A systematic review of the impact of amelogenin peptides on periodontal regeneration

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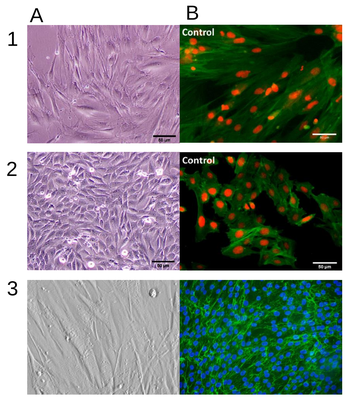
Background

- Periodontitis is a gum disease that damages the periodontium, which is composed of cementum and bone as mineralized tissue, and of gum and periodontal ligament as soft tissues. This can result in tooth loss and esthetic disfigurement.[1]
- Periodontal regenerative therapies consist of regenerating these tissues, as part of the attachment apparatus.
- Enamel matrix derivative (EMD) is a heat-treated preparation derived from enamel matrix proteins (EMPs) of developing porcine teeth. Amelogenin makes up 95% of its protein content.
- Certain amelogenin splicing variants have significant positive effects on wound healing, bone formation and root resorption, making it the subject of many periodontal regeneration studies.
- Disadvantages of using EMDs during therapeutic procedures are (1) the use of animal-derived preparations & (2) the use of complex proteins, which carry risks of animal-to-human transmission and antigenicity.[2]
- **This systematic review will primarily focus on recombinant and synthetic amelogenin variants and analyze their effects on periodontal regeneration, in order to better understand the individual effects of the EMD components.**



Main cell types that were studied:

Fig 1A. Light microscopy of image of cultured Human Gingival Fibroblasts (HGF) isolated from human gingiva and cryopreserved.[3]

Fig 2A. Light microscopy image of cultured mouse cementoblast cell line OCCM.30 that were commercially available.[3]

Fig 1B** and **2B. Fluorescent microscopy images of Phalloidin-FITC labelled actin filaments and Propidium Iodide (PI) labelled nuclei of gingival fibroblasts and cementoblasts (respectively) [3].

Fig 3A. Light microscopy of Human Periodontal Ligament Fibroblasts (HPLF) [4].

Fig 3B. Fluorescent microscopy image of HPLF cells that are immunostained for Fibronectin, 200x.[4]

Methodology

Key words (sources: PubMed, Scopus) (Title/Abstract) search

('Amelogenin')
AND
('Synthetic' OR 'Artificial' OR 'Recombinant')
AND
('Regenerat*' OR '*Mineralization' OR 'Healing')
AND
('Periodon*')

Inclusion criteria:

1. Synthetic or recombinant amelogenin peptides
2. Evaluation of the biological effects on cells or tissues
3. Within the realm of periodontal regeneration

Exclusion criteria:

1. No review or short communications
2. Studies published within the last 15 years (2002 - 2017) – the major period of publications on this topic

Methodology (cont'd)

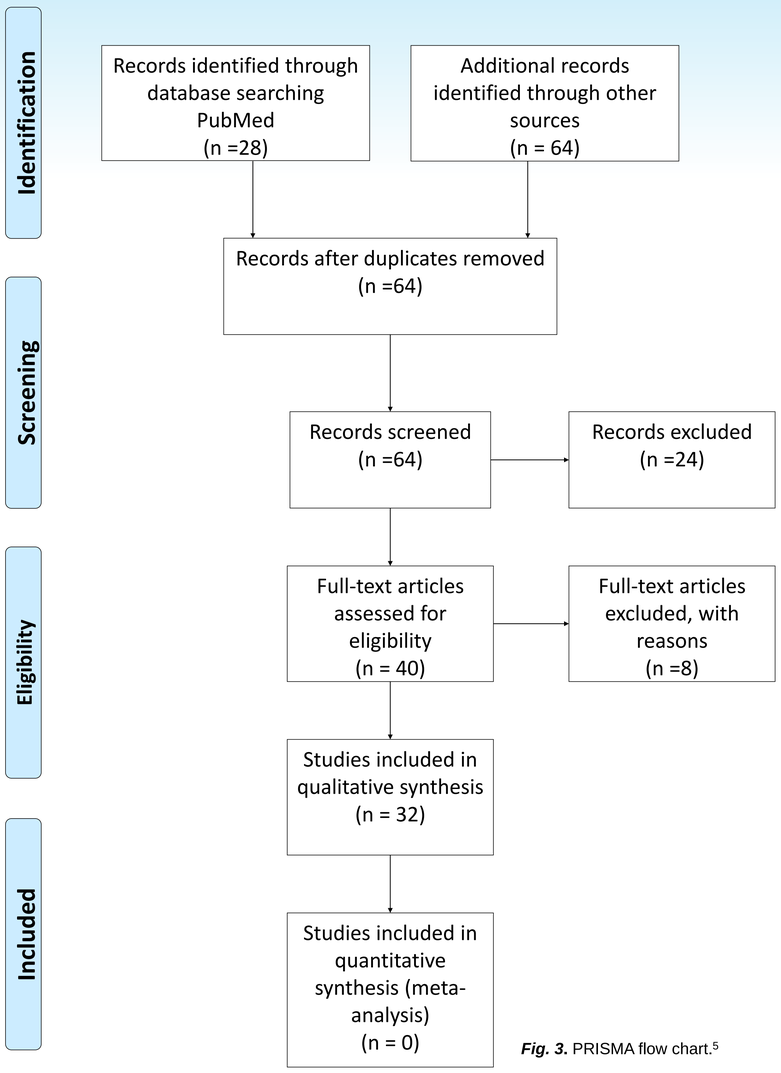


Fig. 3. PRISMA flow chart.[5]

Results

Parameters based on the characteristics of periodontal regeneration:

- **(A) cell adhesion** (5 studies)
- **(B) proliferation** (18 studies)
- **(C) migration** (10 studies)
- **(D) mineralization** (9 studies)
- **(E) wound healing** (1 study)
- **(F) angiogenesis** (4 studies)
- **(G) differentiation** (14 studies)
- **(H) gene expression** (9 studies).

Cell types that were studied:

- **(I) human gingival fibroblasts** (HGF) (2 studies)
- **(J) periodontal ligament cells** (PDL) (18 studies)
- **(K) cementoblasts** (8 studies)
- **(L) mesenchymal stem cells** (MSC) (3 studies)
- **(M) human umbilical vein endothelial cells** (HUVEC) (2 studies)
- **(N) other** types of cells and/or extracellular components (11 studies)

Tyrosine-rich amelogenin peptide (TRAP)

- no sig effect on (B) of (K) and (I).
- ↑ (C) for (M) and (I)
- no sig effect on (D); ↑ (F); ↑ (H)

Synthetic amelogenin peptide (WYQNMIR)

- ↑ (B) of (J) and (L).
- ↑ (C) of (J); ↑ (G); ↑ (H); ↑ (D).

Leucine-rich amelogenin peptide (LRAP)

- Contradicting results for (B) and (C) for (J) and (K).
- ↑ (G); ↓ (D)

Human recombinant amelogenin (rh174)

- ↑ (B) of (K) and (J) and (L)
- ↑ (G) and (H)
- ↑ (D) and (F)

Murine recombinant amelogenin

- ↑ (A) and (B) and (C) of (J)
- ↑ (G) and (D)

Porcine recombinant amelogenin

- ↑ (A) of (I); ↑ (B) for (I) and (J)
- ↓ (C) of (I)
- ↑ (D)

Discussion

- Amelogenin products showed varied responses on different cell types and different characterstics of periodontal regeneration.
- No specific peptide elicits a response in all aspects of regeneration studied.
- It is the mixture of amelogenin products that will ultimately allow for targeted regeneration of periodontal tissues.
- Most of the studies tested recombinant variants of amelogenin, with only a few that tested a synthetic amelogenin peptide (WYQNMIR) and synthetic TRAP.
- Using synthetic peptides that are short decreases the chance of eliciting an immunological response, which helps to solve the limitations of enamel matrix derivatives (EMD), such as the therapeutically used Emdogain™.
- A limitation of the review is grouping the effects of some of the recombinants together when there was not enough information provided in the article to make distinctions.
- I.e. some articles did not specify exact molecular weights of the peptides that were being tested, so the reviewers had to make categorizations based on the contexts given and combine the effects in that manner.

Conclusions & Future Directions

- This review systematically summarizes the results of the research that has been conducted to find new and improved techniques for periodontal tissue regeneration.
- **It will allow for synthetic amelogenin peptide mixtures to be developed so that they will target certain cell types and elicit various responses to counteract the effects of periodontitis.**
- **Developing synthetic peptides will eliminate the immunological response problems of EMDs as well as the need for animal-based derivatives in a more cost and time-effective manner.**

References

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