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Dental Science

SMART BIOMATERIAL IN DENTISTRY, SAP P11-4 (SELF ASSEMBLING PEPTIDE): A REVIEW

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ABSTRACT Self-assembling peptides (SAP) have been effectively utilized to design novel biomimetic nanomaterials which have tremendous applications in many of the fields including dentistry. SAP P11-4 was introduced to remineralize enamel by providing matrix mediated mineralization. These short chain peptides have the property of assembling into a three dimensional structure on the surface of the tooth resembling the extracellular matrix, thereby promote regeneration. Hence, the aim of this review is to expound on the remineralisation potential of SAP P11-4.

KEYWORDS : self assembling peptide, SAP P11-4, matrix mediated mineralization, biomimetic, extracellular matrix

INTRODUCTION

Self assembly is the autonomous organization of individual components into patterns or structures without human intervention. Self-assembly has been defined as "the noncovalent interaction of two or more molecular subunits to form an aggregate whose novel structure and properties are determined by the nature and positioning of the individual components."[1]It is the inherent ability of numerous multimeric biological structures to assemble from their component parts through random movements of molecules and formation of weak chemical bonds between surfaces with complementary shapes.

Proteins are the fundamental components and building blocks of all living cells. They are composed of one or more chains of amino acids. Two or more amino acids linked by a peptide bond form a peptide molecule. Large numbers of peptide molecules arrange themselves in different fashions to make up different kinds of proteins (Fig; 1). The self-assembly process is highly dependent on the peptide sequence, concentration, pH, presence of salts, and time or kinetics.[2] Self-assembling peptides (SAP) have been effectively utilized to design novel biomimetic nanomaterials which have tremendous applications in many of the fields including dentistry.[3]

USES OF SAP

1. In the treatment of early dental carious lesions.[4,15,19,11]
2. To improve remineralisation of erosive lesions of enamel.[5]
3. Can be used as a scaffold for bone formation in periodontal tissue regeneration.[6]
4. Can act as a as a scaffold for dental stem cells for engineering both soft and mineralized matrices in dental tissue regeneration.[7,8]
5. Self-assembled peptides have been used to enhance various types of cell growth and differentiation, including bone, cartilage, vessel, heart, and neural systems.[9,10] For example, the self-assembled peptide scaffolds made of RADA16-I and RADA16-II peptides have been used to enhance neural cell attachment, differentiation, and neurite outgrowth during in vitro studies, as well as to promote active synapse formation during in vivo studies.[11]

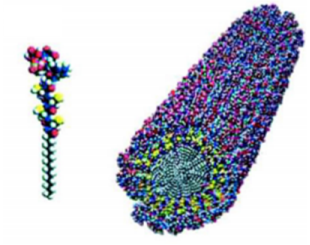


Fig 1; Self-assembled peptide amphiphile nanofibers.

The tooth enamel is the most highly mineralised and uniquely organized outermost covering of the tooth. During enamel development, enamel matrix proteins, themselves known to form self assembling supramolecular structures, which is believed to control the morphology of the hydroxyapatite crystals, ultimately determining the physico-mechanical properties of the mature tissue.[12,13]

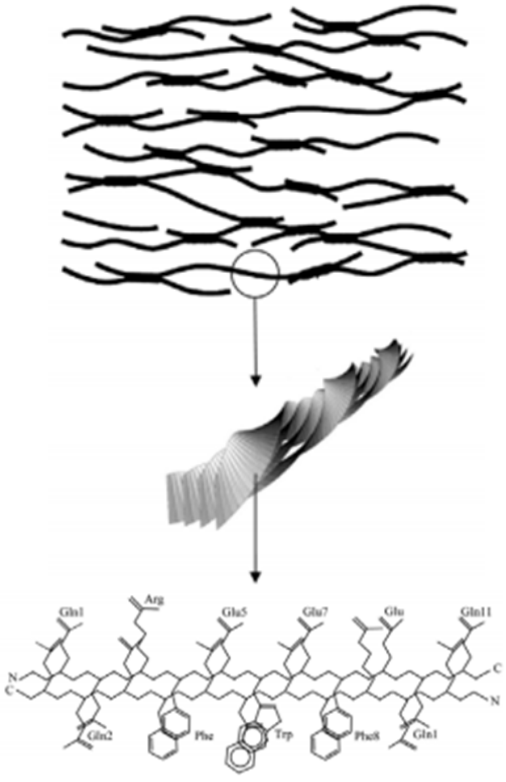
This enamel is constantly subjected to numerous challenges within the oral environment However, unlike other skeletal structures mature enamel cannot be regenerated due to lack of functional capacity of ameloblasts.[14] With this inherent limitation any drop in pH below the critical value initiates the demineralization process. Caries occurs due to an imbalance of the remineralization and demineralization equilibrium. Once the demineralisation exceeds 30% it causes irreversible damage to the enamel.[4] Hence early detection and management of these reversible incipient lesions using non-invasive methods are recommended.

Various remineralizing agents are available for non-invasive management of these incipient lesions. The most important and extremely effective are fluorides, whose local efficacy has been thoroughly investigated. In recent years, several materials have been introduced which penetrate an initial lesion as liquid resin (ICON caries infiltrant) or can promote remineralization by releasing calcium and phosphate (e.g, casein phosphopeptide- amorphous calcium phosphate, CPP-ACP complex). Furthermore, products based on nanohydroxyl apatite (e.g, BioRepair) have been proposed for "repairing" enamel.[15] However, these agents failed to achieve matrix mediated mineralization similar to the natural process. To surpass this situation, self assembling peptide (SAP) P11-4 was introduced to regenerate enamel by providing matrix mediated mineralization. These short chain peptides have the property of assembling into a three dimensional structure on the surface of the tooth resembling the extracellular matrix, thereby promote regeneration.[16,17] SAP P11-4 has been developed and patented by The University of Leeds, (UK). The Swiss company Credentis has licensed the peptide technology and markets it under the registered trademark CUROLOX® TECHNOLOGY.

MECHANISM OF ACTION OF SAP P11-4

Proteins of the developing enamel ECM – themselves known to form self-assembling supramolecular structures have long been thought to control initial mineral deposition ('nucleation') and subsequent crystal growth.[18] The self-assembling peptide P11-4 consists of the natural occurring amino acids Glutamine, Glutamic acid, Phenylalanine, Tryptophan, Serine and Arginine; is designed to form fibrils at a low pH and to be monomeric in solutions with higher pH. The dissolved Ca^{2+} is attracted by the negative charged surfaces and phosphorylated erine residues in the peptide.

The possible hypothesis explained for matrix mediated mineralization by SAP P11-4 is that bioactive peptide synthesized from amino acids diffused into the porosities and assembled within the voids in subsurface lesion into a three dimensional fibrillar scaffold resembling extracellular matrix (Fig; 2).[19] Assembled P11-4 forms scaffold-like structures with negative charge domains, mirroring biological macromolecules in mineralised tissue extracellular matrices (ECM). This act as a nucleus for hydroxyapatite, which initiates tissue regeneration by attracting calcium and phosphate ions from saliva resulting in increased Ca: P ratio. Furthermore, when peptides assemble into fibres, it contains clusters of negative charges made up of four Glu residues providing a potential Ca^{2+} binding site. These binding sites are approximately 9.4 A apart, the distance normally present in the natural hydroxyapatite crystal.[20] The structural resemblance of these peptides to the biological macromolecules in mammalian skeleton accounts for the peptides to provide matrix mediated mineralization.



Fig; 2. Schematic representation of a self-assembled fibrillar network and its relationship with individual self-assembled fibrils and peptide primary structure.

VARIOUS STUDIES ON REMINERALISATION POTENTIAL OF SAP P11-4

Peptide treatment significantly increased net mineral gain due to a combined effect of increased mineral gain and inhibition of mineral loss. In addition, P 11-4 in its assembled form was shown to induce hydroxyapatite nucleation. Various studies have been conducted so far on the remineralisation potential of SAP 11-4.

Takahashi F et al investigated the effect of self-assembling peptide P11-4 (Curodont Repair, CDR) on bovine enamel remineralization by measuring changes in ultrasonic propagation velocity. The result showed that increase in sonic velocity was found for specimens treated with CDR and he concluded that CDR application has an ability to promote bovine enamel remineralization.[21]

Sindhura V et al evaluated the remineralizing efficacy of self assembling peptide (SAP) P11 4 qualitatively and quantitatively using scanning electron microscopy (SEM) and energy dispersive X ray (EDX), respectively. CPP ACP showed a significant increase in Ca:P ratio (2.04 ± 0.2) with irregular surface calcific deposition at 1 week interval and this reduced with time (1.87 ± 0.11 at 3 month interval). Whereas P 11-4 showed a significant increase in Ca: P ratio (1.95 ± 0.10) with uniform ion deposition suggestive of hydroxyapatite nucleation over a 3 month period and he could conclude that SAP P11 4 exhibited superior remineralization with uniform mineral deposition compared to CPP ACP at 3 month interval.[4]

M. Alkilzy et al investigated the in vivo safety and clinical efficacy of P11-4 in combination with fluoride varnish in the treatment of initial occlusal carious lesions and compared it with the current clinical gold standard fluoride varnish alone. A randomized controlled single-blind study was conducted on children aged >5 years. The findings of the study demonstrated that biomimetic mineralization facilitated by P11-4 in combination with fluoride is a simple, safe, and effective non-invasive treatment for early carious lesions and is superior to the present clinical gold standard of fluoride treatment alone.[22]

Bronton PA et al determined the safety and potential clinical efficacy of a single application of P11-4 on early enamel lesions. Efficacy evaluation suggested that treatment with P11-4 significantly decreased lesion size ($p = 0.02$) after 30 days and shifted the apparent progression of the lesions from 'arrested/progressing' to 'remineralising'.[18]

Suda S et al evaluated the effect of Curodont Repair (contains the self-assembling peptide P11-4) on acid erosion prevention in bovine enamel using ultrasonography and found that the application of enamel matrix derivatives and self-assembling peptides on erosive lesions can prevent the progress of erosion and encourage remineralization.[23]

Kirkham J et al determined the effect of an anionic peptide applied to caries-like lesions in human dental enamel under simulated intra-oral conditions of pH cycling. Peptide treatment significantly increased net mineral gain by the lesions, due to both increased remineralization and inhibition of demineralization, on a day-by-day basis throughout the five-day cycling period[12].

Eventhough the studies have revealed the peculiar uniform remineralisation pattern of SAP P11-4 similar to natural process we do not yet know whether the peptides are susceptible to proteolytic degradation. This might limit their use, especially as a surface treatment which necessitates further studies on this aspect.

CONCLUSION

The self assembling peptides have provided a new direction to preventive dentistry. From this literature review, the remineralisation potential of SAP P11-4 is quite evident. Thus self-assembling peptides offer a potentially exciting route to "smart" dental biomaterials, though much work remains to be carried out. Further work is clearly required to clarify the precise mechanism(s) of their observed actions, in longer-term *in situ* and *in vivo* studies.

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