a central role in tooth development [10]. The expression of BMP4 begins in the dental lamina epithelium and in the mesenchyme during the formation of tooth bud indicating that the odontogenic potential is

transferred from the epithelium to mesenchyme. Other BMP members that closely relate to tooth development include BMP2 and BMP7. Recently, Huang et al. [17], found that BMP9 regulates tooth development by odontoblastic and odontogenic differentiation.

FGFs are secretory protein ligands that are necessary for development, tissue homeostasis and metabolism. FGF8 and FGF9 are detected in the initiation stage of tooth development whereas FGF10 is detected in the dental epithelium and mesenchyme. The expression of FGF3, FGF4, FGF9, FGF15 and FGF20 are detected in the primary enamel knot after its formation while FGF3, FGF10 and FGF18 are found in the mesenchyme [11]. The expression of FGF4 and FGF20 are restricted to the formation of secondary enamel knots in the late bell stage.

The Wnt family consists of a group of secretory ligands that activate several receptor mediated pathways [12]. In the Wnt/ β -catenin pathway, binding of Wnt ligands to Frizzled (FZ) receptors and LDL receptor related protein (LRP)

family co-receptors cause β -catenin accumulation, nuclear translocation, and transcriptional activation by complexes of β -catenin and LEF/TCF transcription factor family members. Activation of Wnt/ β -catenin signalling initiates the de-novo formation of ectodermal appendages related to teeth [13]. Several Wnt genes are broadly expressed in oral and dental epithelium, while others are up regulated in developing teeth. Loss of LEF1 causes arrested tooth development at the late bud stage, loss of expression of a direct LEF1/ β -catenin target gene FGF4, and failure of survival of dental epithelial cells [14].

The mammalian hedgehog (Hh) family includes the sonic hedgehog (SHH), the Indian hedgehog (IHH) and the desert hedgehog (DHH) pathways that encode SHH, IHH and DHH proteins respectively. SHH is the only Hh ligand that is expressed in teeth. The expression of SHH is present in the oral epithelium prior to invagination, and in the tooth epithelium during the tooth development [15]. SHH expression that begins at the bud stage is restricted to the enamel knot at the cap stage [16]. It is also expressed in the surrounding inner enamel epithelium and in the stratum intermedium cells. The decrease or loss of SHH expression leads to a cap stage tooth rudiment, which has a severely disrupted morphology [17].

The TNF family consists of more than 15 members most of which are important regulators of host defence, immunity and inflammation. One family member, RANKL/osteoprotegerin ligand and its receptor RANK are essential for osteoclast survival and differentiation. To date, two members of the TNF superfamily, EDA-A1 and EDA-A2, two splice variants of the same gene have been implicated in tooth development [18].

Other growth factors

Nerve growth factor (NGF) and epidermal growth factor (EGF) were the first growth factors to be discovered in the 1960's. They were also among the first to be analysed in association with tooth development and they have a role in cell proliferation, differentiation and mineralisation events during odontogenesis, paralleling their role in the development of nervous system. Hepatocyte growth factor (HGF) and its receptor c-met are expressed in dental mesenchyme and epithelium respectively. A function in tooth development was indicated because morphogenesis was inhibited when antisense oligonucleotides were added to cultures of cap stage tooth germs [19].

Stem cells

What are stem cells? Our body is made up of different types of cells which have come into existence due to the fusion of egg and sperm which in turn gives rise to a fertilised egg. All the different types of cells come from a pool of stem cells in the early embryo. In the various stages of life, the different types of stem cells give rise to specialised cells or differentiated cells according to the

function that is to be performed. The process by which the unspecialised stem cells give rise to the many different specialised cells in the body has intrigued scientists seeking to create medical treatments to replace the lost tissues for decades.

Potency of stem cells

The capacity of a cell to differentiate into specialised cells and to be able to give rise to any mature cell is called potency [20] (Figure 1).

Totipotent stem cells can differentiate into embryonic and extra-embryonic cells.

Pluripotent stem cells are the descendants of totipotent stem cells and can differentiate into nearly all cell types. These are the ideal cells for regenerative medicine.

Multipotent stem cells can differentiate into a number of closely related cells.

Oligopotent stem cells can differentiate into a few cells like lymphoid or myeloid cells.

Unipotent stem cells can produce only one type of cell.

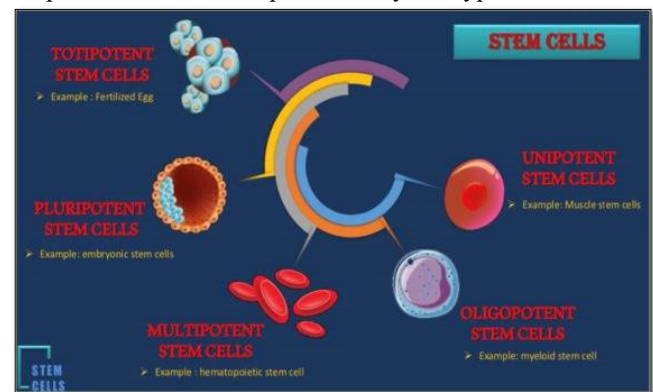


Figure 1. Types of stem cells based on potency.

Types of stem cells

1. Embryonic stem cells (ESCs)
2. Adult stem cells (ASCs)
3. Induced pluripotent stem cells (iPSCs)
4. Perinatal stem cells (PSCs)

The first three types of stem cells are not elaborated in this review. We are only discussing about the perinatal cells and their probable role in tooth regeneration.

Perinatal stem cells

Extra-embryonic tissues are routinely discarded at parturition so little ethical value exists regarding the harvest of stem cells. The comparatively large volume of extra embryonic tissues and ease of physical manipulation theoretically increases the number of stem cells that can be harvested [21,22].

Hematopoietic stem cells (HSC) are the only perinatal stem cells currently being used for treatment of patients. A host of novel stem cell sources have been identified from perinatal sources which include umbilical cord blood (UCB), Wharton's jelly matrix cells (WJCs), amniotic fluid mesenchymal stem cells (AFs), amniotic cavity epithelial stem cells (AECs), umbilical vein cells (UVs), multipotent cells of human term placenta, chimeric progenitor cells and progestational maternal peripheral blood [21].

The advantages of using fetal stem cells are summarised in **Table 2**.

Table 2. Advantages of using foetal derived cells for tissue engineering.

Autologous cell source
Cryopreservation possible
Obtained easily at various stages
Low risk of contamination
Low immunogenic properties
Cell source providing different types of cells including progenitor cells
Excellent cell growth capacity
Tumorigenic potential lower compared to omnipotent cells

Umbilical cord blood (UCB)

The first cord blood transplant (CBT) was performed in a child with Fanconi's anaemia in France. He received cryopreserved cord blood units (CBU) from a sibling. CBUs can be collected either pre or post-delivery. The umbilical vein is cannulated and approximately 100 cc of blood is drawn into a bag containing citrate anti-coagulant. Products are frozen in 10% dimethyl sulfoxide (DMSO). The plasma and red blood cells can be reduced before preservation to allow easier storage and reduction of cellular debris [23] (**Figure 2**).

Therapeutic potential of umbilical cord blood (UCB)

UCB represents the best source for therapeutic HSCs for several reasons.

It contains a higher percentage of HSCs than adult blood or marrow because of the transitioning of site of haematopoiesis from foetal liver to bone marrow at birth. HSCs from UCB engraft with a lower frequency and severity of graft versus host disease (GvHD) even with incomplete recipient – donor HLA (human leukocyte antigen) match [24]. The diversity of cryo-preserved HSCs in UCB banks augments possibilities for greater patient–donor matches, since they are more representative of the general population, as compared to bone marrow donor programs [25]. Various methods of isolation of umbilical cord mesenchymal stem cells (MSCs) have been described. Care should be taken to remove contaminated material from the cord. CB itself is a source of MSCs but the rate of recovery is generally low. The blood vessels present within the cord are another source of MSCs. The whole cord is cut into segments of 1 cm length which are further cut into sub-millimetre particles which are frozen in autologous cord plasma with 10% DMSO.

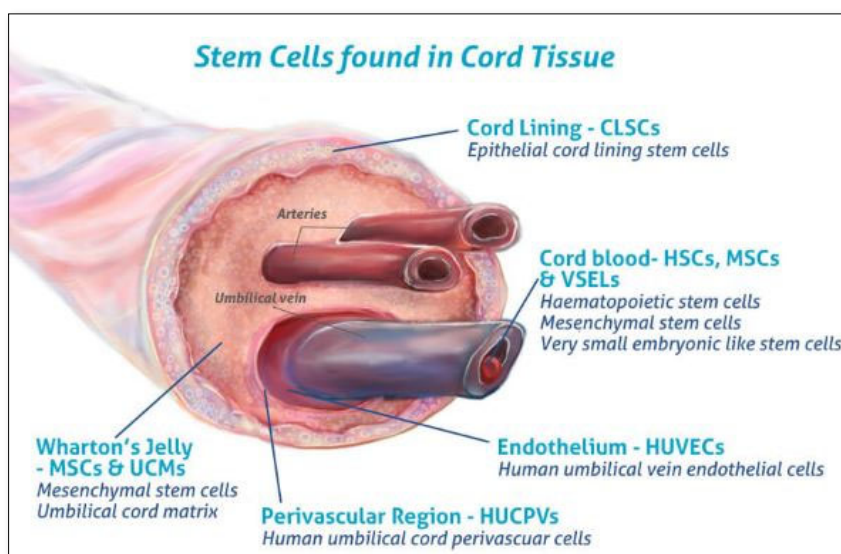


Figure 2. The human umbilical cord showing its components.

HSCs have the ability to differentiate into any of the blood cells and cellular blood components in the body. They have been used in medical treatment for over 25 years and currently treat over 80 blood and bone related conditions. Unlike HSCs, MSCs readily differentiate into neurons as well as bone, cartilage, muscle and fat tissue cells. MSCs aren't currently FDA approved for treatment but researchers are very excited about their potential in emerging fields of gene therapy and cellular repair [26].

Wharton's jelly matrix

Mesenchymal stromal cells (MSCs) are derived from wharton's jelly matrix. They can be isolated from perivascular, intervacular and sub-amnion zones. Wharton's jelly cells (WJCs) are not derived from umbilical blood but rather from the cushioning matrix between umbilical vessels [27]. The WJCs meet the criteria of MSCs i.e., they self-renew and can be differentiated into various cell types. A large number of WJCs can be rapidly isolated – 10000-15000 cells/cm of human UC to ten times this number of cells/cm have been reported. WJCs also have the same immune properties of other MSCs [28-30].

WJCs are similar to adult derived MSCs in that they are multipotent, CD34, CD45 and HLA class II negative and CD73, CH90, CD105 positive and can be engineered to express exogenous proteins. In addition, they proliferate faster and have a greater ex-vivo expansion compared to BM-MSCs. Another reason to use foetal cells is that there is age related exhaustion of BM-MSCs and this was elucidated by Heecheen et al. in 2004 [31].

Amniotic fluid

Amniotic fluid (AF) can be sampled by amniocentesis at any point starting from week 14 until the end of pregnancy, a procedure that is already being performed in many pregnancies to identify congenital abnormalities or to determine sex. However, amniocentesis should not be performed in the first trimester because a number of fetal limb defects were shown after early amniocentesis. AF cells can be obtained from a small amount of fluid. These cells take about 20-24 h to double in number, which is faster than for UC cells [32].

Epithelial cells (AE) are readily identified as a single layer adjacent to the amniotic fluid on one side and basement membrane on the other side. While AE cells reside on the inner layer of the amniotic membrane, amniotic mesenchymal stromal cells (aMSCs) form the outer layer [33,34].

Both the cell types have been extensively investigated for their properties using a number of in-vitro and in-vivo markers. Technical issues have prevented researchers from investigating whether a single human AE or aMSC cell can differentiate into cells representative of all three germ layers after clonal expansion [35,36].

Nevertheless, it is widely accepted that multiple cell types can be derived by culturing either AE or aMSC cells under appropriate conditions. Furthermore, extracting the cells from amniotic fluid bypasses the problems associated with a technique called donor-recipient HLA matching, which involves transplanting cells [37].

16-20 ml of AF is collected. It is not known whether AF cells are purely foetal or derived partly from placenta as well. AF cells have physical characteristics of both embryonic and adult cells. Based on their morphological characteristics, they can be classified into epithelioid, amniotic fluid specific and fibroblastoid. They can be differentiated into six different lineages - endothelial, neurogenic, osteogenic, hepatic, adipogenic and myogenic [36].

Umbilical vein

MSCs have been isolated from sub-endothelium of umbilical vein. It was first described by Romanov's lab. These cells are shown to be similar in properties to MSCs from BM. They have osteogenic ability and multilineage potential.

Placental cells

Placenta derived stem cells (PDSCs) can be obtained from dissociated placental tissue based on plastic adherence, a technique widely employed in harvesting BM-MSCs. PDSCs express numerous mesenchymal surface markers including CD29 and CD44. They exist in a multi-differentiated state simultaneously expressing ectodermal, mesodermal and endodermal genes. They are highly proliferative cells [38] (Figure 3).

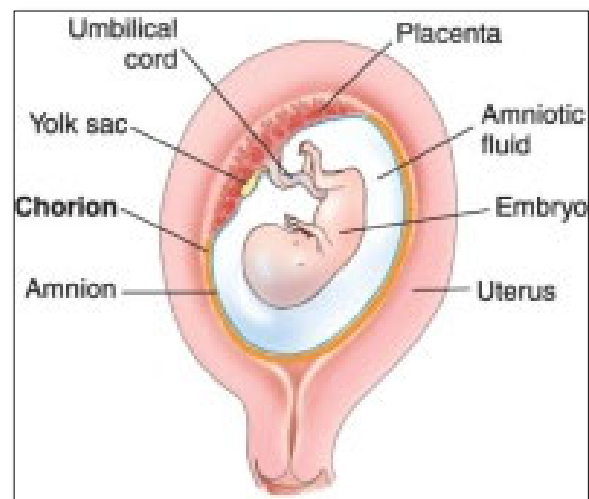


Figure 3. The human placenta.

DISCUSSION-WHOLE TOOTH REGENERATION

Tooth is a complex biological organ. Tooth loss is the most common organ failure. Tissue engineering of teeth requires the coordinated formation of correctly formed crowns, roots and periodontal ligament. The preliminary step in tooth

tissue engineering is understanding the requirements of a defined tooth crown formation. The generation of a whole tooth that can be implanted will require complete recapitulation of the odontogenic developmental program involving epithelial-mesenchymal cell interactions with the resultant structure being capable to integrate with the host vasculature. Numerous factors such as the cell lines used, the culture medium, culture time may account for the variability of results [39].

Natural structures are highly vascularised to provide teeth with proper nutrients and to remove unwanted products. The presence of a nervous system to modulate pain is also very important for longevity of tissues. Since dental implants are not innervated, it is not uncommon for them to get fractured due to excessive forces while chewing. Regenerating teeth that are vascularised and innervated would be a significant improvement over the current tooth replacement strategies [39].

There are two approaches involved in whole tooth regeneration:

- *In-vitro* cultured and expanded progenitor cell populations seeded onto scaffolds and implanted *in vivo*.
- *In-vivo* implantation of immature tooth structure grown *in-vitro* (Figure 4).

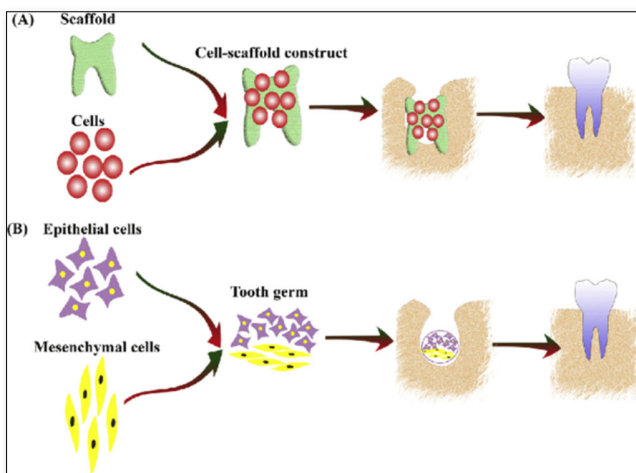


Figure 4. Two current approaches of tooth engineering.

Earlier studies showed the regeneration of tooth crowns from partially dissected tooth germs under suitable conditions. Of all the dental structures, only enamel is incapable of regenerating its original structure while the other tissues possess the capacity in varying degrees depending on multiple factors. Since the cellular component constitutes the living part of a tissue, the regenerative process is cell dependant [40].

By applying traditional tissue engineering techniques, tooth like structures can be regenerated from biodegradable

polymer scaffolds seeded with stem cells. A study was performed with rat tooth germ cells grown in the omentum of mice. Although harvested implants contained anatomically correct teeth which closely resembled natural teeth, they formed in a disoriented way and did not adopt the shape and size of the scaffold. However, these results have confirmed the cell reaggregation ability of dissociated tooth germs [39].

In vitro cell culture methods are being developed and constantly improved but the task of finding stem cell populations that can replace dental epithelium and mesenchyme continues based on the findings that dental epithelium can be created from non-tooth bearing areas and non-dental mesenchyme can participate in odontogenesis on interaction with inductive dental epithelium. These experiments show that the non-dental tissues can be instructed to develop teeth [41,42].

ETHICAL CONSIDERATIONS

Human embryonic cells are valuable resources for new biotechnological developments but the controversy about the nature of human embryo and its ambivalent moral status makes it difficult to justify destroying an embryo for use as a source of raw material for tissue engineering. Because of these limitations of ESCs, pluripotent stem cells obtained from other sources besides the foetus, like the perinatal stem cells discussed in this review are gaining considerable attention. Since these tissues are discarded at the time of birth, it is a simple and safe means of harvesting stem cells. Because of their least invasiveness, amniotic fluid and placenta are considered the most appealing ones [43].

There are ethical considerations in tissue engineering research as well, like the degree of invasiveness of the methods. An *in vitro* experiment is free of risk but the implantation of cultivated cells implies the risk of contamination and incompatibility. The risks involved in the methods of tissue engineering need to be evaluated based on their effects on the body in order to engineer tissues nearer to the natural structure and function. Finally, there are unexpected risks in any new experimental therapies. The important issue is to not ignore them and the general considerations of these risks should be mentioned in the informed consent [44].

CONCLUDING REMARKS

Tissue engineering is progressing rapidly and creating a new era for therapeutic medicine. Tissue engineering was just an idea a few decades ago but today, it is a therapy for various conditions. The paradigms of tissue engineering have variable outcomes, and a true and biological tissue regeneration has not yet been achieved. From recent experiments, it has been established that teeth can be produced from stem cells of both dental and non-dental origin. The development of such teeth requires regulation of the regenerative events in order to achieve proper tooth size

and shape as well as the development of new technologies to facilitate these processes [6,7]. The practical use of perinatal stem cells for dental tissue engineering applications is at an early stage. The functional tooth eruption process in adult jaws has to be controlled. Based on the current efforts, it can be speculated that clinically relevant bioengineered functional tooth therapies for humans may be available in the near future [45].

REFERENCES

1. Honda MJ, Tsuchiya S, Sumita Y, Sagara H, Ueda M (2007) The sequential seeding of epithelial and mesenchymal cells for tissue-engineered tooth regeneration. *Biomaterials* 28: 680-689.
2. Neel EAA, Chrzanowski W, Salih VM, Kim HW, Knowles JC (2014) Tissue engineering in dentistry. *J Dent* 42: 915-928.
3. Duailibi SE, Duailibi MT, Vacanti JP, Yelick PC (2006) Prospects for tooth regeneration. *Periodontology* 2000 41: 177-187.
4. Yoshida K, Yoshida N, Aberdam D, Meneguzzi G, Schmitt FP, et al. (1998) Expression and localization of laminin-5 subunits during mouse tooth development. *Dev Dyn* 211: 164-176.
5. Bluteau G, Luder HU, Bari CD, Mitsiadis TA (2008) Stem cells for tooth engineering. *Eur Cell Mater* 16: 1-9.
6. O'brien FJ (2011) Biomaterials & scaffolds for tissue engineering. *Materials today* 14: 88-95.
7. Monteiro N, Yelick PC (2017) Advances and perspectives in tooth tissue engineering. *J Tissue Eng Regen Med* 11: 2443-2461.
8. Lutolf MP, Hubbell JA (2005) Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. *Nat Biotechnol* 23: 47-55.
9. Kempen DH, Lu L, Kim C, Zhu X, Dhert WJ, et al. (2006) Controlled drug release from a novel injectable biodegradable microsphere/scaffold composite based on poly (propylene fumarate). *J Biomed Mater Res* 77: 103-111.
10. Jia S, Zhou J, Gao Y, Baek JA, Martin JF, et al. (2013) Roles of Bmp4 during tooth morphogenesis and sequential tooth formation. *Development* 140: 423-432.
11. Porntaveetus T, Tanaka YO, Basson MA, Moon AM, Sharpe PT, et al. (2011) Expression of fibroblast growth factors (Fgfs) in murine tooth development. *J Anat* 218: 534-543.
12. Logan CY, Nusse R (2004) The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol* 20: 781-810.
13. Tamai K, Semenov M, Kato Y, Spokony R, Liu C, et al. (2000) LDL-receptor-related proteins in Wnt signal transduction. *Nature* 407: 530-535.
14. Pinson KI, Brennan J, Monkley S, Avery BJ, Skarnes WC (2000) An LDL-receptor-related protein mediates Wnt signalling in mice. *Nature* 407: 535-538.
15. Zhang YD, Chen Z, Song YQ, Chao LIU, Chen YP (2005) Making a tooth: Growth factors, transcription factors and stem cells. *Cell Res* 15: 301-316.
16. Vaahtokari A, Aber T, Jernvall J, Keranen S, Thesleff I (1996) The enamel knot as a signalling centre in the developing mouse tooth. *Mech Dev* 54: 39-44.
17. Huang D, Ren J, Li R, Guan C, Feng Z, et al. (2020) Tooth Regeneration: Insights from tooth development and spatial-temporal control of bioactive drug release. *Stem Cell Rev Rep* 16: 41-55.
18. Odgren PR, Kim N, MacKay CA, Savas AM, Choi Y, et al. (2003) The role of RANKL (TRANCE/TNFSF11), a tumor necrosis factor family member, in skeletal development: Effects of gene knockout and transgenic rescue. *Connect Tissue Res* 44: 264-271.
19. Cohen S, Carpenter G (1975) Human epidermal growth factor: isolation and chemical and biological properties. *Proc Natl Acad Sci* 72: 1317-1321.
20. Bindu AH, Srilatha B (2011) Potency of various types of stem cells and their transplantation. *J Stem Cell Res Ther* 1: 115.
21. Cetrulo K, Cetrulo Jr CL, Taghizadeh RR (2013) Perinatal stem cells. *John Wiley & Sons*.
22. Marcus AJ, Woodbury D (2008) Foetal stem cells from extra-embryonic tissues: Do not discard. *J Cell Mol Med* 12: 730-742.
23. Chow R, Nademanee A, Rosenthal J, Karanes C, Jaing TH, et al. (2007) Analysis of hematopoietic cell transplants using plasma-depleted cord blood products that are not red blood cell reduced. *Biol Blood Marrow Transplant* 13: 1346-1357.
24. Gebbie K, Hanna K, Meyer EA (2005) Cord blood: Establishing a national hematopoietic stem cell bank program. *National Academies Press*.
25. Schröder CP, Wisman GBA, Jong SD, Graaf WTAVD, Ruiters MHJ, et al. (2001) Telomere length in breast cancer patients before and after chemotherapy with or without stem cell transplantation. *Br J Cancer* 84: 1348-1353.

26. Lim IJ, Phan TT (2014) Epithelial and mesenchymal stem cells from the umbilical cord lining membrane. *Cell Transplant* 23: 497-503.
27. Can A, Karahuseyinoglu S (2007) Concise review: Human umbilical cord stroma with regard to the source of fetus-derived stem cells. *Stem Cells* 25: 2886-2895.
28. Troyer DL, Weiss ML (2008) Concise review: Wharton's Jelly-derived cells are a primitive stromal cell population. *Stem Cells* 26: 591-599.
29. Wang XY, Lan Y, He WY, Zhang L, Yao HY, et al. (2008) Identification of mesenchymal stem cells in aorta-gonad-mesonephros and yolk sac of human embryos. *Blood* 111: 2436-2443.
30. Karahuseyinoglu S, Cinar O, Kilic E, Kara F, Akay GG, et al. (2007) Biology of stem cells in human umbilical cord stroma: in situ and in vitro surveys. *Stem Cells* 25: 319-331.
31. Lutjemeier B, Troyer DL, Weiss ML (2010) Wharton's jelly-derived mesenchymal stromal cells. *Perinatal stem cells*, pp: 79-97.
32. Delo DM, Coppi PD, Bartsch Jr G, Atala A (2006) Amniotic fluid and placental stem cells. *Methods Enzymol* 419: 426-438.
33. Mamede AC, Carvalho MJ, Abrantes AM, Laranjo M, Maia CJ, et al. (2012) Amniotic membrane: From structure and functions to clinical applications. *Cell Tissue Res* 349: 447-458.
34. Danforth DN, Hull RW (1958) The microscopic anatomy of the foetal membranes with particular reference to the detailed structure of the amnion. *Am J Obstet Gynecol* 75: 536-550.
35. Wang Y, Jiang F, Liang Y, Shen M, Chen N (2016) Human amnion-derived mesenchymal stem cells promote osteogenic differentiation in human bone marrow mesenchymal stem cells by influencing the ERK1/2 signaling pathway. *Stem Cells Int* 2016: 4851081.
36. Miki T (2011) Amnion-derived stem cells: In quest of clinical applications. *Stem Cell Res Ther* 2: 25.
37. Rennie K, Gruslin A, Hengstschläger M, Pei D, Cai J, et al. (2012) Applications of amniotic membrane and fluid in stem cell biology and regenerative medicine. *Stem Cells Int* 2012: 13.
38. Yen BL, Huang HI, Chien CC, Jui HY, Ko BS, et al. (2005) Isolation of multipotent cells from human term placenta. *Stem Cells* 23: 3-9.
39. Yelick PC, Sharpe PT (2019) Tooth Bioengineering and Regenerative Dentistry. *J Dent Res* 98: 1173-1182.
40. Yen AHH, Sharpe PT (2008) Stem cells and tooth tissue engineering. *Cell Tissue Res* 331: 359-372.
41. Kollar EJ, Fisher C (1980) Tooth induction in chick epithelium: Expression of quiescent genes for enamel synthesis. *Sci* 207: 993-995.
42. Mina M, Kollar EJ (1987) The induction of odontogenesis in non-dental mesenchyme combined with early murine mandibular arch epithelium. *Arch Oral Biol* 32: 123-127.
43. Miki T, Triolo F (2016) Functional dualism of perinatal stem cells. In *Perinatal Tissue-Derived Stem Cells*. Humana Press, Cham, pp: 1-20.
44. Laren AM (2001) Ethical and social considerations of stem cell research. *Nature* 414: 129-131.
45. Chai Y, Slavkin HC (2003) Prospects for tooth regeneration in the 21st century: A perspective. *Microsc Res Techniq* 60: 469-479.