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Review Article

Biomaterials and biotechnology for periodontal tissue regeneration: Recent advances and perspectives

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Abstract

Periodontal tissues are organized in a complex three-dimensional (3D) architecture, including the alveolar bone, cementum, and a highly aligned periodontal ligament (PDL). Regeneration is difficult due to the complex structure of these tissues. Currently, materials are developing rapidly, among which synthetic polymers and hydrogels have extensive applications. Moreover, techniques have made a spurt of progress. By applying guided tissue regeneration (GTR) to hydrogels and cell sheets and using 3D printing, a scaffold with an elaborate biomimetic structure can be constructed to guide the orientation of fibers. The incorporation of cells and biotic factors improves regeneration. Nevertheless, the current studies lack long-term effect tracking, clinical research, and in-depth mechanistic research. In summary, periodontal tissue engineering still has considerable room for development. The development of materials and techniques and an in-depth study of the mechanism will provide an impetus for periodontal regeneration.

Introduction

Human tissue defects caused by diseases or traumas are challenges for medicine because human tissues have limited capabilities for regeneration and cannot meet the demand for in situ repair or ectopic tissue and organ transplantation.[1-3] In recent years, with the progress of materials science and cellular and molecular biology, a brand new field, called tissue engineering and regenerative medicine, has developed as a promising strategy to alleviate the organ shortage crisis.[4,5] Advanced manufacturing plays an essential role in this field.

Functional periodontal regeneration is a synergy of several factors (Figure 1). This review aims to highlight new frontiers in periodontal regeneration with a perspective on the application of biomaterials and emerging biotechnology. By summarizing their advantages and disadvantages, as well as existing possible solutions, this review provides references for future research directions.

Physiological structure and regeneration forms of periodontal tissue

Physiological structure of periodontal tissue

Periodontal tissue refers to a supporting tissue around teeth. It supports and fixes teeth in the alveolar socket and plays a decisive role in the retention and function of teeth. The components of periodontal tissue include the periodontal ligament (PDL), the cementum covering the surface of the tooth root, and the alveolar bone (Figure 2).[6]

Periodontal ligament

The PDL, composed of connective tissue, is located in the space between the cementum and alveolar socket, with a thickness of 0.15–0.38 mm.[7,8] It is composed of cells, matrix, fiber bundles, nerves, and blood vessels. PDL fiber bundles are synthesized by PDL fibroblasts, and both ends are embedded in the cementum and alveolar bone, which are called Sharpey's fibers.[9] The PDL has the functions of tooth retention, tooth nutrition, occlusal force dispersion, proprioception, sensory perception, and the ability to repair damaged periodontal tissue.[9,10]

Cementum

In terms of anatomy, the cementum is a part of the tooth, but it is a part of the periodontium in terms of function. Its primary role is to provide attachment points for Sharpey's fibers.[11] Cementum is a thin and mineralized tissue covering the roots. There are two main structural forms: acellular cementum and cellular cementum. Acellular cementum is a calcified extracellular matrix with no cells. It is distributed on the surface of the dentin from the neck to the middle third of the root and is very important for attachment to the PDL. There are many depressions in the extracellular matrix of cellular cementum containing cementocytes. The cellular cementum mainly covers the root tip and plays a role in tooth movement and adaptation to the bite force after tooth germination.[12] There is a layer of uncalcified cementum on the surface

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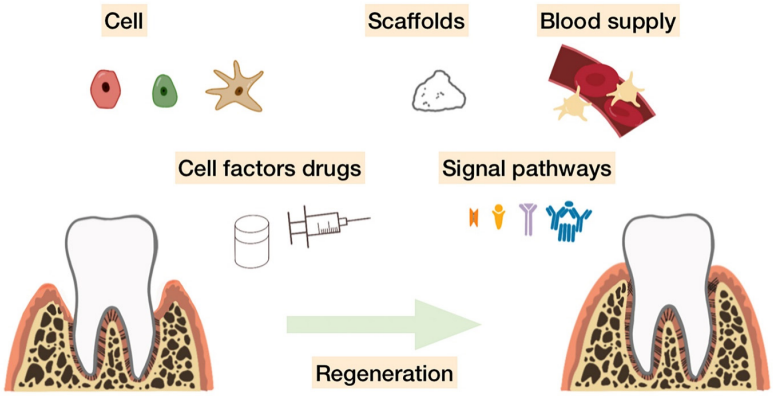

Figure 1. The factors involved in periodontal regeneration.

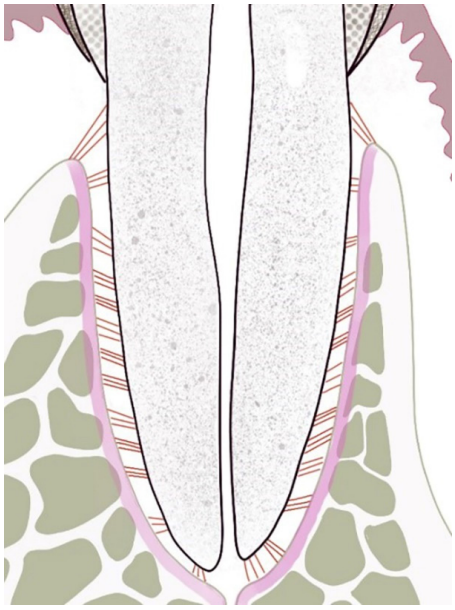

Figure 2. Schematic diagram of the basic structure of periodontal tissues.

of the cementum, which is called cementoid. Through deposition, the cementum gradually thickens, forming a lamellar structure. The function of the cementum is to combine the periodontal tissues with teeth through Sharpey's fibers and repair root surface damage through the deposition of cementum.[13]

Alveolar bone

Alveolar bone is the socket in which the tooth roots are embedded in the upper and lower jaws, consisting of outer cortical plates of compact bone, a central substantia spongiosa, and bone lining the alveolus. The bone lining is where the PDL fiber bundles attach.[7] The proper alveolar bone can be rebuilt due to stress. This function comes from the PDL.[14]

Forms of periodontal tissue regeneration

There are three main forms of periodontal tissue healing: long epithelial integration, PDL regeneration, and osseointegration (Figure 3).

Long epithelial integration

Long epithelial binding is a stable form of healing. Compared with normal epithelium, it has lower cell proliferation ability.[15] In the healing of periodontal tissues, oral epithelial cells will quickly form elongated junctional epithelium to facilitate organisms to resist bacterial infections. Epithelial cells quickly crawl and grow from the epithelium of the gingival surface to the wound surface, occupying the surface of the tooth root first until the surface of the tooth root is covered by thin and long combined epithelium, which affects the formation of new cementum on the surface of the tooth root and affects the integrity of periodontal attachment. This elongation of the combined epithelium usually leads to subgingival plaque formation and subsequent inflammation.

Periodontal ligament regeneration

PDL regeneration is the ideal way of healing, which refers to the restoration of the lost PDL tissue to its original form and function. It involves the cooperation of two hard tissues (cementum and alveolar bone) and two soft tissues (gingiva and PDL).[16] The surface of the tooth root exposed in the periodontal pocket forms new cementum, and at the same time, new alveolar bone is formed. When the two are regenerated, one end of the PDL fiber is buried in the cementum, and the other end is buried in the alveolar bone, forming new periodontal tissue.

Osseointegration

Osseointegration, also known as bone ankylosis, is a process of the human immune system in which hard tissue is dissolved on the surface of the tooth root. When the tooth root is rebsorbed externally, and the damaged area is > 20%, bone remodeling is faster than the formation of cementum-like tissue; therefore, the cementum and dentin on the surface of the tooth root are rebsorbed by osteoclasts and replaced by bone tissue.[17] The PDL is not formed, and the root and alveolar bone are closely connected.

Materials for periodontal tissue regeneration

Several materials are used as scaffolds for tissue engineering and regenerative medicine. The materials used for regenerating tissues must be biocompatible and biodegradable. Moreover, the degradation rate of

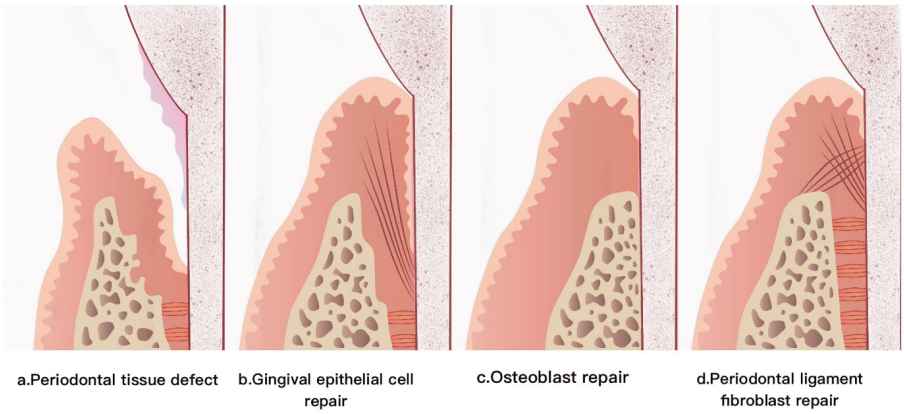

Figure 3. Three types of repair of periodontal defects.

the scaffolds should be consistent with the target tissue regeneration rate.[18]

Polymers are common materials used for tissue engineering and regenerative medicine. They are classified as natural and synthetic polymers. Natural polymers are organic in origin and have good biocompatibility and biodegradability but insufficient mechanical properties. Synthetic polymers are produced industrially from inorganic sources and classified as absorbable and nonabsorbable polymers. Resorbable polyesters are predominant among synthetic polymers, including polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), polylactic-polyglycolic acid (PLGA), polyethylene glycol (PEG), and PEG with PLGA (PEG-PLGA).[19] Among them, the most representative synthetic polymer is PCL.

PCL, an FDA-approved linear synthetic bioresorbable aliphatic polyester, has excellent thermal stability and is able to mold into different forms, which makes it different from the other materials used in scaffolds for tissue engineering.[20-22] Moreover, it is hydrophobic and can hinder access to the medium and control drug dissolution.[23] Unfortunately, due to its hydrophobicity, PCL is detrimental to cell attachment, proliferation, and differentiation.[24] Hence, surface modifications are necessary. As PCL is easy to process, it has been used to repair various tissue defects via three-dimensional (3D) printing.

Materials for alveolar bone regeneration

In the early days of periodontal tissue regeneration, researchers first focused on the regeneration of bone defects. Bone defects are the most important and obvious manifestation of periodontal defects and can be clearly observed in clinical x-ray examinations. Once the alveolar bone has rebsorbed, the tooth loses its bone support and loosens gradually, falling off eventually.

Bioactivity, biocompatibility, and biodegradability are critical concerns in scaffold design, with important roles in bone regeneration.[25-28] Moreover, the key parameters of porosity, stiffness, and viscoelasticity can regulate cell adhesion, proliferation, and osteogenesis differentiation.[29-36] Well-designed scaffolds can provide cells with sustainable regenerative factors and physical and biological support, mobilizing stem cells to regenerate the defect cavity.[37-40]

Collagen,[41] chitosan,[42,43] and gelatin[44] are representative natural biomaterials with a favorable bone regenerative capacity because they share a similar extracellular matrix with the host and are suitable for cell migration, proliferation, and osteogenic differentiation. Interestingly, the in vivo metabolic components of these natural biomaterials are needed in the bone tissue reconstruction process.

In addition, synthetic polymer-based biomaterials derived from a series of polymerization and crosslinking processes are designed purposefully with the expected properties and functions. Among them, PLGA and PCL[45] with nontoxic, gelling, filming, and capsuling properties have found widespread applications.

Calcium phosphate (CaP)-based bioceramics[46,47] have found widespread applications, especially injectable CaP, with strong formability and flexibility. Nevertheless, the degradation of injectable CaP is limited, hindering the growth of new bones; therefore, it would be necessary to introduce porous materials with an enhanced degradation rate. Moreover, alloys are also a widely used bone repair material. The properties of natural or synthetic materials alone are slightly inferior, but when they are combined, a better bone repair result is realized.[48]

A macroporous structure[49] whose pores are > 100 μm allows angiogenesis and the migration of bone cells. It imitates the bone tissue structure and can significantly improve bone repair outcomes. Additionally, osteoinductive factors (e.g., bone morphogenetic protein-2 (BMP-2),[50] fibroblast growth factor-2 (FGF-2), insulin growth factor (IGF), and platelet-derived growth factor-BB (PDGF-BB)) have essential roles in promoting osteogenesis.

Materials for periodontal ligament and cementum regeneration

The PDL is the most important functional part of periodontal tissue, and its regeneration is of great significance. However, the PDL is a very thin layer of connective tissue between the alveolar bone and

cementum. The morphology and structure are exquisite. Natural materials (such as collagen, chitosan, and gelatin)[51-53] and synthetic materials (such as PCL[54,55] and PLGA[56]) are also suitable for PDLs. Moreover, because of their excellent fluidity and plasticity, hydrogel materials are very suitable for repairing PDL defects.

Some researchers have optimized the properties of hydrogels by designing a green route to fabricate strong, supertough, regenerated cellulose films with tightly stacked and long-range aligned cellulose nanofibers. The study showed that this unique hierarchical structure could induce the adhesion and directional arrangement of cardiomyocytes, showing the potential for an oriented culture of cardiomyocytes in vitro. This advantage may be promising for inducing the directional arrangement of PDL fibers.[57-59]

PCL can be electrospun[55,60] and electrostatically written[61] to produce PDL scaffolds. In particular, electrostatic direct writing technology, whose rotation direction is controllable, is very suitable for guiding the directional arrangement of PDL fibers.

Few studies have fabricated scaffolds for the cementum because it occupies too little space. In studies that have produced a three-layer periodontal composite scaffold, the cementum layer is made of PCL/amelogenin[62] or chitin-poly (lactic-co-glycolic acid) (LGA)/nanobioactive glass ceramic (nBGC)/cementum protein-1.[63] The addition of amelogenin and cementum protein 1 promotes cementum regeneration.

Treatment for periodontal regeneration

Guided tissue regeneration

The most commonly used clinical technology is guided tissue regeneration (GTR), a basic treatment applied to patients with periodontal defects. GTR uses membrane barriers that prevent epithelial cell proliferation and stimulate bone regeneration of the defect.[64] GTR can be used only in some clinical cases, such as intraosseous defects and class II fissure defects. Several types of GTR membranes have been developed with improved physicochemical, mechanical, and biological properties to increase bone growth.[65,66] However, GTR mainly promotes the repair of bone defects, while the regeneration of the PDL and cementum is still difficult to achieve.

Hydrogel

Many agents and bioactive factors with strong anti-inflammatory, bone anabolic, and fiber anabolic effects have been studied preclinically, and their feasibility of periodontitis therapy has been confirmed. Hence, suitable drug delivery is necessary. Hydrogels are a good option because of their good fluidity, injectability, and biocompatibility.[67,68] The emergence of photo-crosslinked hydrogels[69,70] and thermosensitive hydrogels[67,71-73] optimizes the performance of hydrogels as space-occupying scaffolds for periodontal defects. Hydrogels are crosslinked using a photoinitiator and a light lamp. The in situ thermoresponsive hydrogels maintain their fluidity at low temperatures, facilitating local injection through thin needles. Once administered in vivo, the solution solidifies into a hydrogel at body temperature, which would help maintain the drug payload for a long time in the periodontal pocket. In terms of biocompatibility and cell delivery, hydrogels also have excellent performance.[74-77]

Cell sheets

Tissue engineering strategies based on cells and cell sheets have been widely used for periodontal tissue regeneration. Cell sheets, a strategy for seeding cell delivery to the periodontal defect area, have been introduced to regenerate periodontal tissues.[3,78] The obtained cell sheet is placed between the root and alveolar bone. Human dental follicle cells and[79] periodontal ligament stem cells (PDLSCs)[80-82] have been used to seed the cells.

The crosstalk of various cells is of great significance; for example, Zhang et al[78] demonstrated that the crosstalk between PDLSCs and jaw bone marrow-derived mesenchymal stem cells in cell sheets facilitates the regeneration of complex periodontium-like structures. Yang et al[83] demonstrated that human urine-derived stem cells promote the proliferation and osteogenic and cementogenic differentiation of PDLSCs in a ratio-dependent manner through noncontact coculture and further accelerate the regeneration of new structures by PDLSC sheets with osteogenic matrix in vivo. Safi et al[84] isolated both PDLSCs and bone marrow mesenchymal stem cells and used them in a coculture method to induce more PDL cells to create three-layered cell sheets for reconstructing the natural PDL. By layering PDL cells and osteoblast-like cells on a temperature-responsive culture dish, Raju et al[85] fabricated a three-dimensional complex cell sheet composed of a bone-ligament structure. Ectopic and orthotopic transplantation results showed that the complex cell sheet group anatomically regenerated the bone-ligament structure along with the functional connection of PDL-like fibers to the tooth root and alveolar bone. Hence, coculture and crosstalk of cells provide a promising new strategy for the physiological and functional regeneration of periodontal tissue.

Moreover, decellularized PDL cell sheets, which are a new technology, have also been confirmed to promote periodontal regeneration.[86]

3D printing

3D printing is an emerging field, but there are few applications in periodontal tissue engineering, leaving a broad research space. 3D printing is a state-of-the-art additive manufacturing to turn 3D digital models into complex organs or other tissue constructs by fusing or depositing materials layer by layer through the head, nozzle, or another printer technology.[87] Compared with the conventional tissue engineering methods, 3D printing has some apparent advantages. The conventional tissue engineering techniques cannot precisely control

the pore size, geometry, and interconnectivity of the scaffolds; therefore, it is impossible to fabricate complex biomimetic tissue structures.[88] Tissue constructs fabricated by conventional methods are too simplified to adapt to the native cellular microenvironment,[89] while 3D printing is more likely to fabricate complex, precise, and individualized biomimetic tissue constructs with reproducibility and repeatability.[90-95]

3D printing technology emerged in the 1980s. Charles Hull invented the world's first 3D printer (stereolithography) in 1983.[96,97] Since then, 3D printing techniques have made prompt advances. In 1987, selective laser sintering (SLS) was invented by Dr. Carl Deckard. In 1989, fusion deposition modeling (FDM) was devised by Scott Crump. Currently, in addition to SLS and FDM, the most popular 3D printing techniques are inkjet bioprinting, extrusion printing/bioprinting, and stereolithography.

The 3D printing technique uses computer-assisted design and manufacturing after a CT scan. The scaffolds can be made of one or several materials, such as natural polymers, synthetic polymers, or both. They can be monophasic or multiphasic and tend to recreate the architectural structure of the periodontal tissue. Stem cells and/or growth factors can enhance bioactivity and promote regeneration.

The ability to engineer bone-ligament interfaces is of significant interest for craniofacial systems.[98-101] The integration of polarized fibers oriented to a mineralizing surface promotes adequate maturation and important biomechanical properties of the tissue, which regulates tissue adaptability and its long-term stability.[54] Various approaches have been studied to encourage spatiotemporal control of multi-tissue formation and integration.[102,103]

It is not easy to regenerate a single tissue, and periodontal regeneration involves three tissue types, which is even more difficult. Bone defects are the most obvious and often the largest defect; therefore, bone restoration is the first to attract researchers' attention. The PDL, as an important functional component, carries out the functions of sensation, cushioning, nutrition, reconstruction, and restoration of alveolar bone and cementum, which cannot be ignored. As a result, with the development of science and technology, researchers began to produce biphasic scaffolds, including PDL cavities and alveolar bone cavities, to achieve the regeneration of alveolar bone and PDL fibers and form cementum.[55,56] Another study found that adding a CAP coating to the alveolar bone scaffold can increase osteoconductivity and achieve more bone regeneration.[60] Studies have also made a three-layer scaffold, including alveolar bone, PDL, and cementum, and added growth factors that can promote its regeneration in different parts to achieve the regeneration of three tissue types.[62]

A very important issue in periodontal regeneration is the directional arrangement of PDL fibers, which is an essential factor in determining its function. Therefore, in some scaffolds, a structure to guide the arrangement of the fibers is designed. For example, in Park's research, perpendicularly oriented channels were set to guide the direction of the fibers.[56] Later, the team developed a fiber guiding scaffold to replace the previous random porous structure.[54] A more favorable guiding fiber arrangement effect was realized.

Park et al[104] continued to conduct in-depth research on guiding the direction of PDL fibers. In 2014, they reported using directional freeze-casting techniques to control pore directional angulations and create topographies mimicking the alveolar crest and horizontal, oblique, and apical fibers of natural PDLs. Freeze casting is a simple approach that can create submicron-level porous constructs via aqueous materials[105,106] because freezing conditions can control the microscopic patterns of ice crystals, and the regularity of ice growth can provide unidirectionally or radially oriented pores within the internal architectures.[107] Other researchers on Park's team have explored the effects of different depths and widths on grooved pillars for cell alignment, demonstrating increased cell alignment further from the pillar boundary in films with grooves compared to non-grooved pillars, with increased alignment in deeper-grooved (30 μm) pillars compared to shallow-grooved (15 μm) pillars.[108] Moreover, a study added oriented nanofibers to the scaffold to guide the arrangement of new fibers.[109] The electrostatic direct writing method is a new technology that is also effective in guiding the direction of the fiber.[61]

Interestingly, scholars have extended the reconstruction of the PDL to implants. Cell sheets were applied around titanium implants. The results showed that cementum-like and PDL-like tissues were partly observed on the titanium surface.[110,111]

In contrast with alveolar bone and PDL, the cementum has received less attention. On the one hand, the cementum is too thin, and the repair space is too small, which makes the production of 3D printing scaffolds very difficult. On the other hand, too few studies have focused on the mechanism of cementum formation. The cementum is secreted by cementoblasts. However, the regulatory mechanism of PDL stem cells or other stem cells differentiated into cementoblasts is not clear. Cementum formation may be related to the interaction between PDL cells and dentin.

In 2015, Rasperini et al[112] reported the first case of applying a 3D-printed scaffold to patients with clinical periodontal defects. Although this case was unsuccessful in the long term, it provided valuable experience for the clinical applications of periodontal regeneration. There was a large labial soft and osseous defect in the patient's mandible. They designed and 3D-printed the scaffold using medical-grade PCL. Recombinant human platelet-derived growth factor-BB was delivered to the scaffold's internal compartment. In the 13th month, the scaffold became exposed. Eventually, a larger dehiscence and wound failure were observed, and the entire scaffold was

removed. The evaluation of the scaffold showed primarily connective tissue healing and minimal evidence of bone repair. The slow degradation rate of PCL might be the main cause of failure. The degradation rate of PCL did not match the rate of tissue formation, which caused the exposure of the scaffold and the invasion of bacteria. In addition, the structure of the scaffold was also of great significance. A highly porous structure inside the scaffold may promote the formation of blood vessels, which is beneficial to bone formation.

Discussion

Periodontal regeneration is significant to stomatology, but true periodontal regeneration is hard to achieve. The structure of periodontal tissue is very complicated. The sandwich structure of two kinds of hard tissues with a layer of soft tissue makes the construction of periodontal restoration difficult.

At present, the rise of bioprinting provides a fresh impetus for periodontal regeneration. The continuous development of hydrogel materials will make them very promising periodontal restoration materials.[63,67,68,74,113-115] The excellent biocompatibility, fluidity, plasticity, and injectability make hydrogels a suitable material to combine with bioprinting, particularly photo-crosslinked hydrogels and thermosensitive hydrogels.

The weak mechanical properties of hydrogel materials can also be solved by adding cellulose.[58,59,116] In addition, technology for the directional arrangement of cellulose in hydrogels has also been developed, which may greatly promote the development of technology for guiding the arrangement of PDL fibers.[57,117,118]

However, the long-term effect of the method of guiding the orientation of the fibers is not clear. Moreover, the direction of the fibers may be inextricably linked to the surrounding force field. The adaptation of PDL cells to the bite force prompts them to continuously rebuild the PDL fibers and finally form a suitable arrangement direction.[119]

Last but not least, the crucial point is the lack of understanding of the mechanism of periodontal tissue formation, especially cementum. In recent years, scholars have begun to study the mechanism of cementum regeneration, and the achievements are promising.[120] CEMP1 and its peptide fragments have been confirmed to significantly affect cementum regeneration.[121-124] Enamel-associated proteins and some other proteins have also been confirmed by related studies to promote cementum regeneration.[120] Research on the mechanism and signaling pathways of cementum regeneration is still lacking, and there is broad room for research.

Conclusion

3D printing and bioprinting technology are promising technologies in periodontal regeneration. In the meantime, materials are developing by leaps and bounds. Only when researchers have a deeper understanding of the periodontal regeneration mechanism and technology continues to develop and improve can it be possible to apply their achievement to construct restorations and finally realize real periodontal regeneration.

Authors' Contribution

RD, UC, and YX contributed to conceptualization, data curation, formal analysis, methodology, project administration, resources, software, writing an original draft, writing, review, and editing. YH and TX were conceptualization and supervision leads and finally read and revised the article.

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Ethics Approval

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Competing Interests

The authors declare no conflicts of interest.

References

1. Matai I, Kaur G, Seyedsalehi A, McClinton A, Laurencin CT. Progress in 3D bioprinting technology for tissue/organ regenerative engineering. Biomaterials. 2020;226:119536. doi: 10.1016/j.biomaterials.2019.119536.
2. Ma Y, Xie L, Yang B, Tian W. Three-dimensional printing biotechnology for the regeneration of the tooth and tooth-supporting tissues. Biotechnol Bioeng. 2019;116(2):452-68. doi: 10.1002/bit.26882.
3. Ishikawa I, Iwata T, Washio K, Okano T, Nagasawa T, Iwasaki K, et al. Cell sheet engineering and other novel cell-based approaches to periodontal regeneration. Periodontol 2000. 2009;51:220-38. doi: 10.1111/j.1600-0757.2009.00312.x.
4. Amrollahi P, Shah B, Seifi A, Tayebi L. Recent advancements in regenerative dentistry: a review. Mater Sci Eng C Mater Biol Appl. 2016;69:1383-90. doi: 10.1016/j.msec.2016.08.045.
5. Bittner SM, Guo JL, Melchiorri A, Mikos AG. Three-dimensional printing of multilayered tissue engineering scaffolds. Mater Today (Kidlington). 2018;21(8):861-74. doi: 10.1016/j.mattod.2018.02.006.
6. Fawzy El-Sayed KM, Dörfer CE. Animal models for periodontal tissue engineering: a knowledge-generating process. Tissue Eng Part C Methods. 2017;23(12):900-25. doi: 10.1089/ten.TEC.2017.0130.
7. Nanci A, Bosshardt DD. Structure of periodontal tissues in health and disease. Periodontol 2000. 2006;40:11-28. doi: 10.1111/j.1600-0757.2005.00141.x.
8. Hassell TM. Tissues and cells of the periodontium. Periodontol 2000. 1993;3:9-38. doi: 10.1111/j.1600-0757.1993.tb00230.x.
9. Hirashima S, Kanazawa T, Ohta K, Nakamura KI. Three-dimensional ultrastructural imaging and quantitative analysis of the periodontal ligament. Anat Sci Int. 2020;95(1):1-11. doi: 10.1007/s12565-019-00502-5.
10. Berkovitz BK. Periodontal ligament: structural and clinical correlates. Dent Update. 2004;31(1):46-54. doi: 10.12968/denu.2004.31.1.46.
11. Grzesik WJ, Narayanan AS. Cementum and periodontal wound healing and regeneration. Crit Rev Oral Biol Med. 2002;13(6):474-84. doi: 10.1177/154411130201300605.
12. Foster BL. Methods for studying tooth root cementum by light microscopy. Int J Oral Sci. 2012;4(3):119-28. doi: 10.1038/ijos.2012.57.
13. Ripamonti U. Developmental pathways of periodontal tissue regeneration: developmental diversities of tooth morphogenesis do also map capacity of periodontal tissue regeneration? J Periodontal Res. 2019;54(1):10-26. doi:

10.1111/jre.12596.
14. Feller L, Khammissa RA, Schechter I, Thomadakis G, Fourie J, Lemmer J. Biological events in periodontal ligament and alveolar bone associated with application of orthodontic forces. ScientificWorldJournal. 2015;2015:876509. doi: 10.1155/2015/876509.
15. Noguchi S, Ukai T, Kuramoto A, Yoshinaga Y, Nakamura H, Takamori Y, et al. The histopathological comparison on the destruction of the periodontal tissue between normal junctional epithelium and long junctional epithelium. J Periodontal Res. 2017;52(1):74-82. doi: 10.1111/jre.12370.
16. Xiong J, Gronthos S, Bartold PM. Role of the epithelial cell rests of Malassez in the development, maintenance and regeneration of periodontal ligament tissues. Periodontol 2000. 2013;63(1):217-33. doi: 10.1111/prd.12023.
17. Wu JY, Li X, Wang CL, Ye L, Yang J. [Research progress on the pathogenesis of inflammatory external root resorption]. Hua Xi Kou Qiang Yi Xue Za Zhi. 2019;37(6):656-9. doi: 10.7518/hxkq.2019.06.015.
18. Hassanajili S, Karami-Pour A, Oryan A, Talaei-Khozani T. Preparation and characterization of PLA/PCL/HA composite scaffolds using indirect 3D printing for bone tissue engineering. Mater Sci Eng C Mater Biol Appl. 2019;104:109960. doi: 10.1016/j.msec.2019.109960.
19. Ceccarelli G, Presta R, Benedetti L, Cusella De Angelis MG, Lupi SM, Rodriguez YBR. Emerging Perspectives in Scaffold for Tissue Engineering in Oral Surgery. Stem Cells Int. 2017;2017:4585401. doi: 10.1155/2017/4585401.
20. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. J Control Release. 2016;234:41-8. doi: 10.1016/j.jconrel.2016.05.034.
21. Siddiqui N, Asawa S, Birru B, Baadhe R, Rao S. PCL-based composite scaffold matrices for tissue engineering applications. Mol Biotechnol. 2018;60(7):506-32. doi: 10.1007/s12033-018-0084-5.
22. Gruber SMS, Ghosh P, Mueller KW, Whitlock PW, Lin CY. Novel process for 3D printing decellularized matrices. J Vis Exp. 2019(143):10.3791/58720. doi: 10.3791/58720.
23. Zupančič Š, Casula L, Rijavec T, Lapanje A, Luštrik M, Fadda AM, et al. Sustained release of antimicrobials from double-layer nanofiber mats for local treatment of periodontal disease, evaluated using a new micro flow-through apparatus. J Control Release. 2019;316:223-35. doi: 10.1016/j.jconrel.2019.10.008.
24. Sharifi F, Atyabi SM, Norouzian D, Zandi M, Irani S, Bakhshi H. Polycaprolactone/carboxymethyl chitosan nanofibrous scaffolds for bone tissue engineering application. Int J Biol Macromol. 2018;115:243-8. doi: 10.1016/j.ijbiomac.2018.04.045.
25. Li Y, Xiao Y, Liu C. The horizon of materiobiology: a perspective on material-guided cell behaviors and tissue engineering. Chem Rev. 2017;117(5):4376-421. doi: 10.1021/acs.chemrev.6b00654.
26. Yang D, Xiao J, Wang B, Li L, Kong X, Liao J. The immune reaction and degradation fate of scaffold in cartilage/bone tissue engineering. Mater Sci Eng C Mater Biol Appl. 2019;104:109927. doi: 10.1016/j.msec.2019.109927.
27. Kossover O, Cohen N, Lewis JA, Berkovitch Y, Peled E, Seliktar D. Growth factor delivery for the repair of a critical size tibia defect using an acellular, biodegradable polyethylene glycol-albumin hydrogel implant. ACS Biomater Sci Eng. 2020;6(1):100-11. doi: 10.1021/acsbiomaterials.9b00672.
28. Ji X, Yuan X, Ma L, Bi B, Zhu H, Lei Z, et al. Mesenchymal stem cell-loaded thermosensitive hydroxypropyl chitin hydrogel combined with a three-dimensional-printed poly(ε-caprolactone) /nano-hydroxyapatite scaffold to repair bone defects via osteogenesis, angiogenesis and immunomodulation. Theranostics. 2020;10(2):725-40. doi: 10.7150/thno.39167.
29. Lee TT, García JR, Paez JI, Singh A, Phelps EA, Weis S, et al. Light-triggered in vivo activation of adhesive peptides regulates cell adhesion, inflammation and vascularization of biomaterials. Nat Mater. 2015;14(3):352-60. doi: 10.1038/nmat4157.
30. Hou S, Niu X, Li L, Zhou J, Qian Z, Yao D, et al. Simultaneous nano- and microscale structural control of injectable hydrogels via the assembly of nanofibrous protein microparticles for tissue regeneration. Biomaterials. 2019;223:119458. doi: 10.1016/j.biomaterials.2019.119458.
31. Huang D, Huang Y, Xiao Y, Yang X, Lin H, Feng G, et al. Viscoelasticity in natural tissues and engineered scaffolds for tissue reconstruction. Acta Biomater. 2019;97:74-92. doi: 10.1016/j.actbio.2019.08.013.
32. Zhang K, Wang S, Zhou C, Cheng L, Gao X, Xie X, et al. Advanced smart biomaterials and constructs for hard tissue engineering and regeneration. Bone Res. 2018;6:31. doi: 10.1038/s41413-018-0032-9.
33. Wu J, Cao L, Liu Y, Zheng A, Jiao D, Zeng D, et al. Functionalization of silk fibroin electrospun scaffolds via BMSC Affinity peptide grafting through oxidative self-polymerization of dopamine for bone regeneration. ACS Appl Mater Interfaces. 2019;11(9):8878-95. doi: 10.1021/acsami.8b22123.
34. Wang Q, Huang Y, Qian Z. Nanostructured surface modification to bone implants for bone regeneration. J Biomed Nanotechnol. 2018;14(4):628-48. doi: 10.1166/jbn.2018.2516.
35. Hu Q, Liu M, Chen G, Xu Z, Lv Y. Demineralized bone scaffolds with tunable matrix stiffness for efficient bone integration. ACS Appl Mater Interfaces. 2018;10(33):27669-80. doi: 10.1021/acsami.8b08668.
36. Xie J, Zhang D, Zhou C, Yuan Q, Ye L, Zhou X. Substrate elasticity regulates adipose-derived stromal cell differentiation towards osteogenesis and adipogenesis through β-catenin transduction. Acta Biomater. 2018;79:83-95. doi: 10.1016/j.actbio.2018.08.018.
37. Gu Z, Huang K, Luo Y, Zhang L, Kuang T, Chen Z, et al. Double network hydrogel for tissue engineering. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2018;10(6):e1520. doi: 10.1002/wnan.1520.
38. Brokesh AM, Gaharwar AK. Inorganic biomaterials for regenerative medicine. ACS Appl Mater Interfaces. 2020;12(5):5319-44. doi: 10.1021/acsami.9b17801.
39. Yao Q, Liu H, Lin X, Ma L, Zheng X, Liu Y, et al. 3D interpenetrated graphene foam/58S bioactive glass scaffolds for electrical-stimulation-assisted differentiation of rabbit mesenchymal stem cells to enhance bone regeneration. J Biomed Nanotechnol. 2019;15(3):602-11. doi: 10.1166/jbn.2019.2703.
40. Farokhi M, Mottaghitalab F, Shokrgozar MA, Ou KL, Mao C, Hosseinkhani H. Importance of dual delivery systems for bone tissue engineering. J Control Release. 2016;225:152-69. doi: 10.1016/j.jconrel.2016.01.033.
41. Mazzoni E, D'Agostino A, Iaquinta MR, Bononi I, Trevisiol L, Rotondo JC, et al. Hydroxylapatite-collagen hybrid scaffold induces human adipose-derived mesenchymal stem cells to osteogenic differentiation in vitro and bone regrowth in patients. Stem Cells Transl Med. 2020;9(3):377-88. doi: 10.1002/sctm.19-0170.
42. Aguilar A, Zein N, Harmouch E, Hafdi B, Bornert F, Offner D, et al. Application of chitosan in bone and dental engineering. Molecules. 2019;24(16):3009. doi: 10.3390/molecules24163009.
43. Demirtaş TT, Irmak G, Gümüşderelioğlu M. A bioprintable form of chitosan hydrogel for bone tissue engineering.

Biofabrication. 2017;9(3):035003. doi: 10.1088/1758-5090/aa7b1d.
44. Ishiko-Uzuka R, Anada T, Kobayashi K, Kawai T, Tanuma Y, Sasaki K, et al. Oriented bone regenerative capacity of octacalcium phosphate/gelatin composites obtained through two-step crystal preparation method. J Biomed Mater Res B Appl Biomater. 2017;105(5):1029-39. doi: 10.1002/jbm.b.33640.
45. Li Y, Li Q, Li H, Xu X, Fu X, Pan J, et al. An effective dual-factor modified 3D-printed PCL scaffold for bone defect repair. J Biomed Mater Res B Appl Biomater. 2020;108(5):2167-79. doi: 10.1002/jbm.b.34555.
46. Prins HJ, Schulten EA, Ten Bruggenkate CM, Klein-Nulend J, Helder MN. Bone regeneration using the freshly isolated autologous stromal vascular fraction of adipose tissue in combination with calcium phosphate ceramics. Stem Cells Transl Med. 2016;5(10):1362-74. doi: 10.5966/sctm.2015-0369.
47. Raucci MG, Fasolino I, Pastore SG, Soriente A, Capeletti LB, Dessuy MB, et al. Antimicrobial imidazolium ionic liquids for the development of minimal invasive calcium phosphate-based bionanocomposites. ACS Appl Mater Interfaces. 2018;10(49):42766-76. doi: 10.1021/acsami.8b12696.
48. Zhuang Y, Liu Q, Jia G, Li H, Yuan G, Yu H. A biomimetic zinc alloy scaffold coated with brushite for enhanced cranial bone regeneration. ACS Biomater Sci Eng. 2021;7(3):893-903. doi: 10.1021/acsbiomaterials.9b01895.
49. Mastrogiacomo M, Scaglione S, Martinetti R, Dolcini L, Beltrame F, Cancedda R, et al. Role of scaffold internal structure on in vivo bone formation in macroporous calcium phosphate bioceramics. Biomaterials. 2006;27(17):3230-7. doi: 10.1016/j.biomaterials.2006.01.031.
50. Park SY, Kim KH, Kim S, Lee YM, Seol YJ. BMP-2 gene delivery-based bone regeneration in dentistry. Pharmaceutics. 2019;11(8):393. doi: 10.3390/pharmaceutics11080393.
51. Kenry, Liu B. Recent advances in biodegradable conducting polymers and their biomedical applications. Biomacromolecules. 2018;19(6):1783-803. doi: 10.1021/acs.biomac.8b00275.
52. Song R, Murphy M, Li C, Ting K, Soo C, Zheng Z. Current development of biodegradable polymeric materials for biomedical applications. Drug Des Devel Ther. 2018;12:3117-45. doi: 10.2147/dddt.s165440.
53. Lauritano D, Limongelli L, Moreo G, Favia G, Carinci F. Nanomaterials for periodontal tissue engineering: chitosan-based scaffolds. A systematic review. Nanomaterials (Basel). 2020;10(4):605. doi: 10.3390/nano10040605.
54. Park CH, Rios HF, Jin Q, Sugai JV, Padial-Molina M, Taut AD, et al. Tissue engineering bone-ligament complexes using fiber-guiding scaffolds. Biomaterials. 2012;33(1):137-45. doi: 10.1016/j.biomaterials.2011.09.057.
55. Vaquette C, Fan W, Xiao Y, Hamlet S, Hutmacher DW, Ivanovski S. A biphasic scaffold design combined with cell sheet technology for simultaneous regeneration of alveolar bone/periodontal ligament complex. Biomaterials. 2012;33(22):5560-73. doi: 10.1016/j.biomaterials.2012.04.038.
56. Park CH, Rios HF, Jin Q, Bland ME, Flanagan CL, Hollister SJ, et al. Biomimetic hybrid scaffolds for engineering human tooth-ligament interfaces. Biomaterials. 2010;31(23):5945-52. doi: 10.1016/j.biomaterials.2010.04.027.
57. Ye D, Cheng Q, Zhang Q, Wang Y, Chang C, Li L, et al. Deformation drives alignment of nanofibers in framework for inducing anisotropic cellulose hydrogels with high toughness. ACS Appl Mater Interfaces. 2017;9(49):43154-62. doi: 10.1021/acsami.7b14900.
58. Ye D, Chang C, Zhang L. High-strength and tough cellulose hydrogels chemically dual cross-linked by using low- and high-molecular-weight cross-linkers. Biomacromolecules. 2019;20(5):1989-95. doi: 10.1021/acs.biomac.9b00204.
59. Ye D, Lei X, Li T, Cheng Q, Chang C, Hu L, et al. Ultrahigh tough, super clear, and highly anisotropic nanofiber-structured regenerated cellulose films. ACS Nano. 2019;13(4):4843-53. doi: 10.1021/acsnano.9b02081.
60. Costa PF, Vaquette C, Zhang Q, Reis RL, Ivanovski S, Hutmacher DW. Advanced tissue engineering scaffold design for regeneration of the complex hierarchical periodontal structure. J Clin Periodontol. 2014;41(3):283-94. doi: 10.1111/jcpe.12214.
61. Lian M, Han Y, Sun B, Xu L, Wang X, Ni B, et al. A multifunctional electrowritten bi-layered scaffold for guided bone regeneration. Acta Biomater. 2020;118:83-99. doi: 10.1016/j.actbio.2020.08.017.
62. Lee CH, Hajibandeh J, Suzuki T, Fan A, Shang P, Mao JJ. Three-dimensional printed multiphase scaffolds for regeneration of periodontium complex. Tissue Eng Part A. 2014;20(7-8):1342-51. doi: 10.1089/ten.TEA.2013.0386.
63. Sowmya S, Mony U, Jayachandran P, Reshma S, Kumar RA, Arzate H, et al. Tri-layered nanocomposite hydrogel scaffold for the concurrent regeneration of cementum, periodontal ligament, and alveolar bone. Adv Healthc Mater. 2017;6(7):1601251. doi: 10.1002/adhm.201601251.
64. Soldatos NK, Stylianou P, Koidou VP, Angelov N, Yukna R, Romanos GE. Limitations and options using resorbable versus nonresorbable membranes for successful guided bone regeneration. Quintessence Int. 2017;48(2):131-47. doi: 10.3290/j.qi.a37133.
65. Bottino MC, Thomas V, Schmidt G, Vohra YK, Chu TM, Kowolik MJ, et al. Recent advances in the development of GTR/GBR membranes for periodontal regeneration--a materials perspective. Dent Mater. 2012;28(7):703-21. doi: 10.1016/j.dental.2012.04.022.
66. Sam G, Pillai BR. Evolution of barrier membranes in periodontal regeneration-"are the third generation membranes really here?". J Clin Diagn Res. 2014;8(12):ZE14-7. doi: 10.7860/jcdr/2014/9957.5272.
67. Tan J, Zhang M, Hai Z, Wu C, Lin J, Kuang W, et al. Sustained release of two bioactive factors from supramolecular hydrogel promotes periodontal bone regeneration. ACS Nano. 2019;13(5):5616-22. doi: 10.1021/acsnano.9b00788.
68. Mou J, Liu Z, Liu J, Lu J, Zhu W, Pei D. Hydrogel containing minocycline and zinc oxide-loaded serum albumin nanopartical for periodontitis application: preparation, characterization and evaluation. Drug Deliv. 2019;26(1):179-87. doi: 10.1080/10717544.2019.1571121.
69. Chichiricco PM, Riva R, Thomassin JM, Lesoeur J, Struillou X, Le Visage C, et al. In situ photochemical crosslinking of hydrogel membrane for guided tissue regeneration. Dent Mater. 2018;34(12):1769-82. doi: 10.1016/j.dental.2018.09.017.
70. Liu J, Xiao Y, Wang X, Huang L, Chen Y, Bao C. Glucose-sensitive delivery of metronidazole by using a photo-crosslinked chitosan hydrogel film to inhibit Porphyromonas gingivalis proliferation. Int J Biol Macromol. 2019;122:19-28. doi: 10.1016/j.ijbiomac.2018.09.202.
71. Chen N, Ren R, Wei X, Mukundan R, Li G, Xu X, et al. Thermoresponsive hydrogel-based local delivery of simvastatin for the treatment of periodontitis. Mol Pharm. 2021;18(5):1992-2003. doi: 10.1021/acs.molpharmaceut.0c01196.
72. Wang B, Booij-Vrieling HE, Bronkhorst EM, Shao J, Kouwer PHJ, Jansen JA, et al. Antimicrobial and anti-inflammatory thermo-reversible hydrogel for periodontal delivery. Acta Biomater. 2020;116:259-67. doi: 10.1016/j.actbio.2020.09.018.
73. Pan J, Deng J, Luo Y, Yu L, Zhang W, Han X, et al. Thermosensitive hydrogel delivery of human periodontal stem cells overexpressing platelet-derived growth factor-BB enhances alveolar bone defect repair. Stem Cells Dev.

2019;28(24):1620-31. doi: 10.1089/scd.2019.0184.
74. Nagy K, Láng O, Láng J, Perczel-Kovách K, Gyulai-Gaál S, Kádár K, et al. A novel hydrogel scaffold for periodontal ligament stem cells. Interv Med Appl Sci. 2018;10(3):162-70. doi: 10.1556/1646.10.2018.21.
75. Fraser D, Nguyen T, Benoit DSW. Matrix control of periodontal ligament cell activity via synthetic hydrogel scaffolds. Tissue Eng Part A. 2021;27(11-12):733-47. doi: 10.1089/ten.TEA.2020.0278.
76. Shen Z, Kuang S, Zhang Y, Yang M, Qin W, Shi X, et al. Chitosan hydrogel incorporated with dental pulp stem cell-derived exosomes alleviates periodontitis in mice via a macrophage-dependent mechanism. Bioact Mater. 2020;5(4):1113-26. doi: 10.1016/j.bioactmat.2020.07.002.
77. Liu L, Guo S, Shi W, Liu Q, Huo F, Wu Y, et al. Bone marrow mesenchymal stem cell-derived small extracellular vesicles promote periodontal regeneration. Tissue Eng Part A. 2021;27(13-14):962-76. doi: 10.1089/ten.TEA.2020.0141.
78. Zhang H, Liu S, Zhu B, Xu Q, Ding Y, Jin Y. Composite cell sheet for periodontal regeneration: crosstalk between different types of MSCs in cell sheet facilitates complex periodontal-like tissue regeneration. Stem Cell Res Ther. 2016;7(1):168. doi: 10.1186/s13287-016-0417-x.
79. Yang H, Li J, Hu Y, Sun J, Guo W, Li H, et al. Treated dentin matrix particles combined with dental follicle cell sheet stimulate periodontal regeneration. Dent Mater. 2019;35(9):1238-53. doi: 10.1016/j.dental.2019.05.016.
80. Zhao B, Chen J, Zhao L, Deng J, Li Q. A simvastatin-releasing scaffold with periodontal ligament stem cell sheets for periodontal regeneration. J Appl Biomater Funct Mater. 2020;18:2280800019900094. doi: 10.1177/2280800019900094.
81. Park JY, Park CH, Yi T, Kim SN, Iwata T, Yun JH. rhBMP-2 pre-treated human periodontal ligament stem cell sheets regenerate a mineralized layer mimicking dental cementum. Int J Mol Sci. 2020;21(11):3767. doi: 10.3390/ijms21113767.
82. Amir LR, Soeroso Y, Fatma D, Sunarto H, Sulijaya B, Idrus E, et al. Periodontal ligament cell sheets and RGD-modified chitosan improved regeneration in the horizontal periodontal defect model. Eur J Dent. 2020;14(2):306-14. doi: 10.1055/s-0040-1709955.
83. Yang X, Xiong X, Zhou W, Feng G, Zhang Y, Dai H, et al. Effects of human urine-derived stem cells on the cementogenic differentiation of indirectly-cocultured periodontal ligament stem cells. Am J Transl Res. 2020;12(2):361-78.
84. Safi IN, Mohammed Ali Hussein B, Al-Shammari AM. In vitro periodontal ligament cell expansion by co-culture method and formation of multi-layered periodontal ligament-derived cell sheets. Regen Ther. 2019;11:225-39. doi: 10.1016/j.reth.2019.08.002.
85. Raju R, Oshima M, Inoue M, Morita T, Huijiao Y, Waskitho A, et al. Three-dimensional periodontal tissue regeneration using a bone-ligament complex cell sheet. Sci Rep. 2020;10(1):1656. doi: 10.1038/s41598-020-58222-0.
86. Jiang Y, Liu JM, Huang JP, Lu KX, Sun WL, Tan JY, et al. Regeneration potential of decellularized periodontal ligament cell sheets combined with 15-deoxy-Δ(12,14)-prostaglandin J2 nanoparticles in a rat periodontal defect. Biomed Mater. 2021;16(4):045008. doi: 10.1088/1748-605X/abee61.
87. Jamróz W, Szafraniec J, Kurek M, Jachowicz R. 3D printing in pharmaceutical and medical applications - recent achievements and challenges. Pharm Res. 2018;35(9):176. doi: 10.1007/s11095-018-2454-x.
88. Zhang L, Yang G, Johnson BN, Jia X. Three-dimensional 3D printed scaffold and material selection for bone repair. Acta Biomater. 2019;84:16-33. doi: 10.1016/j.actbio.2018.11.039.
89. Zhang YS, Duchamp M, Oklu R, Ellisen LW, Langer R, Khademhosseini A. Bioprinting the cancer microenvironment. ACS Biomater Sci Eng. 2016;2(10):1710-21. doi: 10.1021/acsbiomaterials.6b00246.
90. Brunello G, Sivolella S, Meneghello R, Ferroni L, Gardin C, Piattelli A, et al. Powder-based 3D printing for bone tissue engineering. Biotechnol Adv. 2016;34(5):740-53. doi: 10.1016/j.biotechadv.2016.03.009.
91. Thattaruparambil Raveendran N, Vaquette C, Meinert C, Samuel Ipe D, Ivanovski S. Optimization of 3D bioprinting of periodontal ligament cells. Dent Mater. 2019;35(12):1683-94. doi: 10.1016/j.dental.2019.08.114.
92. Valot L, Martinez J, Mehdi A, Subra G. Chemical insights into bioinks for 3D printing. Chem Soc Rev. 2019;48(15):4049-86. doi: 10.1039/c7cs00718c.
93. Zhu C, Pascall AJ, Dudukovic N, Worsley MA, Kuntz JD, Duoss EB, et al. Colloidal materials for 3D printing. Annu Rev Chem Biomol Eng. 2019;10:17-42. doi: 10.1146/annurev-chembioeng-060718-030133.
94. Chen MY, Skewes J, Desselle M, Wong C, Woodruff MA, Dasgupta P, et al. Current applications of three-dimensional printing in urology. BJU Int. 2020;125(1):17-27. doi: 10.1111/bju.14928.
95. Wang C, Huang W, Zhou Y, He L, He Z, Chen Z, et al. 3D printing of bone tissue engineering scaffolds. Bioact Mater. 2020;5(1):82-91. doi: 10.1016/j.bioactmat.2020.01.004.
96. Cheng GZ, San Jose Estepar R, Folch E, Onieva J, Gangadharan S, Majid A. Three-dimensional printing and 3D slicer: powerful tools in understanding and treating structural lung disease. Chest. 2016;149(5):1136-42. doi: 10.1016/j.chest.2016.03.001.
97. Lee JW, Chu SG, Kim HT, Choi KY, Oh EJ, Shim JH, et al. Osteogenesis of adipose-derived and bone marrow stem cells with polycaprolactone/tricalcium phosphate and three-dimensional printing technology in a dog model of maxillary bone defects. Polymers (Basel). 2017;9(9):450. doi: 10.3390/polym9090450.
98. Guldberg RE. Spatiotemporal delivery strategies for promoting musculoskeletal tissue regeneration. J Bone Miner Res. 2009;24(9):1507-11. doi: 10.1359/jbmr.090801.
99. Mao JJ, Giannobile WV, Helms JA, Hollister SJ, Krebsbach PH, Longaker MT, et al. Craniofacial tissue engineering by stem cells. J Dent Res. 2006;85(11):966-79. doi: 10.1177/154405910608501101.
100. Place ES, Evans ND, Stevens MM. Complexity in biomaterials for tissue engineering. Nat Mater. 2009;8(6):457-70. doi: 10.1038/nmat2441.
101. Spalazzi JP, Dagher E, Doty SB, Guo XE, Rodeo SA, Lu HH. In vivo evaluation of a multiphased scaffold designed for orthopaedic interface tissue engineering and soft tissue-to-bone integration. J Biomed Mater Res A. 2008;86(1):1-12. doi: 10.1002/jbm.a.32073.
102. Yang PJ, Temenoff JS. Engineering orthopedic tissue interfaces. Tissue Eng Part B Rev. 2009;15(2):127-41. doi: 10.1089/ten.teb.2008.0371.
103. Wang DA, Varghese S, Sharma B, Strehin I, Fermanian S, Gorham J, et al. Multifunctional chondroitin sulphate for cartilage tissue-biomaterial integration. Nat Mater. 2007;6(5):385-92. doi: 10.1038/nmat1890.
104. Park CH, Kim KH, Rios HF, Lee YM, Giannobile WV, Seol YJ. Spatiotemporally controlled microchannels of periodontal mimic scaffolds. J Dent Res. 2014;93(12):1304-12. doi: 10.1177/0022034514550716.
105. Deville S, Saiz E, Nalla RK, Tomsia AP. Freezing as a path to build complex composites. Science. 2006;311(5760):515-8. doi: 10.1126/science.1120937.
106. Ma H, Hu J, Ma PX. Polymer scaffolds for small-diameter vascular tissue engineering. Adv Funct Mater. 2010;20(17):2833-41. doi: 10.1002/adfm.201000922.
107. Deville S, Saiz E, Tomsia AP. Freeze casting of

hydroxyapatite scaffolds for bone tissue engineering. Biomaterials. 2006;27(32):5480-9. doi: 10.1016/j.biomaterials.2006.06.028.
108. Pilipchuk SP, Monje A, Jiao Y, Hao J, Kruger L, Flanagan CL, et al. Integration of 3D printed and micropatterned polycaprolactone scaffolds for guidance of oriented collagenous tissue formation in vivo. Adv Healthc Mater. 2016;5(6):676-87. doi: 10.1002/adhm.201500758.
109. Jiang W, Li L, Zhang D, Huang S, Jing Z, Wu Y, et al. Incorporation of aligned PCL-PEG nanofibers into porous chitosan scaffolds improved the orientation of collagen fibers in regenerated periodontium. Acta Biomater. 2015;25:240-52. doi: 10.1016/j.actbio.2015.07.023.
110. Washio K, Tsutsumi Y, Tsumanuma Y, Yano K, Srithanyarat SS, Takagi R, et al. In vivo periodontium formation around titanium implants using periodontal ligament cell sheet. Tissue Eng Part A. 2018;24(15-16):1273-82. doi: 10.1089/ten.TEA.2017.0405.
111. Lee UL, Yun S, Cao HL, Ahn G, Shim JH, Woo SH, et al. Bioprinting on 3D printed titanium scaffolds for periodontal ligament regeneration. Cells. 2021;10(6):1337. doi: 10.3390/cells10061337.
112. Rasperini G, Pilipchuk SP, Flanagan CL, Park CH, Pagni G, Hollister SJ, et al. 3D-printed bioresorbable scaffold for periodontal repair. J Dent Res. 2015;94(9 Suppl):153S-7S. doi: 10.1177/0022034515588303.
113. Xu X, Gu Z, Chen X, Shi C, Liu C, Liu M, et al. An injectable and thermosensitive hydrogel: Promoting periodontal regeneration by controlled-release of aspirin and erythropoietin. Acta Biomater. 2019;86:235-46. doi: 10.1016/j.actbio.2019.01.001.
114. Yoshida W, Matsugami D, Murakami T, Bizenjima T, Imamura K, Seshima F, et al. Combined effects of systemic parathyroid hormone (1-34) and locally delivered neutral self-assembling peptide hydrogel in the treatment of periodontal defects: an experimental in vivo investigation. J Clin Periodontol. 2019;46(10):1030-40. doi: 10.1111/jcpe.13170.
115. Pei Y, Ye D, Zhao Q, Wang X, Zhang C, Huang W, et al. Effectively promoting wound healing with cellulose/gelatin sponges constructed directly from a cellulose solution. J Mater Chem B. 2015;3(38):7518-28. doi: 10.1039/c5tb00477b.
116. Zhang T, Cheng Q, Ye D, Chang C. Tunicate cellulose nanocrystals reinforced nanocomposite hydrogels comprised by hybrid cross-linked networks. Carbohydr Polym. 2017;169:139-48. doi: 10.1016/j.carbpol.2017.04.007.
117. Zou J, Wu S, Chen J, Lei X, Li Q, Yu H, et al. Highly efficient and environmentally friendly fabrication of robust, programmable, and biocompatible anisotropic, all-cellulose, wrinkle-patterned hydrogels for cell alignment. Adv Mater. 2019;31(46):e1904762. doi: 10.1002/adma.201904762.
118. Huang Q, Li Y, Fan L, Xin JH, Yu H, Ye D. Polymorphic calcium alginate microfibers assembled using a programmable microfluidic field for cell regulation. Lab Chip. 2020;20(17):3158-66. doi: 10.1039/d0lc00517g.
119. de Jong T, Bakker AD, Everts V, Smit TH. The intricate anatomy of the periodontal ligament and its development: Lessons for periodontal regeneration. J Periodontal Res. 2017;52(6):965-74. doi: 10.1111/jre.12477.
120. Arzate H, Zeichner-David M, Mercado-Celis G. Cementum proteins: role in cementogenesis, biomineralization, periodontium formation and regeneration. Periodontol 2000. 2015;67(1):211-33. doi: 10.1111/prd.12062.
121. Arroyo R, López S, Romo E, Montoya G, Hoz L, Pedraza C, et al. Carboxy-terminal cementum protein 1-derived peptide 4 (CEMP1-p4) promotes mineralization through Wnt/β-catenin signaling in human oral mucosa stem cells. Int J Mol Sci. 2020;21(4):1307. doi: 10.3390/ijms21041307.
122. Komaki M, Iwasaki K, Arzate H, Narayanan AS, Izumi Y, Morita I. Cementum protein 1 (CEMP1) induces a cementoblastic phenotype and reduces osteoblastic differentiation in periodontal ligament cells. J Cell Physiol. 2012;227(2):649-57. doi: 10.1002/jcp.22770.
123. Choi H, Jin H, Kim JY, Lim KT, Choung HW, Park JY, et al. Hypoxia promotes CEMP1 expression and induces cementoblastic differentiation of human dental stem cells in an HIF-1-dependent manner. Tissue Eng Part A. 2014;20(1-2):410-23. doi: 10.1089/ten.TEA.2013.0132.
124. Correa R, Arenas J, Montoya G, Hoz L, López S, Salgado F, et al. Synthetic cementum protein 1-derived peptide regulates mineralization in vitro and promotes bone regeneration in vivo. Faseb j. 2019;33(1):1167-78. doi: 10.1096/fj.201800434RR.