Review Article

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THE FIBRILLIN STRATEGY OF PERIODONTAL LIGAMENT REGENERATION: THE NEW RESCUER !!!

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ABSTRACT:

The current researches revolve around the ways and means to regenerate the most integral part of periodontium: Periodontal ligament. All the previous studies based on embryonic development, stem cell biology and tissue engineering technologies contribute to the advanced strategies which can be employed to regenerate what is lost to periodontitis. PDL stem cells and the cytokine network that involved PDL formation and dental follicle cell growth and differentiation, have been well characterized at the molecular level. To approach this criticism, it is essential to understand the molecular mechanisms of PDL development to identify the appropriate functional molecules of inducing differentiation of stem cells into periodontal lineage cells for successful reconstruction of periodontal tissue. Hence, an ECM administration therapy involving ADAMTSL6 β has the capacity to facilitate drug discovery for treating periodontal diseases, and MFS-associated disorders.

Key Words: microfibrillin, periodontal regeneration, marfan's syndrome

INTRODUCTION

The current researches revolve around the ways and means to regenerate the most integral part of periodontium: Periodontal ligament. All the previous studies based on embryonic development, stem cell biology and tissue engineering technologies contribute to the advanced strategies which can be employed to regenerate what is lost to periodontitis. PDL stem cells and the cytokine network that involved PDL formation and dental follicle cell growth and differentiation, have been well characterized at the molecular level. Based on these results, regeneration of periodontal tissues is being made clinically possible by the transplantation of mesenchymal stem cells which can differentiate into PDL cells, cementoblasts and osteoblasts, or through the local application of cytokines to stimulate the proliferation and differentiation of these stem cells.[1]

This review article brings the contribution of extracellular matrix in periodontal ligament regeneration through the promotion of microfibril assembly as a novel therapeutic strategy for the essential functional recovery of periodontal tissue.

OVERVIEW OF PERIODONTAL LIGAMENT:

The periodontal ligament is the connective tissue layer between the cementum covering of the tooth root and the alveolar bone. The ligament forms a link between the tooth and the

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bone, thus providing support, protection and sensory input for the masticatory system. The PDL has essential roles in tooth support, homeostasis, and repair, and isinvolved in the regulation of periodontal cellular activities such as cell proliferation, apoptosis, the secretion of extracellular matrices, resorption and repair of the root cementum, and remodeling of the alveolar bone.[2]

DENTAL FOLLICE FORMATION:

The PDL is derived from the dental follicle (DF), which is located within the outer mesenchymal cells of the tooth germ and can generate a range of periodontal tissues including the PDL, cementum and alveolar bone. The differentiation of the DF proceeds as follows:

(1) During the tooth root forming stage, the Hertwig's epithelial root sheath (HERS) comprising the inner-and outer-dental epithelia that initiate tooth root dentin formation is fragmented into the Mallasez epithelium resting on the tooth root surface

(2) The DF migrates to the surface of the tooth root and differentiates into cementoblasts to form the cementum matrix

(3) At almost the same time, the DF differentiates into the PDL on the cementoblasts in order to insert collagen fibers, known as Sharpey's fibers, into the cementum matrix. Fiber insertion also takes place along the alveolar bone

(4) Both bone- and PDL-derived fibers finally coalesce in the PDL to form the intermediate plexus, which resembles tendinous tissue.[3]

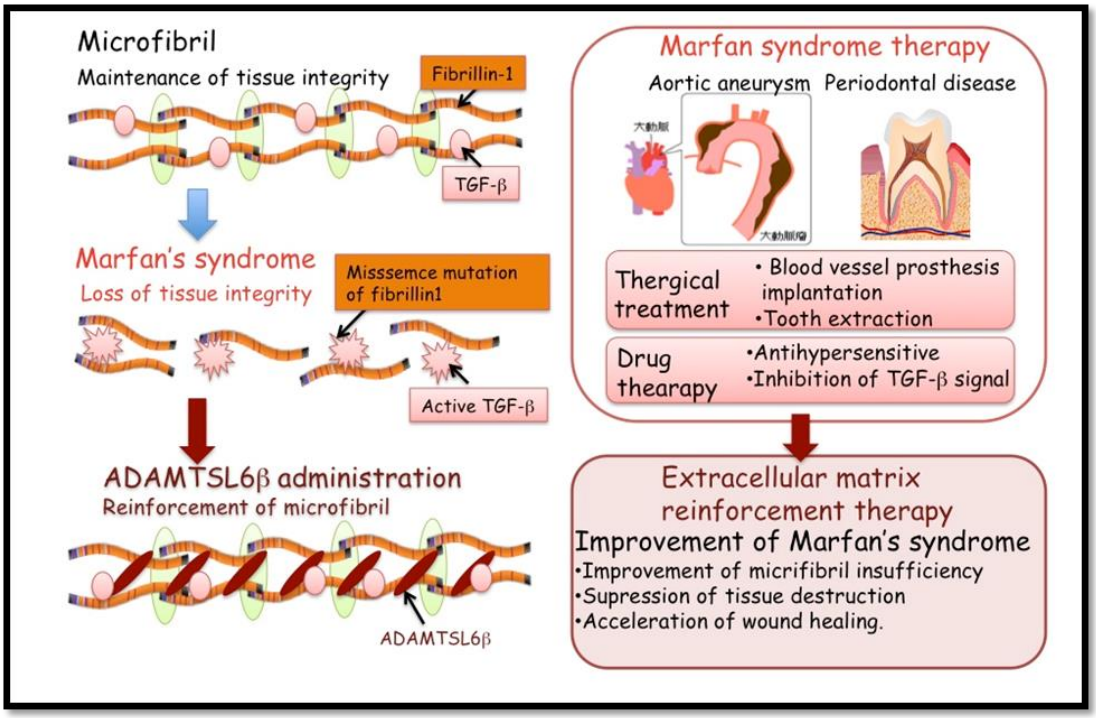
ESSENTIALITY OF MICROFIBRIL: THE SAVIOUR

Global gene expression analysis of PDL forming stage have revealed that ECM components including type I collagen,type III collagen, lumican, decorin, periostin, f-spondin, tenascin-N, fibrillin-1and PLAP1/aspirin are highly expressed during PDL formation.

FIBRILLIN-1 THE KEY COMPONENT BEHIND REGULATION:

Various mouse models of Marfan's syndrome (MFS) have been established via gene targeting or missense mutations, with germline mutations in fibrillin-1 leading to progressive connective tissue destruction due to fibrillin-1 fragmentation in association with an insufficiency of fibrillin-1 microfibril formation.[4] MFS have been shown to increase the susceptibility to severe periodontal disease due to a dysfunction of the PDL through a microfibril insufficiency, suggesting that fibrillin-1 microfibril formation plays a central role in PDL formation . MFS patient have been shown that periodontal disease is progressed severely compared with non MFS patient.[5]

CURRENT STRATEGY INVOLVED IN TREATING MARFAN'S SYNDROME:



Schematic representation of the MFS and ECM administration therapy as a novel therapeutic strategy for the treatment of MFS. Left panel: Fibrillin-1 comprises insoluble extracellular matrix components in connective tissue microfibrils and provides limited elasticity to tissues through fibrillin-1 microfibril formation. Missense mutations of fibrillin-1 leading to progressive connective tissue destruction due to fibrillin-1 fragmentation in association with an insufficiency of fibrillin-1 microfibril formation. ADAMTSL6 β is essential for fibrillin-1 microfibril formation and suggest a novel therapeutic approach to the treatment of MFS through the promotion of ADAMTSL6 β -mediated fibrillin-1 microfibril assembly. Right Panel: A variety of MFS therapies have been developed, including surgical therapy for aortic root aneurysms that are life-threatening, traditional medical therapies such as β-adrenergic receptor blockade for slow aortic growth and to decrease the risk of aortic dissection, and novel approaches based on new insights such as the deregulation of TGF-β activation. ECM reinforcement therapy which induces restoration of properly formed microfibrils by ADAMTSL6 β is essential not only for improvement of the predominant symptoms of MFS, but also for the suppression of excessive TGF-β signaling induced by microfibril disassembly.[6]

ECM ADMINISTRATION THERAPY SERVES TO BE A NOVEL APPROACH IN PDL REGENRATION:

The novel ADAMTSL family molecules ADAMTSL6 α and 6 β were recently identified by in silico screening for novel ECM proteins produced from a mouse full-length cDNA database (FANTOM). These proteins are localized in connective tissues, including the skin, aorta and perichondrocytes. Among ADAMTSL6, ADAMTSL6 β has shown to associated with fibrillin-1 microfibrils through its direct interaction with the N-terminal region of fibrillin-1 and promotes fibrillin-1 matrix assembly in vitro and in vivo. These findings suggest a potential clinical application of ADAMTSL6 β as a novel MFS therapy by promoting fibrillin-1 microfibril assembly and regulating TGF-β activation.[7]

It is also suggested that the administration of fibrillin-1 microfibrils provides a novel therapeutic strategy for the treatment of periodontal disease.

In situ hybridization analysis revealed that ADAMSL6 β was strongly expressed in the PDL forming stage of the DF however ADAMSL6 β expression was significantly downregulated in the adult PDL. Immunohistochemical analysis further revealed that ADAMSL6 β is detectable in assembled microfibril-like structures during the PDL forming stage of the DF, and in organized microfibrils in the adult PDL. Because developmental processes involve similar mechanisms to

wound healing, we next determined whether ADAMSL6 β is involved in PDL microfibril assembly during wound healing using a tooth replantation model. Histochemical analysis revealed that both fibrillin-1 and ADAMSL6 β expressions were found to be clearly induced during wound healing of PDL, but to decrease again after healing. These findings suggested that ADAMSL6 β was involved in microfibril formation during PDL formation/regeneration.[8-9]

CONCLUSION:

Although partial regeneration of the periodontal tissue has been established, novel treatment must be developed corresponding to regenerate large defect destroyed by severe periodontal disease. To approach this criticism, it is essential to understand the molecular mechanisms of PDL development to identify the appropriate functional molecules of inducing differentiation of stem cells into periodontal lineage cells for successful reconstruction of periodontal tissue. Hence, an ECM administration therapy involving ADAMTSL6 β has the capacity to facilitate drug discovery for treating periodontal diseases, and MFS-associated disorders.

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