Development of preventive medicine for aortic aneurysm and dissection of Marfan syndrome

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Marfan's syndrome (MF) is a severe, systemic disorder of connective tissue formation and can lead to aortic aneurysm and dissection, ocular lens dislocation, emphysema, bone overgrowth and severe periodontal disease. MF has an estimated prevalence of 1 in 5,000-10,000 individuals. Various mouse models of MF 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. Hence, it is largely accepted that MF is caused by insufficient fibrillin-1 microfibril formation in various connective tissues.

A variety of MFS therapies have been developed, including surgical therapy for aortic root aneurysm and dissection (AAD) that are life-threatening, traditional medical therapies such as β-adrenergic receptor or angiotensin II receptor blockers for slow aortic growth and to decrease the risk of AAD. However these treatments did not prevent tissue destruction in the AAD of MF. To develop preventive strategy for AAD, it will be necessary to identify molecular mechanisms of microfibril formation and an appropriate fibrillin-1 microfibril associated molecule（figure.1）. Recently we have identified novel extracellular matrix, ADAMTSL6β that associate with fibrillin-1 microfibrils to promote fibrillin-1 matrix assembly. In addition, recombinant ADAMTSL6β able to reorganize structurally damaged microfibril in the periodontal ligament, a tooth supporting connective tissue of MF mice model. These findings suggest a potential clinical application of ADAMTSL6β as a novel preventive medicine for AAD of MF by regeneration of fibrillin-1 microfibril assembly（figure.2）.

Our findings provide evidence for the contributions of ADAMTSL6β-mediated fibrillin-1 microfibril assembly to alleviation of MFS manifestations. We thereby introduce the concept that an ECM reinforcement therapy such as ADAMTSL6β administration which induces microfibril assembly, should be considered in the development of future mechanism-based therapeutics for the improvement of connective tissue disorders such as MFS. Since tissue destruction occurs continuously in AAD in MF, chronic administration of ADAMTSL6β required for the stabilization of microfibrils to prevent progressive tissue destruction. This approach will facilitate drug discovery for preventive medicine of MF and related connective tissue disorders（figure.3）.

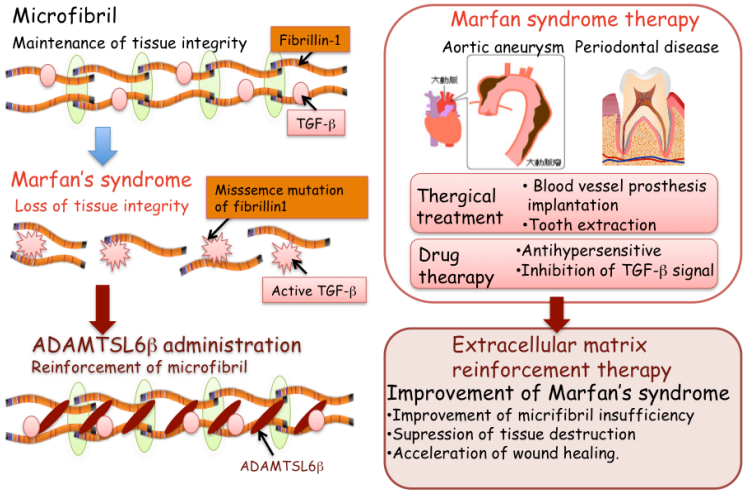

Fig. 1. Schematic representation of the MF and ECM reinforcement therapy as a novel therapeutic strategy for the treatment of MF.

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. ADAMTSL6β is essential for fibrillin-1 microfibril formation and suggest a novel therapeutic approach to the preventive treatment of MF through the promotion of ADAMTSL6β-mediated fibrillin-1 microfibril assembly.

Right Panel : A variety of MF 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. ECM reinforcement therapy which induces restoration of properly formed microfibrils by ADAMTSL6β is essential for improvement of the predominant symptoms including aortic aneurysm and dissection in MF.

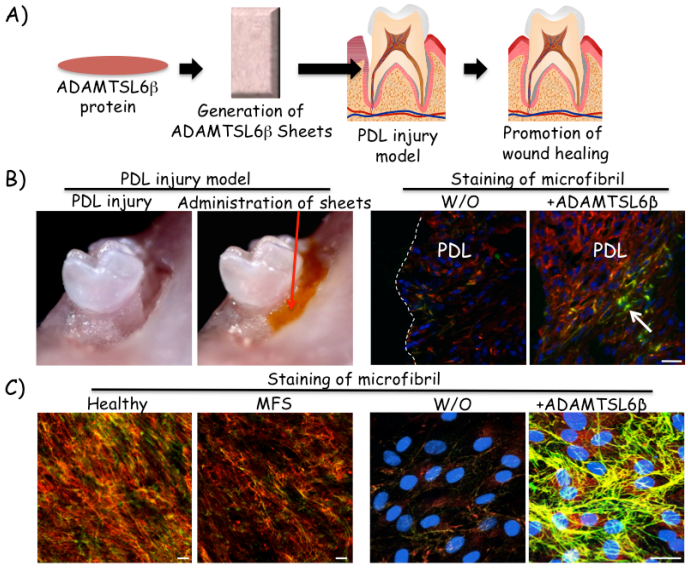

Fig. 2 ADAMSL6β improves microfibril disorder in PDL from an MF model.

A) Schematic representation of the local administration of recombinant ADAMSL6β into a periodontal ligament (PDL) injury model

B) After injury of PDL by dislocation, collagen gel-containing recombinant ADAMSL6β was then injected into the injured PDL (left). Immunohistochemical analysis showed an improvement in fibrillin-1 microfibril assembly (arrowheads) induced by the injection of recombinant ADAMSL6β. WO:Without treatment of ADAMSL6β.

C) Histological analysis of PDL cells obtained from MF treated with recombinant ADAMTSL6β. PDL cells obtained from MF patients showed microfibril insufficiency compared with PDL cells

obtained from healthy patient (left). Administration of ADAMSL6β marked improvement of microfibril assembly in PDL cells obtained from MF patients (right).

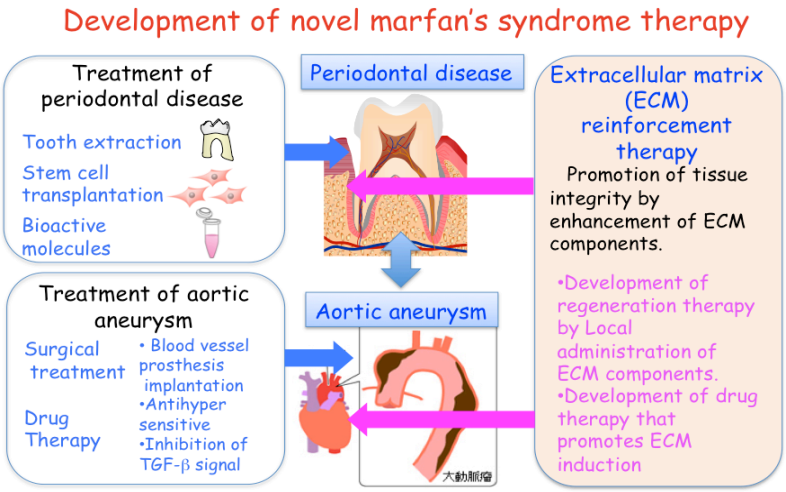

Fig. 3 ECM reinforcement therapy as a novel therapeutic strategy of MF syndrome. ECM reinforcement therapy such as ADAMTSL6β administration which induces microfibril assembly, should be considered in the development of future mechanism-based therapeutics for the improvement of connective tissue disorders such as MF.