Role of Self-Assembling Peptide P11-4 in Dentistry: Mechanism, Clinical Applications, and Recent Advances: A Review.

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Abstract:
Self-assembling peptides (SAPs) represent a novel class of biomimetic materials introduced in dentistry to facilitate non-invasive regeneration of early enamel carious lesions. Among these, self-assembling peptide P11-4 has gained significant attention due to its ability to mimic enamel matrix proteins and promote guided hydroxyapatite formation within subsurface enamel lesions. P11-4 is applied as a low-viscosity monomeric solution that penetrates early non-cavitated carious lesions and undergoes pH-triggered hierarchical self-assembly to form a three-dimensional fibrillar scaffold. This scaffold attracts calcium and phosphate ions from saliva, enabling de novo hydroxyapatite nucleation and true subsurface remineralization, in contrast to conventional fluoride-based therapies that primarily enhance surface mineralization. Increasing in vitro, in situ, and clinical evidence supports the use of P11-4 in the management of white spot lesions, early enamel caries, post-orthodontic demineralization, and enamel repair following bleaching procedures. Recent advances include combination therapies with fluoride, calcium–phosphate systems, and laser-assisted remineralization, as well as expanded applications in regenerative and restorative dentistry. This review summarizes the history, mechanism of action, clinical applications, advantages, limitations, and recent advances of self-assembling peptide P11-4, highlighting its potential role as a smart biomaterial in contemporary minimally invasive dentistry.

Keywords: Self assembling peptides, enamel remineralization, biomimetic dentistry, white spot lesions, minimally invasive dentistry.

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INTRODUCTION:

Dental caries remains one of the most prevalent chronic diseases worldwide and is currently understood as a dynamic and reversible process involving cycles of demineralization and remineralization of dental hard tissues [3,4]. Early enamel caries, clinically manifested as white spot lesions, represents a critical stage at which the disease can be arrested or reversed through non-invasive therapeutic interventions [3].

Self-assembling peptides (SAPs) are short protein fragments capable of spontaneously organizing into highly ordered nano- or microstructures such as fibers, ribbons, and hydrogels through non-covalent interactions including hydrogen bonding, electrostatic forces, and hydrophobic interactions [1]. Due to their tunable molecular architecture,

biocompatibility, and responsiveness to environmental cues, SAPs have gained significant attention in biomedical applications including tissue engineering, drug delivery, and regenerative medicine [1]. Their ability to mimic natural extracellular matrices makes them particularly attractive for dental hard tissue regeneration.

Self-assembling peptide has been recently introduced to promote hard tissueregeneration for treating early non-cavitated carious lesions. These are rationally designed biomimetic peptides that can undergo spontaneous hierarchical self-assembly in response to specific environmental conditions, forming three-dimensional fibrillar scaffolds that promote enamel remineralization.

P11-4 is a self-assembling peptide that mimics the function of enamel matrix proteins, serving as a template for de novo hydroxyapatite formation within early carious lesions. P11-4 is a synthetically engineered, biomimetic peptide composed of naturally occurring amino acids that has the ability to self-assemble into a three-dimensional fibrillar scaffold within early carious enamel lesions. It mimics the function of amelogenin-derived enamel matrix proteins and promotes guided hydroxyapatite crystal nucleation and growth, leading to subsurface enamel remineralization rather than superficial mineral deposition.

Over the past decade, increasing in vitro, in situ, and clinical evidence has demonstrated the efficacy of P11-4 in the management of early non-cavitated enamel caries, post-orthodontic white spot lesions, and enamel demineralization following bleachingprocedures [2,3,5]. Recent advances have further expanded its potential applications through combination therapies, integration with calcium–phosphate systems, laser-assisted remineralization protocols, and investigation of its role as a pre-restorative enamel conditioning agent [4,8]. These developments position self-assembling peptides as "smart biomaterials" with significant relevance to regenerative and conservative dentistry.

Therefore, the aim of this review is to comprehensively discuss the mechanism of action, clinical applications, advantages, limitations, and recent advances of self-assembling peptide P11-4 in dentistry.

HISTORY AND DEVELOPMENT

Dental caries is now understood as a dynamic, reversible process characterized by cycles of demineralization and remineralization. Early clinical manifestations such as white spot lesions (WSLs) are reversible if remineralization is promoted. Increased understanding of the biological caries process and the philosophy of minimal intervention dentistry led to interest in non-invasive regenerative approaches. Natural enamel matrix proteins guide hydroxyapatite crystal growth duringtooth development, but these proteins are lost after enamel maturation, limiting natural repair. Conventional remineralizing agents (fluoride, CPP-ACP, tricalcium phosphate) primarily act by surface mineral deposition [4,6]. To overcome this limitation, biomimetic strategies were introduced. Self-assembling peptide P11-4 was developed as a synthetic analogue of enamel matrix proteins to enable guided enamel regeneration in post-eruptive teeth [3,4].

- **Early 2000s**: Advances in peptide chemistry and supramolecular biology led to the concept of **peptide self-assembly** for biomedical applications.
- **Mid-2000s**: Researchers developed **β-sheet-forming peptides** capable of nucleating hydroxyapatite, inspired by the role of **amelogenin** in enamel formation.
- **Development of P11-4**: P11-4 was rationally designed with alternating **hydrophilic and hydrophobic amino acids**, enabling hierarchical self-assembly. The peptide was later commercialized under CUROLOX® technology (e.g., Curodont Repair / Protect) for non-invasive management of early enamel caries.
- **Shift in caries philosophy**: The modern understanding of caries as a **dynamic, reversible process** encouraged development of **biomimetic remineralizing agents**, positioning SAPs as a new class beyond fluoride and calcium-phosphate systems.

Initial laboratory and in vitro investigations demonstrated that P11-4 could penetrate deeply into subsurface enamel porosities and promote mineral deposition from within the lesion rather than on the enamel surface alone [6]. These promising findings

led to early clinical safety and feasibility trials, which confirmed that the material was biocompatible, non-invasive, and well tolerated when applied to early carious lesions [5]. The clinical translation of this technology culminated in the commercialization of P11-4-based products under CUROLOX® technology for the management of non-cavitated enamel caries [5].

Subsequent in vitro, in situ, and randomized clinical trials expanded the evidence base for P11-4, demonstrating its effectiveness in the management of white spot lesions, post-orthodontic demineralization, and earlyenamel caries, both as a standalone therapy and in combination with fluoride-based systems [2,3,7]. These studies reinforced the concept that self-assembling peptides function as biomimetic scaffolds rather than conventional remineralizing agents, offering enhanced subsurface remineralization and improved lesion aesthetics.

CLASSIFICATION AND THEIR MOLECULAR STRUCTURES

Self-assembling peptides can be classified based on their secondary structure and mode of molecular organization, which determine the type of supramolecular nanostructures they form and their functional applications in biomedical and dental sciences [1].

1. **β-sheet–forming peptides:**

B-sheet–forming peptides are short peptides, typically consisting of 12–16 amino acids, with an alternating arrangement of hydrophilic (charged) and hydrophobic residues. This molecular design promotes the formation of β-sheet secondary structures, which further self-assemble into higher-order nanostructures such as nanofibers, ribbons, tapes, or fibrils. These peptides generally exist initially as low-viscosity monomeric solutions, allowing deep penetration intosubsurface enamel porosities before undergoing self-assembly [1].

2. α-helix (Coiled-coil) peptides:

α-helix or coiled-coil peptides adopt an α-helical secondary structure and organize into coiled-coil motifs. Their molecular architecture is based on repeating heptad sequences (a–g), in which hydrophobic residues at specific positions stabilize the helical bundle,while charged residues contribute to intermolecular interactions and structural stability [1].

3. Collagen-like peptides (CLPs):

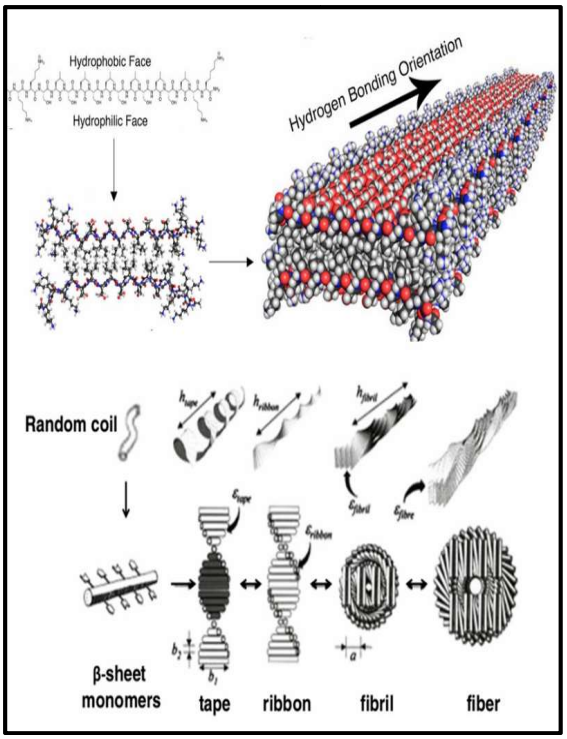
Collagen-like peptides (CLPs) are characterized by a repetitive Gly–X–Y tripeptide sequence, where X and Y are commonly proline and hydroxyproline. This unique sequence enables the formation of a triple-helical structure, closely mimicking the molecular architecture of natural collagen [1].

4. Elastin-like polypeptide es (ELPs):

Elastin-like polypeptides (ELPs) consist of repeating pentapeptide sequences (VPGXG), where X represents any amino acid except proline. These peptides exhibit unique conformational behavior and can undergoreversible structural transitions in response to environmental stimuli [1].

4. Peptide amphiphiles:

Peptide amphiphiles possess a distinct molecular design comprising a hydrophobic alkyl (lipid) tail linked to a peptide head group, which may include β-sheet-forming or bioactive sequences. This amphiphilic nature drives spontaneous self-assembly into organized nanostructures through hydrophobic interactions and hydrogen bonding [1].



(A) β-Sheet forming short peptides with alternating ionic complementary properties. [1]

(B) Short amphiphilic β-sheet peptides that self-assemble into anti-parallel nano tapes and further aggregate into ribbons and higher order structures. In a recent paper, shorter sequences (P9-6 and P7-6) with aliphatic hydrophobic resides (in green) were demonstrated to form fibrillar structures. [1]

MECHANISM OF ACTION

The demineralization action of self-assembling peptide P11-4 occurs through multiple sequential steps, they are as follows:

1. Diffusion into Early Carious Lesions:
Self-assembling peptide P11-4 is applied in a low-viscosity, monomeric solution, which enables it to diffuse effectively into the subsurface porosities of early, non-cavitated enamel carious lesions [6]. Owing to its small molecular size and fluid consistency, the peptide penetrates deeply into the lesion body rather than remaining on the enamel surface.

2.pH-TriggeredSelf-Assembly:
Within the acidic microenvironment of an initial carious lesion (pH < 7.4), P11-4 undergoes a conformational transformation. The peptide transitions from a soluble monomeric state into β-sheet secondary structures, which then hierarchically assemble into tapes, ribbons, fibrils, and ultimately fibers. This process leads to the formation of a three-dimensional scaffold within the lesion body [1,6].

3. Biomimetic Enamel Matrix Formation:
The three-dimensional fibrillar scaffold formed by P11-4 closely mimics the natural enamel extracellular protein matrix present during amelogenesis. The negatively charged glutamate residues distributed along the peptide fibrils exhibit a strong affinity for calcium ions, facilitating their localized concentration within the lesion [6].

4. Nucleation of Hydroxyapatite:
The peptide scaffold serves as a biomimetic nucleation template for de novo hydroxyapatite crystal formation. Calcium and phosphate ions derived from saliva are attracted and deposited along the scaffold, promoting guided and oriented crystal growth within the lesion body rather than superficial mineral precipitation [6,7].

5. Lesion Regeneration:
Progressive mineral deposition occurs from within the lesion toward the enamel surface, resulting in restoration of enamel density, microhardness, and structural integrity. This regenerative process fundamentally differs from fluoride-based remineralization, which predominantly enhances surfacemineralization without effectively rebuilding the subsurface lesion architecture [2,6].

CLINICAL APPLICATIONS

1. White Spot Lesions (WSLs): It has been proven to significantly increase surface microhardness and is particularly effective in the management of post-orthodontic and early enamel carious lesions. Additionally, it demonstrates superior remineralization potential when compared with CPP-ACP and nanohydroxyapatite.

2. Early Non-Cavitated Enamel Caries: It enables non-invasive management of dental caries by arresting lesion progression at the non-cavitated stage and is particularly useful in patients with a high risk of caries.

3. Post-Orthodontic Demineralization: It enhances enamel recovery around brackets and bands.

4. Post-Bleaching Enamel Repair: It improves the enamel microstructure following peroxide-induced demineralization and enhances the shear bond strength of composite resin to bleached enamel, although short-term studies have shown it to be inferior to nR5 technology.

5. Adjunct to Restorative Dentistry: It improves substrate quality prior to adhesive restorations and supports minimally invasive restorative protocols by facilitating biomimetic enamel repair through guided mineral deposition. When used as an adjunct to fluoride or CPP-ACPF, it enhances remineralization efficacy, promotes subsurface mineral deposition, and improves the aesthetic appearance of enamel lesions.

6. Adjunct to Laser-Assisted Remineralization: Studies show enhanced uptake and remineralization

when combined with Er:YAG laser irradiation, due to increased enamel permeability.

7. Whitening and Surface Enhancement (Adjunct Use): When combined with hydroxyapatite suspensions, P11-4 improves particle adhesion, enhancing optical properties of enamel.

ADVANTAGES AND LIMITATIONS

Overall, the material is biomimetic and biologically inspired, providing a non-invasive and painless approach that promotes subsurface remineralization by mimicking natural enamel formation, with high biocompatibility and suitability for minimal intervention dentistry. However, its remineralization effect is time dependent and often requires repeated or long-term application, offers limited immediate benefitscompared with fluoride-based surface treatments, has insufficient evidence regarding long-term clinical durability, is less effective on cavitated lesions, and has shown no significant anti-erosive effect in some studies.

RECENT ADVANCES

1. Combination therapies:

Recent research has focused on combination approaches to enhance the remineralization potential of self-assembling peptides (SAPs). These include laser-assisted remineralization strategies such as the use of SAPs in conjunction with Er:YAG lasers, as well as their combination with hydroxyapatite or other calcium–phosphate–based systems to promote synergistic mineral deposition [8].

2. Improved delivery systems:

Efforts to optimize peptide delivery have led to the development of improved application protocols aimed at enhancing lesion penetration. Surface pre-treatments, such as the use of sodium hypochlorite (NaOCl), have been investigated to increase enamel permeability and facilitate deeper diffusion of SAPs into demineralized areas [4].

3. Expanded applications:

Beyond enamel remineralization, ongoing research is exploring the potential of SAPs in dentin remineralization and their integration with restorative materials. This expansion broadens their applicability in conservative and restorative dentistry.

4. Focus on regenerative dentistry:

Self-assembling peptides are increasingly classified as "smart biomaterials" due to their ability to respond to local oral environmental conditions, such as pH changes. This property positions them as key materials in the evolving field of regenerative dentistry [1,6].

5. Use as a pre-restorative enamel conditioning agent:

SAPs are being investigated for use as pre-restorative enamel conditioning agents to enhance enamel quality prior to adhesive or restorative procedures, potentially improving bonding and long-term restoration performance [6,7].

6. Integration with hydroxyapatite suspensions:

Another emerging approach involves the integration of SAPs with hydroxyapatite suspensions, aiming to combine the biomimetic scaffold-forming ability of peptides with readily available mineral sources for enhanced and guided remineralization.

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