SYSTEMATIC REVIEW ARTICLE

Fibromodulin: Structure, Physiological Functions, and an Emphasis on its Potential Clinical Applications in Various Diseases

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ABSTRACT

Fibromodulin (FMOD) is one of the small leucine-rich proteoglycans. A search of the literature did not reveal any paper that specifically reviews the potential clinical applications of FMOD in the management of human diseases. First, the structure and physiological functions of FMOD were reviewed. Then its potential clinical applications in various diseases including diseases of the skin, tendons, joints, intervertebral discs, blood vessels, teeth, uterus, bone and kidney were reviewed. FMOD is able to switch the adult response to skin wounding to the desired fetal response of scarless healing. Lowered levels of FMOD would be desirable in the management of tendinopathy, uterine fibroids, tumors resistant to radiotherapy, glioblastomas, small-cell lung cancer, and primary liver/lung fibrosis. In contrast, increased levels of FMOD would be desirable in the management of acute tendon injuries, osteoarthritis, rheumatoid arthritis, temporo-mandibular disease, joint laxity, intervertebral disc disease, neo-intimal hyperplasia of vein grafts, teeth caries, periodontal disease, endometrial atrophy, osteoporosis and diabetic nephropathy. Furthermore, FMOD may be used as a prognostic marker of cerebrovascular events in patients undergoing carotid endarterectomy and a marker for prostatic cancer. Finally, the use of FMOD in the treatment of symptomatic endometrial atrophy should be explored in women who are unable to use the standard estrogen management for endometrial atrophy. The review concluded that clinical trials in humans should be initiated to investigate the potential therapeutic effects of FMOD.

Key Words: *Fibromodulin, Proteoglycans, Structure, Function, Disease, Human, Scarless healing.*

INTRODUCTION

Fibromodulin (FMOD) is one of the small leucine-rich proteoglycans (SLRPs) found in the extracellular matrix (ECM). It plays several physiological roles such as fibrillogenesis, muscle cell growth, determination of cell fate, and enhancement of angiogenesis.[1] It also participates in the pathogenesis of several pathological conditions such as systemic fibrosis, tumors and atherosclerotic plaques.[2-4] Its gene in humans was mapped to chromosome-1 (1q32).[5]

The search for the current review was done using PubMed database. "Fibromodulin" and "Structure" with no time bar revealed a total of 88 articles; "Fibromodulin" and "Function" with no time bar revealed a total of 444 articles; and "Fibromodulin" and "Disease" with no time bar revealed a total of 104 articles. Repeated articles were omitted and the remaining were scanned. There were no review articles investigating the role of FMOD in various diseases. All articles on the topic investigated specific diseases separately.

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Received: January 20, 2018; Accepted: May 25, 2018.

At first part, the structure and physiological functions of FMOD was described. The review then emphasised the potential clinical applications of FMOD in various diseases.

Basic Structure of FMOD: The SLRPs is a family of 5 classes and include decorin, biglycan, lumican and chondroadherin. FMOD is a class II SLRP. The basic structure is shown in Figure 1. This review will describe the structure in a simplified way. The complex structure is detailed in the literature.[1,6,7]

FMOD is made up of a 12 tandemly organised Leucine-Rich Repeats (LRR). Each LRR is 20-30 amino-acids long with an 11-residue hallmark sequence: LxxLx LxxNxL ("L" being Leucine, "x" being any amino acid, and "N" being Asparagine). At the N-terminal, the N-cap has two conserved di-sulfide bonds (Figure 1).[7]

The crystal structure of FMOD (Figure 2) looks like a curved *solenoid* (a helical coil), derived from Greek (*solen* meaning pipe and *eidos* meaning shape). The curved crystal structure of FMOD also looks like a horse-shoe. Hence, FMOD has two faces: the inner concave face, which has the parallel beta strands (contributed by the LRR; and the outer convex face, which has several inter-woven strands with various structural elements including alpha-helices, polyproline II helices, and beta turns. On the convex side of LRR XI, there is a loop which has the shape of an ear. The ear loop spans from the C terminal cysteine (Cys 334 - 367) of LRR XI to the beta turn of LRR XII.

The inner concave face of all SLRPs (including FMOD) is the main site of ligand-binding. In the ECM, FMOD is present as a monomer. Hence, the binding sites are always available. In contrast, other SLRPs such as decorin and biglycan form dimers; using the concave faces. This indicates that there may be alternative modes of binding.[8] The concave face of FMOD binds to both collagen I and III at two binding sites: LRR 5-7 (a low affinity site) and LRR 11 (a high affinity site).[6,7,9] FMOD also binds to the cross-linking enzyme lysyloxidase near the N-terminal; and this binding activates the enzyme.[10] It is important to note that the structure of FMOD has many structural similarities to another SLRP known as chondroadherin.[7] One main difference in structure is that the "ear" part is replaced by a large C-terminal cap in chondroadherin. Like FMOD, the concave face (towards the C-terminal) binds to collagen I. However, chondroadherin does not bind to collagen III. Furthermore, chondroadherin residues 307-318 (which map to the α-helix of the C-terminal cap) binds to the integrin $\alpha 2$-$\beta 1$.[11]

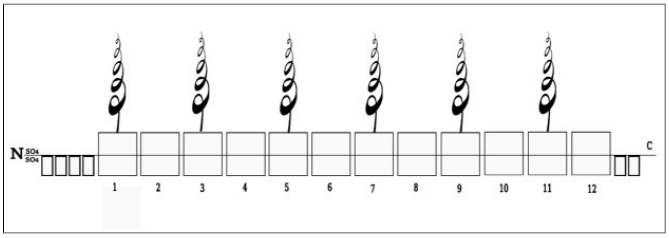

Figure 1: Basic structure of FMOD (N = N-terminal, C = C-terminal).

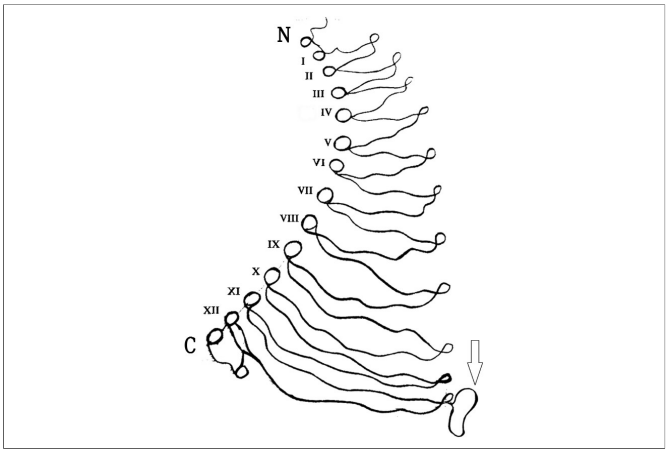

Figure 2: Crystal structure of FMOD (N = N-terminal, C = C-terminal). The arrow points to the "ear" (see text for details).

Finally, the tyrosine-sulfated N-terminal domain of FMOD mimics heparin. This domain has been identified as a third collagen binding site; playing a major role in collagen fibril assembly.[12]

Physiological Functions of FMOD:

1. Normal fiber formation and cross linkage: FMOD is essential for normal collagen fibrillogenesis and normal collagen cross-linkage.[10,13] Fibrillogenesis means the maturation of small to large diameter collagen fibrils. This is mediated via the binding of collagen to the FMOD as mentioned above. FMOD knock-out mice have abnormal small diameter collagen fibers.[14] Lysyl oxidase is an important cross-linking enzyme for collagen. As mentioned in the structure of FMOD, the binding of the enzyme to FMOD increases its activity.[10]

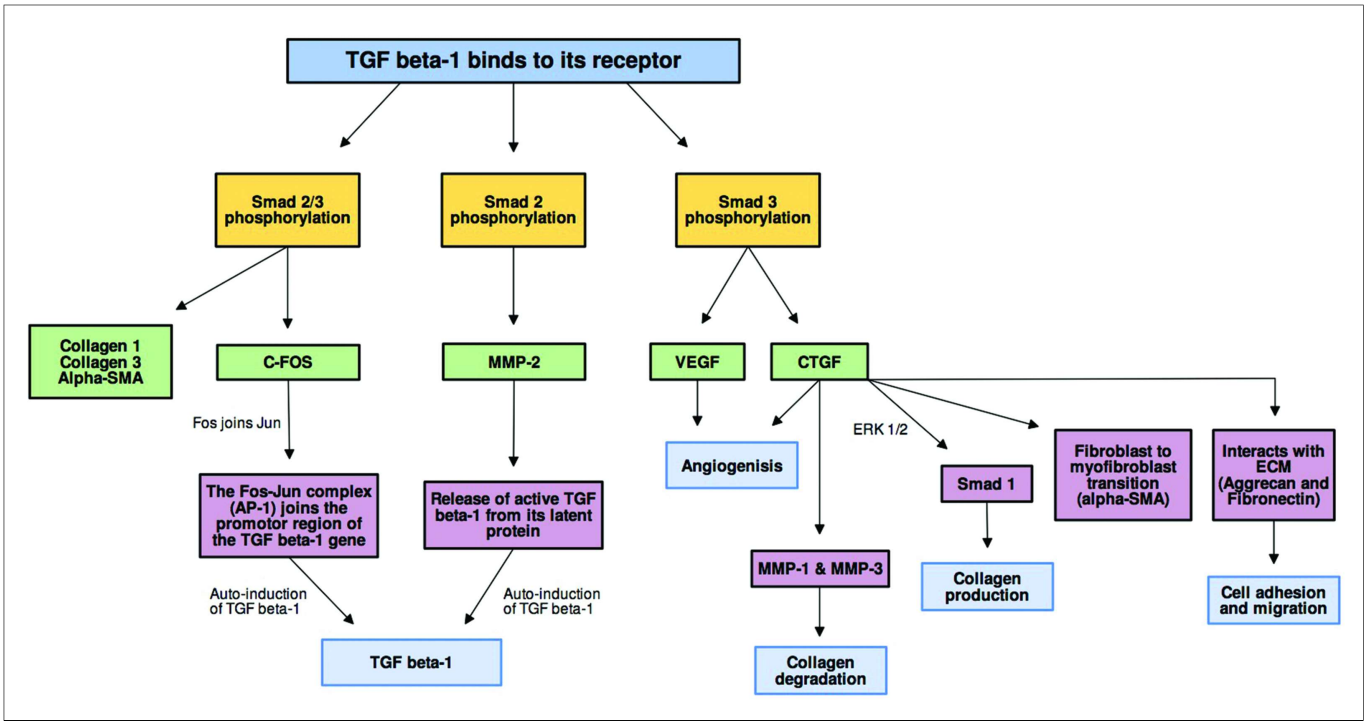

Figure 3: TGFβ1 pathway in relation to FMOD (see text for details).

2. Normal muscle development: The normal muscle development begins with the transformation of muscle satellite cells to myotubes. FMOD maintains the transcriptional activity of myostatin; which participates in myoblast differentiation.[15]

3. Cell fate: FMOD is also known to participate in cell fate. This function is thought to be mediated through the interactions of the N-terminal domain of FMOD that mimics heparin. This site binds to several bioactive factors including fibroblast growth factor 2 (FGF2) and interleukin-10.[16] Hence, cellular re-programming into multipotent cells is possible with the use of FMOD.[17,18]

4. Angiogenesis: FMOD is known to be an important factor mediating angiogenesis, including endothelial cell migration and the formation of capillaries. This occurs through the induction of expression of angiopoietin and vascular endothelial growth factor (VEGF).[19] The angiogenic FGF2 also binds to the N-terminal domain of FMOD that mimics heparin.[16] It is important to note that other members of the SLRPs also play a role in angiogenesis. For example, lumican inhibits angiogenesis; while decorin can act either as a pro-angiogenic or an anti-angiogenic factor.[16]

FMOD in disease and its potential clinical applications:

A. FMOD and skin scarring: Abnormal skin scarring may present in the form of hypertrophic scars or keloids. The transforming growth factor beta-1 (TGFβ1) pathway is the main pro-fibrotic pathway involved in the pathogenesis of abnormal skin scarring.[20] The TGFβ1 protein binds to its surface receptors leading to the phosphorylation of Smad 2 and 3 (Smads are homologous to the Caenorhabditis Elegans protein Sma; and the Drosophila protein, mothers against decapentaplegic (mad)). Smads 2 and 3 combine with Smad 4; and complexes (Smad 2-4 and Smad 3-4 complexes) translocate to the nucleus to trigger target gene transcription including collagen I, collagen III, α-smooth muscle actin (α-SMA), *c-Fos* (The human oncogene *c-Fos* is homologous to the Finkel-Biskis-Jinkins murine osteosarcoma virus oncogene), matrix metallo-proteinase-2 (MMP-2), VEGF, and connective tissue growth factor (CTGF) (Figure 3).[20] It is important to note that collagen, α-SMA and *C-Fos* are induced by Smads 2 and 3. The induction of MMP-2 is Smad 2-dependent; while the induction of VEGF/CTGF is Smad 3-dependent.[21,22] Figure 3 shows the relevant effects secondary to the induction of these proteins in order to explain the action of FMOD in skin wound healing. The induction of the *c-FOS* gene leads to the expression of the *Fos* protein.[23] "*Fos*" joins "*Jun*" (The name *Jun* comes from the Japanese '*ju-nana*,' meaning the number 17; but scientifically, *Jun* stands for avian sarcoma virus 17 oncogene homolog) to form the activator protein 1 (AP-1). A-P-I is a transcription factor that joins the promotor regions of the TGFβ1 gene. This leads to the auto-induction of TGFβ1 protein (auto-induction means that there will be an excessive production of TGFβ1 secondary to TGFβ1 stimulation).[23,24]

The increased expression of MMP2 (which is Smad 2-dependent) promotes the release of active TGFβ1 from its latent protein; also leading to the auto-induction of TGFβ1.[25]

The expressions of VEGF and CTGF are Smad 3-dependent. VEGF leads to enhanced angiogenesis. CTGF has multiple effects: enhancement of angiogenesis, induction of MMP1&3, collagen production via the ERK ½ - Smad 1 (ERK ½ stands for Extracellular signal-Regulated Kinase-1 & 2) pathway, enhanced fibroblast to myofibroblast transition which is associated with an increased expression of α-SMA, and cell adhesion/migration via the interaction of CTGF with several members of the ECM such as aggrecans and fibronectin.[26,27]

Experimentally, the increased expression of FMOD in healing skin wounds, results in a decrease in scar size and improvement of wound healing and tensile strength.[28] This is mediated by three mechanisms. First, FMOD represses the A-P1; and hence, it acts against the auto-induction of TGFβ1.[28] Second, FMOD leads to a rapid but transient Smad 2 activation. Hence, the expression of MMP2 is short-lived; which also acts against the auto-induction of TGFβ1.[28] Finally, FMOD leads to a prolonged Smad 3 activation without altering gene or protein expression.[28] Hence, the sustained low levels of CTGF will lead to enhancement of angiogenesis, cell adhesion/migration, and myofibroblast differentiation; but without excessive collagen production.[28] The lack of excessive collagen within the ECM may be related to the induction of MPP 1 & 3 by CTGF, which will degrade collagen.[27] These FMOD-mediated effects are very similar to what is seen at the molecular level in the scarless fetal skin wound repair.[29,30] Furthermore, fetal fibroblasts are known to have higher levels of α-SMA compared to adult fibroblasts; and during scarless repair, there is increased angiogenesis and expression of VEGF.[31,32] This is why some authors propose that FMOD is able to reduce scarring in adult cutaneous wounds by eliciting a fetal-like phenotype.[28] The clinical use of FMOD to prevent or treat abnormal scars is worth exploring.

B. FMOD and tendinopathy/tendon healing: Tendinopathy is caused by multiple factors such as over use, load-induced ischemia, and repeated minor injuries. It is commonly seen in the Achilles, patellar and supraspinatus tendons. Ectopic calcification of the tendon may also occur and predisposes to tendon rupture. Biochemically, tendinopathy is associated with high collagen III content as well higher expression of SLRPs such as FMOD and bigylcan.[33] In a patellar tendinopathy model, the increased deposition of FMOD was thought to play an important role in its pathogenesis.[34] Decorin (another SLRP) was not

increased in tendinopathy.[34] The suppression of FMOD may also play a role in managing tendinopathy.

Acute tendon injuries are common and healing remains unsatisfactorily. FMOD is known to enhance collagen cross linkage. Delalande *et al*. investigated the effects of liposomal delivery of the FMOD gene in a rat Achilles tendon injury model and showed an accelerated tendon healing.[35] This may provide a new therapeutic strategy for acute tendon injuries in the clinical setting.[35]

C. FMOD and joints: FMOD is an important component of the ECM of the human articular cartilage.[36] In the juvenile and adolescent articular cartilages, FMOD has many keratan sulfate chains. The size of these chains decreases with age.[36]

In osteoarthritis and rheumatoid arthritis, FMOD of the articular cartilage contains fewer keratan sulfate.[37] Furthermore, FMOD is sequestrated in arthritis and the total FMOD content is reduced.[38] In fact, the bigylcan/ FMOD double knock-out mouse is an animal model for osteoarthritis.[39] Hence, the clinical use of FMOD in arthritis may have a potential therapeutic effect.

Temporo-mandibular disorder or (TMD) refers to pain in the jaw joint and muscles. It is much more prevalent in women than in men. One theory of pathogenesis is the protective effect of the male sex hormones. Okamoto *et al*. showed that dehydroepiandrosterone (a precursor of testosterone) had a protective effect on the synovial tissue of the temporo-mandibular joint by enhancing FMOD formation.[40] FMOD may be tried in the management of TMD.

Finally, joint laxity is associated with a reduced level of FMOD in the ligaments supporting the joints.[41] This is expected because ligaments are made of collagen fibers, and FMOD contributes to fibril maturation. In fact, the lumican-FMOD double knock-out mice is a model of joint laxity.[41] Increasing the expression of FMOD in lax ligaments may be a novel treatment of ligament laxity.

D. FMOD and intervertebral disc diseases: Intervertebral disc diseases are seen with several pathologies such as degenerative disc disease, disc herniation, and scoliosis. Brown *et al*. studied the changes in proteoglycans in various disc diseases in humans and found that biglycan and FMOD were the most extensively fragmented proteoglycans.[42] Similar changes were reported in experimentally injured ovine intervertebral discs.[43] Furthermore, FMOD in the human annulus fibrosus exhibited a structural change with increasing age with a shift toward the reduction of keratan sulfate chains of FMOD.[44] The use of FMOD is human degenerative disc disease may have clinical applications in the future.

E. FMOD and blood vessel disease: FMOD is involved in the pathogenesis of atherosclerosis and atherosclerotic plaques. Shami *et al*. studied 153 human plaques obtained by carotid endarterectomy.[45] The expression of FMOD was significantly higher in symptomatic plaques and was highest in plaques obtained from patients with diabetes.[45] Furthermore, a high FMOD expression was associated with a significantly higher incidence of post-operative cerebrovascular events.[45] Hence, FMOD may be used as a prognostic marker of cerebrovascular events in patients undergoing carotid endarterectomy.

Neo-intimal hyperplasia (NIH) is the main mechanism of long-term graft patency failure in vascular surgery. Ranjzad *et al*. showed that adenovirus-mediated gene transfer of FMOD inhibited NIH in an organ culture model of saphenous vein graft.[46] Gene transfer of FMOD has a great potential in improving long-term vein graft patency in vascular surgery.[46]

F. FMOD and dentistry: Normal levels and structure of FMOD are essential for the normal development of dental tissue and the adjacent alveolar bone.[47,48]

In healthy dentine, FMOD is abundant near the tubule walls and under the cusps. In carious teeth, FMOD becomes degraded and the degradation pattern is well correlated with the progression of caries. Furthermore, highly infected areas are associated with the lowest concentration of FMOD.[49] These findings indicate the involvement of FMOD in the pathogenesis of caries progression.

In normal healthy human gingiva, FMOD is highly expressed in the ECM of the gingival epithelial cells, indicating a supportive function to the epithelium.[50] In gingivitis, there is an upregulation of FMOD expression within the inflamed gingival tissue in humans.[51]

In the normal healthy periodontium, FMOD is highly expressed at the interface of the periodontal ligament with the alveolar bone.[51] With FMOD deficiency (such as knock-out animal models), the bone morphogenetic protein pathway is over-activated with an elevated number of osteoclasts around the alveolar bone-periodontal ligament junction. This is associated with an increased expression of RANKL (Receptor Activator of Nuclear-factor Kappa-β Ligand). RANKL binds to its receptor (RANK) and activates osteoclasts; and hence, RANKL is also known as the osteoclast differentiation factor (ODF). This leads to localized resorption of the alveolar bone at the interface with the periodontal ligament.[52] Hence, FMOD is an important factor modulating osteoclastogenesis in periodontal disease.

G. FMOD and gynecological disease: Post-menopausal endometrial tissue atrophy may present with various gynecological symptoms. The level of FMOD expression in the endometrium is dramatically decreased in post-menopausal women compared to menstruating women.[53] The use of FMOD in the treatment of symptomatic endometrial atrophy should be explored in women who are unable to use the standard estrogen management for endometrial atrophy.

Fibroids (leiomyomas) of the uterus are common. These tumors have fibrotic characteristics and have an

extremely high expression of FMOD.[54] Fibroids are also known to have low expression of vitamin D receptors.[55] Halder *et al*. found that vitamin D supplements resulted in both an increase of nuclear vitamin D receptors and a decrease in the expression of FMOD in fibroids.[55] The authors concluded that vitamin D supplements will reduce the expression of FMOD in fibroids; and hence might be an effective, safe, non-surgical treatment method for uterine fibroids.[55]

H. FMOD and cancer: The term tumor barrier function in carcinoma refers to the presence of a dense stroma in the ECM of carcinomas which forms a functional barrier for fluid transport, and impair blood flow.[56,57] This will negatively affect the outcome of chemotherapy and radiotherapy of carcinomas. FMOD is highly expressed in carcinomas with a dense stroma and is considered as the main reason behind the increase in tumor barrier function.[56,57] Olof-Olssen *et al*. showed that the induction of FMOD deficiency decreased the dense stromal collagen network of carcinomas.[56] This is of potential clinical relevance; affecting the accessibility of anti-cancer drugs to carcinomas.[56,57]

Highly metastatic breast cancers are known to have an over-expression of TGFβ1 and nuclear factor-KB (NF-KB) activity.[58] Dawoody-Nejad *et al*. overexpressed FMOD (by adenovirus gene transfer) in highly metastatic 4T1 breast cancer cell lines and demonstrated down-regulation of TGFβ1 and NF-KB; resulting in a decrease in the metastatic potential.[58] Hence, FMOD has a potential clinical application in the management of metastatic breast cancer.

FMOD was found to be highly expressed in prostatic cancer and not in benign prostatic disease.[59,60] Hence, FMOD is a potential biomarker for prostate cancer.[60]

Glioblastomas are one of the most lethal malignant tumors seen by neurosurgeons. Glioblastoma cell migration is known to be mediated through its ability to induce actin stress fiber formation (i.e. inducing myofibroblast-like migratory cells).[61] As mentioned before (Figure 3), FMOD induces fibroblast to myofibroblast transition. Hence, it is of no surprise that FMOD is highly expressed in highly malignant glioblastomas. FMOD silencing is a potential method in the therapeutic intervention of glioblastomas.[61]

Small-cell lung cancer with high malignant potential is known to be associated with high expression of FMOD as well as high expression of angiogenic factors.[62] As mentioned before (Figure 3), FMOD promotes angiogenesis. Ao *et al*. found that silencing FMOD in highly malignant small cell lung cancer resulted in a significant reduction in the expression of angiogenic factors.[62] Hence, silencing FMOD may be a potential clinical therapy for this cancer as well as other cancers in which angiogenic factors are known to play an important role in their malignant potential.[62,63]

Finally, FMOD was found to be a novel tumor associated antigen in chronic lymphocytic leukemia, which allows expansion of specific CD8+ (Cluster of Differentiation 8) autologous T lymphocytes.[64]

I. FMOD and primary liver/lung fibrosis: Primary liver and lung fibrosis are associated with high expression of FMOD.[3,65] Hence, silencing FMOD may play a role in the management of these fibrotic diseases. This should encourage researchers to study the therapeutic effects of FMOD in the management of various systemic fibrotic conditions.

J. FMOD and osteoporosis: As mentioned under dental disorders, FMOD deficiency is associated with the overexpression of the osteoclast differentiation factor RANKL. This leads to localised resorption of the alveolar bone.[52] Generalised osteoporosis results from an imbalance between new bone formation by osteoblasts and old bone resorption by osteoclasts. Kram *et al*. found that FMOD deficiency plays an important role in osteoclastogenesis and in the pathogenesis of osteoporosis.[66] FMOD should be explored further in the management of osteoporosis.

K. FMOD and diabetic nephropathy: Diabetic nephropathy is a progressive disease that leads to renal failure. It is known to be associated with a high TGFβ1 activity. As mentioned earlier (Figure 3), FMOD reduces the auto-induction TGFβ1. Jazi *et al*. induced a high level of FMOD (by gene transfection) in diabetic animals with nephropathy and noted a reduction in TGFβ1 levels.[68] Intra-peritoneal injection of adenoviral vectors expressing FMOD should be investigated further in the management of diabetic nephropathy.[67]

L. FMOD and mucopolysaccharidosis: Mucopolysaccharidosis are a group of inherited disorders with excessive deposition of mucopolysaccharides in various tissues. It leads to progressive skeletal and connective tissue disease. The current enzyme replacement therapy has limited effects on bone and joint disease. Heppner *et al*. found that FMOD plays an important role in the pathogenesis of bone and joint disease in mucopolysaccharidosis.[68] These findings have potential therapeutic implications.

M. FMOD and stem cell-based therapeutics: As mentioned earlier, FMOD plays a role in the cell fate. Stem cell-based therapeutics is a vital component of tissue engineering and regenerative medicine. Hence, FMOD was found to be a novel cell source for bone regeneration,[17] and for programming of human fibroblasts into multipotent cells.[18]

DISCUSSION

FMOD is involved in the pathogenesis of several diseases/disorders which span the medical and surgical fields.

Plastic surgeons have interest in skin scarring. There is no effective treatment of hypertrophic and keloid scars.

Experimentally, FMOD was found to decrease scar size without decreasing the tensile strength of the healing wound. At the molecular level, FMOD is the only known molecule that is able to switch the adult response to skin wounding to the fetal response of scarless wound healing.[28-32]

In the field of orthopedics and rheumatology, FMOD has several potential therapeutic applications. Lowering FMOD in tendons with tendinopathy arrests the pathological process.[33] In contrast, delivery of FMOD to acute tendon lacerations results in accelerated tendon healing.[35] Fragmentation and low levels of FMOD are observed in various joint pathologies (such as osteoarthritis, rheumatoid arthritis, temporo-mandibular disease, and joint laxity) as well as intervertebral disc disease.[37,38,40-44] Hence, restoring the normal levels of FMOD in these conditions is desirable and has potential clinical applications.

In the field of vascular surgery, a high FMOD level in the atherosclerotic plaques is a poor prognostic marker of cerebrovascular event in patients undergoing carotid endarterectomy.[45] In contrast, the induction of FMOD is desirable to improve long-term vein graft patency because FMOD suppresses neo-intimal hyperplasia.[46]

Dental research in relation to FMOD is also relevant clinically because FMOD is involved in the pathogenesis of caries,[49] the progression of gingivitis,[51] and the pathogenesis of alveolar bone resorption secondary to periodontal disease.[52]

In the field of gynecology, estrogen supplements are used to treat symptomatic endometrial atrophy. When estrogen therapy is contraindicated (such as in women with history of breast cancer or deep vein thrombosis), FMOD is an attractive alternative.[53] In contrast, the reduction of expression of FMOD is a potential non-surgical treatment method for uterine fibroids.[54,55]

FMOD has several clinical applications in the field of oncology. A tumor with a dense stroma has a high FMOD level which makes it resistant to chemo- and radio-therapy. Hence, lowering the level of FMOD in these tumors will reduce this resistance.[56,57] The malignant potential of various tumors may also be modified by altering the level of FMOD.[58,61-63] Furthermore, FMOD may be used as a biomarker for prostate cancer.[59,60]

Primary organ fibrosis, osteoporosis, and diabetic nephropathy are difficult to treat. Lowering the levels of FMOD in organ fibrosis;[3,65] and raising the levels of FMOD in osteoporosis[66] and diabetic nephropathy,[67] should be explored in clinical trials.

CONCLUSION

Although the detailed structure and physiological functions of FMOD are well described in the literature, there has been no comprehensive reviews on the potential role of FMOD in the pathogenesis and management of various diseases. The current paper is a review of these potential roles of FMOD. In some pathologies, benefits would be obtained by over-expressing FMOD; and in others, silencing of FMOD is desired. Furthermore, FMOD is a potential biomarker for cancers such as prostatic cancer. It is time for researchers to initiate clinical trials in humans to investigate the potential therapeutic effects of FMOD.

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