Biomimetics - A Niche for Bioinspiration in Endodontics

Preethesh Shetty[1], Ashish Shetty[2], Deep Shah[3], Neha Prakash[3], Safat Sadiq[4], Mohammad Shahid[2], Vinit Patel[1], Raksha Bhat[1]

1. Nitte (Deemed to be University), AB Shetty Memorial Institute of Dental Sciences(ABSMIDS), Department of Conservative Dentistry and Endodontics, Mangaluru, Karnataka, India.
2. A.J.Shetty Institute of Dental Sciences, Mangaluru, Karnataka, India.
3. Bharatiya Vidyapeeth deemed to be University Dental College & Hospital, Sangli.
4. Rekha Dental Centre, UAE.

Abstract

Biomimetic approaches have been widely implemented in several biomedical sectors, including clinical dentistry, over the previous few decades. Endodontics is a speciality of dentistry that deals with various pulp disorders to prevent tooth loss. Traditional methods have included pulp capping, root canal therapy, apexification, and apexogenesis employing specific dental materials. Tissue engineering, on the other hand, has been proposed as a viable clinical strategy to regenerate tooth pulp.

New developments in regenerative endodontics are emerging, resulting in the replacement of diseased and non-vital teeth into a functioning and healthy dentine-pulp complex. Root canal therapy is the standard treatment choice when the tooth pulp is irreversibly injured. This treatment modality entails removing soft tissue and replacing the resulting space with a synthetic material employing the obturation procedure. When stem cells are injected into the root canal with an appropriate scaffold material, tubular dentine and pulp-like tissue development ensues.

The present review aims to examine various biomimetic techniques in regenerative endodontics to highlight current trends and future research potential in this field.

Review (J Int Dent Med Res 2023; 16(3): 1355-1360)

Keywords: Biomimetics, Bioinspiration, endodontics, regeneration, tissue engineering.

Received date: 07 July 2023 **Accept date:** 15 August 2023

Introduction

Biomimetics is a term instituted by Otto Schmitt during the 1950s while contemplating the nerves in a squid. He endeavoured to duplicate and plan an artificial device that could reproduce a similar procedure of synaptic impulse. Biomimetics is characterized as the investigation of the development, structure, or capacity of organically created substances, materials, biological mechanisms, and processes mainly to synthesize artificial items which mimic natural processes. A material manufactured by a biomimetic strategy dependent on regular processes found in natural frameworks is known as a biomimetic material[1].

***Corresponding author:**
Dr. Raksha Bhat, Reader,
Nitte (Deemed to be University), AB Shetty Memorial Institute Of Dental Sciences(ABSMIDS), Department of Conservative Dentistry And Endodontics, Mangaluru, Karnataka, India.
E-mail: drrakshabhat@nitte.edu.in

Biomimicry or biomimetics includes examining nature's best improvements and afterwards mirroring these plans to make new materials. The primary burden with conventional biomaterials utilized in the therapeutic field is that they cannot incorporate with organic frameworks through a cell pathway which can prompt the failure of the material. A biomimetic way to re-establish tooth structure depends on regenerative endodontic methodology by utilising tissue engineering[2].

Biomimetic materials in tissue engineering are materials that have been structured to such an extent that they evoke determined cell reactions intervened by scaffold tethered peptides from extracellular matrix (ECM) proteins; basically, the incorporation of cell-binding peptides into biomaterials through chemical or physical modification. Host-determined molecules are utilized to increase or enhance wound healing, repair and even regeneration of soft and hard tissues. In clinical dentistry, we are tested to plan and create new biomaterials-bone, ligament, dentin, enamel, and periodontal ligament and to give new diagnostics and gene-mediated therapeutics for various oral and systemic infections and disorders[3,4.]

BIOMIMETIC CONCEPTS IN ENDODONTICS

Current therapies use bone morphogenetic proteins and some other growth factors for regenerating hard and soft tissues, including dentin, cementum, bone and periodontal ligament[5]. The benefit of biomimetics, when extended to a macro-structural level, is that it can trigger innovative principles in restorative dentistry. Three procedures have been embraced for the formation of new tissues by mimicking normal biological processes, namely, the utilization of isolated cells or cell substitutes, the addition of biologic tissue inducing molecules such as morphogenetic molecules and the utilization of individual or groups of cells placed on or within biocompatible matrices[6]. A biomimetic approach to restoring tooth structure is based on regenerative endodontic procedures by application of tissue engineering, which opens up a whole new arena for the practitioner[21]. The key elements of tissue engineering are stem cells, morphogens, and a scaffold of the extracellular matrix[7].

Stem cells : Stem cells can continuously divide and produce progeny cells that develop into other cells or tissues. There are two significant types of stem cells, Embryonic and Adult stem cells; their most important properties are their ability to self-renewal and their ability to grow in-vitro. Comparing the different stem cell types, adult stem cells, which have the least amount of ethical concerns, are presently being used in medical therapies and are readily accessible. Postnatal stem cells have been found in almost all body tissues, including dental tissues. To date, eight types of human dental stem cells have been isolated and characterized: Dental pulp stem cells (DPSCs), Stem cells from human exfoliated deciduous teeth (SHED), Stem cells from apical papillae (SCAP), Periodontal ligament stem cells (PDLSCs), Epithelium-originated dental stem cells (EpSC), Mesenchymal stem cells (BMSC), Stem cells from the dental follicle (DFSC), and Endothelial progenitor cells (EPCs)[8,9].

Applications of Bone morphogenic proteins In Dentin Pulp Regeneration: Signalling molecules or morphogens are extracellular secreted signalling molecules that play a crucial role in signalling many of the events of repair and regeneration, including tertiary dentinogenesis, a response of pulp-dentin repair[10]. Growth factors are soluble proteins that act as signalling agents for cells and influence critical functions, such as cell division, matrix synthesis, and tissue differentiation. Primarily, five eminent families of growth factors appear to regulate the process of odontogenesis: Fibroblast growth factor, Bone morphogenic protein (BMP), Hedgehog, Wingless (WNT) and Transforming growth factor[11]. There is evidence suggesting that if the odontoblasts are lost due to cavities, the formation of new pulp cells can be stimulated by the presence of BMPs. These proteins exist in odontoblasts, ameloblasts and the dentin matrix, being capable of inducing undifferentiated pulp cells into odontoblast-like cells — the molecules that belong to the BMPs group act as important signalling molecules, both in dental development as in reparatory processes, stimuli in mature tooth tissue, being isolated initially from the osseous cell-matrix and having the capability to induce ectopically osseous formation[12]. BMP-2 and BMP-4 induce the expression of Msx-I and Msx-2 genes, which function as transcription factors controlling the transcription of other genes, suggesting the widespread signalling functions of' BMP-2 and BMP-4 in morphogenesis and organogenesis[11]. Clarkson et al. reported that, of all studies conducted on animals, with BMPs extracted from purified and recombining BMP-7, these proteins presented as capable of regenerating tubular and intratubular dentin when used on vital exposed pulp[12]. Lianjia et al. reported that a week after pulp protection with BMP, a small sign of inflammation was found; however, at the end of the second week, these signs were gone, and a substantial amount of dentin and osteopontin was observed, being well distinguished in two regions, in the osteopontin and the regular dentin surrounded by osteopontin areas. At the beginning of the third week, dentin formation was inducted, the dentin bridge was completely formed, and the calcification process started[13].

For clinical application, it is essential to the efficiency of the carrying material, which should promote bioaccessibility to the host tissues of the BMP and ensure its uniform and gradual distribution. Among the tested biomaterials as carriers include various extracellular matrix components, combined or isolated, calcium hydrate and calcium phosphate. The structure or the molecular organization of the carrier can contribute to cell guidance and facilitate the reparatory and regenerating process in the newly formed tissues[11]. These morphogenetic factors induce a large amount of dentin on the amputated pulp without affecting the remaining pulp. Inflammatory cytokines are molecules that control the cell behaviour of bone under inflammation, infection and wound healing. The scaffold or the extracellular matrix is a blend of proteins, including collagen, fibronectin, polysaccharide hyaluronic acid, proteoglycans, and laminins, shaping an elastic network surrounding most cells and tissue structures[11-13].

Current scaffolds : The current scaffolds used in tissue engineering can be grouped into three main categories; natural scaffolds, mineral-based scaffolds and synthetic scaffolds. Collagen, lyophilized bone and coral are the most commonly used natural scaffold. The main disadvantage of natural scaffolds is that they often need more structural integrity for their independent use in load-bearing areas. Mineral-based scaffolds usually are made of calcium phosphates in the form of hydroxyapatite or beta Tricalcium phosphate, and by varying the content of calcium, the rate of degradation of these scaffolds can be controlled. They lack the strength of natural scaffolds and are brittle, making them susceptible to fracture, and hence were introduced the synthetic scaffolds. These include porous ceramics, spongiosis collagen, fibrous titanium mesh, poly lactic acid (PLA), polyglycolic acid (PGA), and their copolymers, poly lactic-co-glycolic acid (PLGA), which are all polyester material that degrades within the human body. They have the advantage of being able to function in load bearing but have the disadvantage of lacking osteoinductiveness and the inherent difficulty in obtaining high porosity and regular pore size. This has led researchers to concentrate efforts to engineer scaffolds at the nanostructural level to modify cellular interactions with the scaffold[14].

BIOMIMETIC APPROACHES FOR REGENERATION

Creating and conveying new tissues to replace infected, missing or damaged pulp is alluded to as regenerative endodontics. In any case, the test lies in structuring and manufacturing biomimetic materials like enamel, dentin, cementum, pulp, bone, and periodontal ligament and the focus ought to be on recovering the diseased and necrotic tissues as opposed to replacing them with some conventional substitution materials. Current biomimetic approaches for the recovery of the tooth and its related structures are:

Root canal revascularization : Treatment of the young permanent tooth with a necrotic root canal system and an incompletely developed root is laden with difficulty. The root canal system is frequently hard to completely debride, and the thin dentinal walls increase the risk of a consequent break. Other than the procedure like neurogenesis or acetogenesis, root canal revascularization is a methodology to establish the vitality in a non-vital tooth to permit the repair and regeneration of tissues. The typical revascularization protocol advocates that the immature tooth, diagnosed to have apical periodontitis, ought to be accessed to and irrigated with either 5% NaOCl _ 3% H2O2 or 5.25% NaOCl and Peridex TM (Procter and Gamble, Cincinnati, OH. An antimicrobial agent (either an antibiotic such as metronidazole, ciprofloxacin or ciprofloxacin, metronidazole, minocycline or Ca (OH)2 should be then applied into the root canal system, and the access cavity is sealed. After an average of 3 weeks, in the absence of symptoms, the tooth is reentered, the tissue is irritated until bleeding is started and a blood clot is produced, and then MTA is placed over the blood clot, and the access is sealed. Within the next two years, a gradual increase in root development can be observed. However, revascularization procedures need more standardization of treatment protocols with a myriad of reported techniques, intracanal medicaments and irrigants[15].

Stem cell therapy: The simplest method to administer cells of appropriate regenerative potential is to inject the postnatal stem cells into the disinfected root canal system. Autologous dental stem cells are the most accessible stem cells for this therapy. The eight different postnatal dental stem cells are; Dental pulp stem cells (DPSCs), Stem cells from human exfoliated deciduous teeth (SHED), and Stem cells from the apical papilla (SCAP), more commonly used in the field of regenerative endodontics[41]. The most striking feature of DPSCs is their ability to regenerate a dentin-pulp-like complex that is composed of a mineralized matrix with tubules lined with odontoblasts and fibrous tissue containing blood vessels in an arrangement similar to the dentin-pulp complex found in regular human teeth. The use of SHED might bring advantages for tissue engineering over the use of stem cells from adult human teeth as follows: SHED was reported to have a higher proliferation rate compared with stem cells from permanent teeth, which might facilitate the expansion of these cells in vitro before replantation, SHED cells are retrieved from a tissue that is "disposable" and readily accessible in young patients. It also has the added advantage of abundant cell supply and painless stem cell collection with minimal invasion. In contrast, DPSCs are likely the source of replacement odontoblast. Since these stem cells are in the apical papilla, they are benefited by its collateral circulation, which enables it to survive during the process of pulp necrosis[16,17].

Pulp implantation: In pulp implantation, replacement pulp tissue is created by tissue engineering triad and is transplanted into cleaned and formed root canal systems[45]. One of the potential issues related to the implantation of the cultured pulp tissue is that specific methods might be required to guarantee that the cells legitimately stick to root canal walls. While implanting pulp into the root canals that have blood supply just from the apical end, improved vascularization is required to help its imperativeness. Ongoing endeavours in creating scaffold systems for tissue engineering have been concentrating on making a system that advances angiogenesis for the development of a vascular network. These frameworks are impregnated with growth factors, for example, VEGF (vascular endothelial growth factor) and platelet-derived growth factor or, further, with the expansion of endothelial cells[18,19].

Injectable scaffold delivery :Rigid tissue-engineered scaffold structures help cells utilized in bone and other body regions where the designed tissue is required to give physical support. This will permit tissue-engineered pulp tissue to be controlled in a soft three-dimensional scaffold matrix. Among the injectable biomaterials researched up until now, hydrogels are increasingly alluring in the field of tissue engineering. Hydrogels are injectable platforms that can be conveyed by syringe and can be non-invasive and straightforward to convey into root canal systems. In principle, the hydrogel may advance pulp recovery by giving a substrate for cell proliferation and differentiation into a composed tissue structure[20].

Three-dimensional cell printing : A standout amongst the most encouraging methodologies in tissue designing is the utilization of a 3D scaffold, which gives cell support and direction in the underlying tissue formation stage. The porosity of the framework and inward pore organization affect cell movement and assume a noteworthy job in its biodegradation dynamics, nutrient diffusion, and mechanical stability. To control cell migration and cell interactions inside the scaffold, novel advances fit for delivering 3D structures as per predefined configuration are required[21]. In principle, an ink-jet-like gadget is utilized to administer layers of cells suspended in a hydrogel to reproduce the structure of the tooth pulp tissue. The three-dimensional cell printing strategy can be utilized to position cells correctly, and this technique can make tissue builds that impersonate the natural tooth pulp tissue structure. This may include situating odontoblasts around the periphery, with fibroblasts in the centre. The real test included is the exact orientation of cell suspensions as indicated by the apical and coronal asymmetry of the pulp. Hypothetically, the inconvenience of utilizing the three-dimensional cell printing method is that watchful orientation of the pulp tissue build, as indicated by its apical and coronal asymmetry, would be required amid arrangement into cleaned and formed root canal systems[22].

Gene Therapy: Gene therapy is a technique for conveying genes with viral or nonviral vectors. The gene conveyance in Endodontics is to convey mineralizing genes into pulp tissue to advance tissue mineralization. Viral vectors are hereditarily modified to take out the capacity to cause disease without losing the infectious capacity of the cell. Nonviral delivery systems utilize plasmids, peptides, cationic liposomes, DNA-ligand complex, gene guns, electroporation, and sonoporation to address safety concerns, for example, immunogenicity and mutagenesis. Across the broad clinical application, it still anticipates the advancement of vectors that are safe, affordable, effective, essential for application, and that can the express the required level of the transgene for the suitable long term. In the in vivo approach, the gene is delivered systemically into the circulation system or locally to target tissues by infusion or inhalation. The ex vivo approach includes genetic manipulation of cells in vitro transplanted to the regeneration site. The primary difficulties for gene therapy in the following decade will be the prerequisites to exhibit that gene therapy can give cost-effective and safe long-term treatments for conditions that would otherwise lead to significant pulp necrosis. This indicates the potential of adding growth factors before pulp capping or incorporating them into restorative and endodontic materials to stimulate dentin and pulp regeneration[23].

Bioengineered tooth: A definitive objective of regenerative treatment is to develop fully functional bioengineered organs that can supplant lost or harmed organs following disease, damage, or ageing. Research on the manufacture of teeth from dissociated cells was first performed utilizing tooth germ cells. Whenever explanted, seeded with porcine third affected tooth bud cells, were embedded for 20-30 weeks into cementum, bioengineered teeth were noticeable inside the explants. In any case, the regenerated teeth were not indistinguishable from their naturally formed counterparts[24,25]. Ikeda et al. reported a fully functioning tooth replacement achieved by transplanting a bioengineered tooth germ into an adult mouse's alveolar bone of a lost tooth region. Bioengineered tooth, which was erupted and occluded, had the correct tooth structure, hardness of mineralized tissues for mastication. However, the bioengineered tooth was smaller than the other regular teeth. Also, the authors could not regulate the crown width, cusp position, and tooth patterning, including anterior/posterior and buccal/lingual structures. However, in a more recent study, Oshima et al. showed that the crown widths and the cusp numbers of bioengineered molar could be regulated by the cell manipulation method[26]. Tooth regeneration is an important stepping stone in establishing engineered organ transplantation, which is one of the ultimate goals of regenerative therapies.

Conclusions

The practice of endodontics has grown by leaps and bounds in the past few decades. Replacement of diseased or lost tooth structure with biocompatible restorative materials is currently the order of today, but each of these procedures does have its limitations and drawbacks. Regeneration of the lost tooth structure rather than replacement during treatment will ensure a better prognosis and higher success rate. Hence the future of Endodontics would involve the use of such biomimetic materials which could successfully replace lost enamel, dentine, cementum and even the pulp tissue.

The potentials for the future as individuals live longer and demand higher quality-of life standards are endless and exciting. Nanotechnology has provided chemical molecules to fabricate submicroscopic structures. Tissue engineering provides us with the prospect of using our cells or related cells to renovate, replace, or regenerate dysfunctional organs or tissues. This new era of biomimetics provides the opportunity to introduce and change treatment modalities for many diseases and disorders. By its nature, it is interdisciplinary, and it has tremendous potential for transforming everyday dental practice. Only tight collaborations between engineers, chemists, tissue engineers, material scientists, and biologists will make these next-generation materials a reality.

Declaration of Interest

The authors report no conflict of interest.

References

1. Harkness J.M. An idea man (the life of Otto Herbert Schmitt) *IEEE Eng. Med. Biol. Mag.* 2004;23:20–41. doi: 10.1109/MEMB.2004.1378631.
2. Zafar MS, Amin F, Fareed MA, Ghabbani H, Riaz S, Khurshid Z, Kumar N. Biomimetic Aspects of Restorative Dentistry Biomaterials. Biomimetics (Basel). 2020 Jul 15;5(3):34. doi: 10.3390/biomimetics5030034.
3. Deb S, Chana S. Biomaterials in Relation to Dentistry. Front Oral Biol. 2015;17:1-12. doi: 10.1159/000381686.
4. Diesendruck CE, Sottos NR, Moore JS, White SR. Biomimetic Self-Healing. Angew Chem Int Ed Engl. 2015 Sep 1;54(36):10428-47. doi: 10.1002/anie.201500484.
5. Galli M, Yao Y, Giannobile WV, Wang HL. Current and future trends in periodontal tissue engineering and bone regeneration. Plastic and Aesthetic Research. 2021; 8: 3. http://dx.doi.org/10.20517/2347-9264.2020.176
6. Albuquerque MT, Valera MC, Nakashima M, Nör JE, Bottino MC. Tissue-engineering-based strategies for regenerative endodontics. J Dent Res. 2014 Dec;93(12):1222-31. doi: 10.1177/0022034514549809.
7. Liu H, Lu J, Jiang Q, Haapasalo M, Qian J, Tay FR, Shen Y. Biomaterial scaffolds for clinical procedures in endodontic regeneration. Bioact Mater. 2021 Oct 14;12:257-277. doi: 10.1016/j.bioactmat.2021.10.008.
8. Saito MT, Silvério KG, Casati MZ, Sallum EA, Nociti FH Jr. Tooth-derived stem cells: Update and perspectives. World J Stem Cells. 2015 Mar 26;7(2):399-407. doi: 10.4252/wjsc.v7.i2.399.

9. Volponi AA, Pang Y, Sharpe PT. Stem cell-based biological tooth repair and regeneration. Trends Cell Biol. 2010 Dec;20(12):715-22. doi: 10.1016/j.tcb.2010.09.012.
10. Galler KM, Weber M, Korkmaz Y, Widbiller M, Feuerer M. Inflammatory Response Mechanisms of the Dentine-Pulp Complex and the Periapical Tissues. Int J Mol Sci. 2021 Feb 2;22(3):1480. doi: 10.3390/ijms22031480.
11. Tureckvá J, Sahlberg C, Aberg T, Ruch JV, Thesleff I, Peterkova R. Comparison of expression of the msx-1, msx-2, BMP-2 and BMP-4 genes in the mouse upper diastemal and molar tooth primordia. Int J Dev Biol. 1995 Jun;39(3):459-68.
12. Clarkson BH, Rafter ME. Emerging methods used in the prevention and repair of carious tissues. J Dent Educ. 2001 Oct;65(10):1114-20.
13. Lianjia, Y.; Yuhao, G. & White, F.H. Bovine bone morphogenetic protein-induced dentinogenesis. Clin. Orthop. Rel. Res., 295:305-12, 1993.
14. Xing H, Lee H, Luo L, Kyriakides TR. Extracellular matrix-derived biomaterials in engineering cell function. Biotechnol Adv. 2020 Sep-Oct;42:107421. doi: 10.1016/j.biotechadv.2019.107421.
15. Araújo PRS, Silva LB, Neto APDS, Almeida de Arruda JA, Álvares PR, Sobral APV, Júnior SA, Leão JC, Braz da Silva R, Sampaio GC. Pulp Revascularization: A Literature Review. Open Dent J. 2017 Jan 31;10:48-56. doi: 10.2174/1874210601711010048.
16. Kwack KH, Lee HW. Clinical Potential of Dental Pulp Stem Cells in Pulp Regeneration: Current Endodontic Progress and Future Perspectives. Front Cell Dev Biol. 2022 Apr 11;10:857066. doi: 10.3389/fcell.2022.857066.
17. Smojver I, Katalinić I, Bjelica R, Gabrić D, Matišić V, Molnar V, Primorac D. Mesenchymal Stem Cells Based Treatment in Dental Medicine: A Narrative Review. *International Journal of Molecular Sciences*. 2022; 23(3):1662. https://doi.org/10.3390/ijms23031662
18. Bansal R, Jain A, Mittal S, Kumar T, Kaur D. Regenerative endodontics: a road less travelled. J Clin Diagn Res. 2014 Oct;8(10):ZE20-4. doi: 10.7860/JCDR/2014/8257.5034.
19. Mangione F, EzEldeen M, Bardet C, et al. Implanted Dental Pulp Cells Fail to Induce Regeneration in Partial Pulpotomies. *Journal of Dental Research*. 2017;96(12):1406-1413. doi:10.1177/0022034517725523
20. Chang B, Ahuja N, Ma C, Liu X. Injectable scaffolds: Preparation and application in dental and craniofacial regeneration. Mater Sci Eng R Rep. 2017 Jan;111:1-26. doi: 10.1016/j.mser.2016.11.001.
21. Mohd N, Razali M, Ghazali MJ, Abu Kasim NH. Current Advances of Three-Dimensional Bioprinting Application in Dentistry: A Scoping Review. Materials (Basel). 2022 Sep 15;15(18):6398. doi: 10.3390/ma15186398
22. Nesic D, Schaefer BM, Sun Y, Saulacic N, Sailer I. 3D Printing Approach in Dentistry: The Future for Personalized Oral Soft Tissue Regeneration. J Clin Med. 2020 Jul 15;9(7):2238. doi: 10.3390/jcm9072238.
23. Liu Y, Gan L, Cui DX, Yu SH, Pan Y, Zheng LW, Wan M. Epigenetic regulation of dental pulp stem cells and its potential in regenerative endodontics. World J Stem Cells. 2021 Nov 26;13(11):1647-1666. doi: 10.4252/wjsc.v13.i11.1647.
24. Pagella P, Cordiale A, Marconi GD, Trubiani O, Rasponi M, Mitsiadis TA. Bioengineered tooth emulation systems for regenerative and pharmacological purposes. Eur Cell Mater. 2021 May 10;41:502-516. doi: 10.22203/eCM.v041a32.
25. Yelick PC, Vacanti JP. Bioengineered teeth from tooth bud cells. Dent Clin North Am. 2006 Apr;50(2):191-203, viii. doi: 10.1016/j.cden.2005.11.005.
26. Oshima M, Mizuno M, Imamura A, Ogawa M, Yasukawa M, Yamazaki H, Morita R, Ikeda E, Nakao K, Takano-Yamamoto T, Kasugai S, Saito M, Tsuji T. Functional tooth regeneration using a bioengineered tooth unit as a mature organ replacement regenerative therapy. PLoS One. 2011;6(7):e21531. doi: 10.1371/journal.pone.0021531.