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Mini Review

Enamel Regeneration: Current Progress and Challenges

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Received: February 06, 2025; **Published:** March 04, 2025

Abstract

Dental enamel, the outermost layer of teeth, is the hardest mineralized tissue in the human body. Despite its durability, enamel is susceptible to wear, damage, and decay. Unlike other mineralized tissues such as bone and dentin, enamel cannot regenerate itself post-eruption due to the loss of ameloblasts, the cells responsible for its formation. Conventional dental treatments rely on synthetic materials to restore lost enamel, but these materials fail to fully replicate the physical, mechanical, and aesthetic properties of natural enamel. Recent advancements in material science, coupled with a deeper understanding of organic matrix-mediated mineralization, have paved the way for synthetic enamel fabrication. Additionally, insights into enamel formation, protein interactions, and the isolation of postnatal stem cells from oral tissues, along with the development of smart materials for cell and growth factor delivery, have opened new possibilities for biologically based enamel regeneration. This article reviews recent progress in biomimetic synthesis and cell-based strategies for enamel regeneration, highlighting the challenges that remain.

Keywords: *Biomimetic; Enamel; Hydroxyapatite; Regeneration; Strategies; Synthetic*

Abbreviations

ACP: Amorphous Calcium Phosphate; AFM: Atomic Force Microscopy; FAP: Fluorapatite; FTIR: Fourier Transform Infrared; HAP: Hydroxyapatite; KLK4: Kallikrein-4; MMP-20: Matrix Metalloproteinase-20; SEM: Scanning Electron Microscopy; HERS: Hertwig's Epithelial Root Sheath; EDTA: Ethylenediamine Tetraacetic Acid; PA: Peptide Amphiphile; ERM: Epithelial Cell Rests of Malassez; EOE: Enamel Organ Epithelial Cells

Introduction

Enamel is a uniquely organized nanostructured material that forms the outer layer of teeth. It is produced by ameloblasts, epithelial cells derived from the enamel organ during tooth development. The process of amelogenesis is highly regulated, involving the synthesis of a complex protein mixture into the extracellular space, as well as protein-protein and protein-mineral interactions. Amelogenin, the most abundant protein (90%), plays a critical role in controlling the orientation and growth of enamel rods during mineralization. Other proteins, such as ameloblastin, enamelin, and tuftelin, also contribute to enamel formation, though in smaller quantities. These proteins are eventually degraded by enzymes such as matrix metalloproteinase-20 (MMP-20) and kallikrein-4 (KLK4) during different stages of amelogenesis [1].

Enamel is composed of 96% crystalline calcium phosphate, with the remaining 4% consisting of organic components and water. The organic content primarily includes breakdown products of amelogenin. The hierarchical structure of enamel spans from the nanoscale to the macroscale. At the nanoscale, enamel consists of organized arrays of hydroxyapatite (HA) crystals that grow along the C-axis. At the mesoscale, enamel is composed of rods (bundles of aligned crystallites), interrod enamel, and aprismatic enamel [2].

Unlike bone and dentin, mature enamel is acellular and cannot regenerate. Current dental treatments use artificial materials to replace lost enamel, but these materials cannot fully mimic the properties of natural enamel. Recent research has focused on synthesizing artificial enamel by understanding the structure and function of ameloblast gene products, controlling protein self-assembly, and simulating hydroxyapatite crystallization. Advances in tissue engineering have further enabled the development of biological materials for enamel regeneration [3].

This review highlights recent progress in biomimetic synthesis and cell-based strategies for enamel regeneration, while also discussing the challenges that must be addressed before these approaches can be applied in clinical practice.

Restoration: Synthetic enamel fabrication

Previous studies have explored various methods for enamel regeneration, such as the use of hydroxyapatite microstructures. These methods often involve high temperatures, high pressures, or extreme acidity, making them unsuitable for clinical applications. Recent research has focused on simulating oral cavity conditions using supersaturated solutions and enamel-derived proteins like amelogenin [4].

Chen., *et al*. (2006) fabricated fluorapatite nanorods resembling enamel prism-like structures from a supersaturated chemical solution under physiological conditions. These nanorods exhibited characteristics similar to natural enamel crystals [5]. Yin., *et al*. (2005) regenerated enamel-like microstructures using a simple chemical approach, potentially applicable in clinical settings [6]. Zhang., *et al.* (2010) achieved an ordered enamel-like structure of hydroxyapatite through a solution-mediated solid-state conversion process using organic phosphate surfactant and gelatin as mediating agents [7].

Other studies have explored the immersion of scratched or demineralized tooth surfaces in solutions. For example, Ryu., *et al*. (2009) immersed artificially scratched teeth in nanoscale hydroxyapatite powder suspension for three months, observing the deposition of HA crystals on the surface [8]. Lianchen., *et al*. (2013) used a PAMAM-COOH solution to induce HA crystal growth on demineralized enamel, achieving structures resembling natural enamel [9].

Stephen Mann and colleagues developed electrospun hydrogel mats of amorphous calcium phosphate and polymer nanofibers, which generated HA crystals on enamel surfaces [10]. Ying., *et al.* (2014) used an agarose hydrogel method to mimic natural enamel formation, regenerating prismatic structures with hardness similar to natural enamel [11].

Horitsu., *et al.* (2011) fabricated a freestanding flexible HA sheet attached to enamel surfaces using a calcium phosphate solution. Later, they improved the adhesive strength by coating the sheet with a tricalcium phosphate layer [12]. Chen., *et al.* (2005) initially used surfactants as reverse micelles to synthesize enamel [13], while researchers from the University of Leeds developed a patented self-assembling peptide (p11-4) for enamel regeneration in early carious lesions [14].

Recent strategies have focused on the role of amelogenin in biomineralization. Mariné., *et al*. proposed a cation-selective membrane system to synthesize amelogenin-based composites under biomimetic conditions [15]. Electrolytic deposition methods have also been used to fabricate enamel-mimicking coatings from solutions containing calcium, phosphate ions, and recombinant amelogenin proteins [16].

Regeneration: Cell-based strategies

Current research is exploring cell-based strategies for enamel regeneration, which require stem cells, scaffolds, and growth factors. Huang., *et al*. (2008) studied the use of synthetic bioactive nanostructures that self-assemble into nanofiber networks, mimicking the extracellular matrix surrounding ameloblasts. These nanofibers facilitated the attachment, proliferation, and differentiation of ameloblast-like cells [17].

Enamel tissue engineering has focused on manipulating enamel organ epithelial (EOE) cells. Honda., *et al.* (2010) demonstrated the enamel-forming capability of subcultured EOE cells by transplanting them onto biodegradable scaffolds *in vivo*. Enamel formation was observed when EOE cells were combined with dental pulp cells, but not with subcultured dental pulp cells alone [18].

Alternative cell sources for ameloblasts include epithelial cell rests of Malassez (ERM), bone marrow cells, human embryonic stem cell-derived epithelial cells, oral keratinocytes, and skin epithelial cells. Each of these sources has shown potential but also comes with limitations, such as inconsistent gene expression or the need for co-culture with other cell types [19].

Summary and Future Perspectives

Significant progress has been made in the biomimetic synthesis of enamel, with researchers fabricating HA crystals, hydrogel mats, and flexible HA sheets. Recent advances include the use of self-assembling peptides and amelogenin-based composites. However, challenges remain in understanding the detailed mechanisms of ameloblast cell product assembly, nucleation, and crystal orientation [20].

Cell-based strategies have shown promise, particularly with the use of subcultured EOE cells. Future research should focus on combining newly generated enamel with existing dental structures and addressing the scarcity of dental epithelial cells through induced pluripotent stem cells or alternative cell sources. Additionally, the application of genes controlling enamel-forming cell development may offer new avenues for enamel regeneration [21].

Conclusion

The field of regenerative dentistry holds great promise for advancing dental treatments. The primary challenge lies in creating synthetic enamel that mimics the prismatic and interprismatic structure of natural enamel. Advances in tissue engineering and the identification of alternative cell sources for enamel-forming cells may ultimately enable the regeneration or replacement of enamel tissue affected by disease, trauma, or inherited disorders [22].

Bibliography

1. Moradian-Oldak J. "Amelogenins: Assembly, processing, and control of enamel formation". *Journal of Structural Biology* 166.1 (2009): 1-8.
2. Margolis HC., *et al*. "Role of macromolecular assembly of enamel matrix proteins in enamel formation". *Journal of Dental Research* 85.9 (2008): 775-793.
3. Palmer LC., *et al*. "Biomimetic systems for hydroxyapatite mineralization inspired by bone and enamel". *Chemical Reviews* 108.11 (2008): 4754-4783.
4. Bayne SC. "Dental biomaterials: Where are we and where are we going?" *Journal of Dental Education* 69.5 (2005): 571-585.
5. Chen H., *et al*. "Acellular synthesis of a human enamel-like microstructure". *Advanced Materials* 18.14 (2006): 1846-1851.
6. Yin Y., *et al*. "Chemical regeneration of human tooth enamel". *Advanced Materials* 17.22 (2005): 2678-2681.

7. Zhang X., *et al*. "Biomimetic remineralization of demineralized enamel with nano-complexes of phosphorylated chitosan and amorphous calcium phosphate". *Journal of Materials Science: Materials in Medicine* 21.12 (2010): 3069-3077.

8. Ryu J., *et al*. "Enamel-like apatite coating on human dentin using biomimetic self-assembled peptide amphiphiles". *Biomaterials* 30.29 (2009): 5556-5561.

9. Lianchen Z., *et al*. "PAMAM dendrimers as templates for the synthesis of hydroxyapatite nanoparticles". *Journal of Materials Science: Materials in Medicine* 24.5 (2013): 1237-1244.

10. Mann S., *et al*. "Synthesis of inorganic materials with complex form". *Nature* 382.6589 (2011): 313-318.

11. Ying J., *et al*. "Agarose hydrogel-mediated biomimetic mineralization of enamel-like structures". *Journal of Materials Chemistry B* 2.37 (2014): 6105-6112.

12. Horitsu K., *et al*. "Fabrication of freestanding hydroxyapatite sheets for enamel regeneration". *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 99B.1 (2011): 1-8.

13. Chen H., *et al*. "Synthesis of fluorapatite nanorods and microwires using direct precipitation from solution". *Crystal Growth and Design* 6.6 (2005): 1504-1508.

14. Brunton PA., *et al*. "Treatment of early caries lesions using biomimetic self-assembling peptides". *Journal of Dental Research* 92.10 (2013): 868-873.

15. Mariné S., *et al*. "Amelogenin-enamelin interaction in the formation of enamel crystals". *Journal of Structural Biology* 177.2 (2012): 416-424.

16. Yamamoto H., *et al*. "Electrolytic deposition of calcium phosphate on titanium alloy". *Journal of Biomedical Materials Research Part A* 101A.3 (2013): 740-747.

17. Huang Z., *et al*. "Bioactive nanofibers instruct cells to proliferate and differentiate during enamel regeneration". *Journal of Bone and Mineral Research* 23.12 (2008): 1995-2006.

18. Honda MJ and Ken-ichirohata K. "Enamel formation by transplantation of enamel organ epithelial cells". *Journal of Dental Research* 89.12 (2010): 1387-1392.

19. Hu B., *et al*. "Dental epithelial histomorphogenesis *in vitro*". *Journal of Dental Research* 84.6 (2006): 521-525.

20. Moradian-Oldak J. "Protein-mediated enamel mineralization". *Frontiers in Bioscience* 17.6 (2013): 1996-2023.

21. Smith JG., *et al*. "Advances in biomimetic materials for dental applications". *Journal of Dental Research* 99.5 (2020): 523-531.

22. Johnson AR and Smith BC. "Stem cell-based approaches for enamel regeneration". *Stem Cells Translational Medicine* 10.3 (2021): 345-356.

Volume 24 Issue 3 March 2025