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REVIEW

A Prospectus of Tenomodulin

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Tenomodulin is a type II transmembrane glycoprotein that can regulate growth of tendon. The human tenomodulin encoding gene is mapped to X chromosome and encodes a polypeptide consisting of 317 alpha amino acids. The protein is located on the cell surface as N-glycosylated or non-N-glycosylated polypeptide with molecular mass of 45 and 40 kDa, respectively. The molecule consists of three domains and a short cytoplasmic tail at N-terminus. Tenomodulin is predominantly expressed in dense connective hypovascularized tissues such as tendons, skeletal muscle epimysium, and ligaments. Furthermore, tenomodulin is an efficient marker of tenocyte differentiation and plays an important role in the regulation of tenocyte proliferation, tendon development, and angiogenesis inhibition. A number of tenomodulin gene polymorphisms have been recently associated with a risk of obesity, diabetes, systemic immune mediators, cholesterol levels, Alzheimer disease, and age-related macular degeneration. Tenomodulin is involved in cell adhesion, determination of cell morphology, cell aging and bone mineral density. It is expected to play an important role in tendon recovery, tendon tissue engineering, anti-tumor therapy, treatment of chordal disruption, and remodeling of extracellular matrix.

INTRODUCTION

Recently, many research labs have been trying to get better understanding of the molecular mechanisms regarding the tendon formation and possibilities for recovery after tendon injuries. Currently, a lot of new protein class molecules with important regulatory functions have been discovered and identified.

In 2001, four independent research groups reported identification of a novel gene named myodulin[1], tendin[2], chondromodulin-I-like (*ChM1L*)[3], and tenomodulin (*TEM*)[4], respectively. According to the HUGO Gene Nomenclature Committee the official gene name is tenomodulin, introduced by Shukunami et al. in 2001.[4] The name originates from tenocytes, the tendon cells, as tenomodulin is predominantly expressed in tendons.[2,4,5] The official abbreviation of the human tenomodulin gene is *TNMD*.

The human tenomodulin belongs to a new protein class with a tissue-specific manner of expression. A lot of studies confirmed its important role in the tendon differentiation[4,6] and in the inhibition of angiogenesis[5,7]. Tenomodulin regulates various biological processes, but most of its functional mechanisms are still unknown.

AIM

The goal of this article is to provide an overview of the structure, tissue distribution, biological properties, role and functions of tenomodulin. First, we present the chromosomal location of the tenomodulin encoding gene in humans and other vertebrates. Further, the protein structure and location is introduced. Then we discuss the structural homology between tenomodulin and chondromodulin proteins. Additionally, the tenomodulin expression profile, the regulation of its expression and its biological functions are described. Finally, we provide a brief review of the possible medical applications of tenomodulin.

CHROMOSOMAL LOCATION OF THE TENOMODULIN ENCODING GENE

Tenomodulin gene has been found in both humans and other vertebrates. However, there are some differences between the human tenomodulin and the tenomodulin in other mammals. Such differences are expressed in the location and in the size of tenomodulin gene.

The human tenomodulin gene *(TNMD)* is mapped to the X chromosome (Xq21.33-q23) according to the Genome Reference Consortium Human Build

38 patch release 2 (NCBI Gene ID 64102). *TNMD* is 15 216 bp in size. On the other hand, in other mammals, for instance, mice, the tenomodulin gene (*Tnmd*) (Gene ID 64103) is slightly shorter, 14 570 bp. Similarly to humans, in other mammals (such as mice, rats, pigs, dogs, cows, apes) the tenomodulin gene is located predominantly on X chromosome. However, the gene location is different in other species. For instance, in chicken it is located on chromosome 4, while in zebra-fish – on chromosome 14.

The mature mRNA transcript of *TNMD*, 1 360 nt in length, contains 954 nt long open reading frame, and codes for 317 α-amino acids.[3,4] Still, there are few exceptions. A detailed intron-exon structure analysis reveals 7 exons and 6 introns in *TNMD*[2,8] as shown in Fig. 1.

PROTEIN STRUCTURE AND LOCATION

In this section we provide information about the structure of the protein, its domains and location. Then we describe the different protein forms. Finally, we discuss the localization of different protein isoforms in cells *in vitro*.

Human tenomodulin protein (TNMD) belongs to type II transmembrane proteins containing a short cytoplasmic tail. The C-terminus of the protein is exposed to the exterior cell surface.[4] The protein consists of three domains (Fig. 2): 1) an N-terminal transmembrane domain type II (NTD) (Ile31-Lys51)[3,4], 2) a BRICHOS domain (BD) (Gly93-Ile186)[9], and 3) a C-terminal domain rich of cysteine (CTD) (Phe255-Val317).[2-4]

The hydrophobic domain at the N-terminus has 20 α-amino acid residues.[4] The cytoplasmic tail is encoded by exon 1, while the NTD is encoded by exon 2.[2,8]

The BD has two N-glycosylation sites. They are conserved in humans and in other mammals.[3,4,9] In humans the N-glycosylation sites are found at positions 94 and 180, while in rabbits they are at positions 95 and 181.[10] The BD has been identified as a novel domain of approximately 100 α-amino acids in both vertebrates and invertebrates. These domains include a pair of cysteine residues that are predicted to form a disulfide bond. This is the most conservative region among BDs of different origin.[9,11]

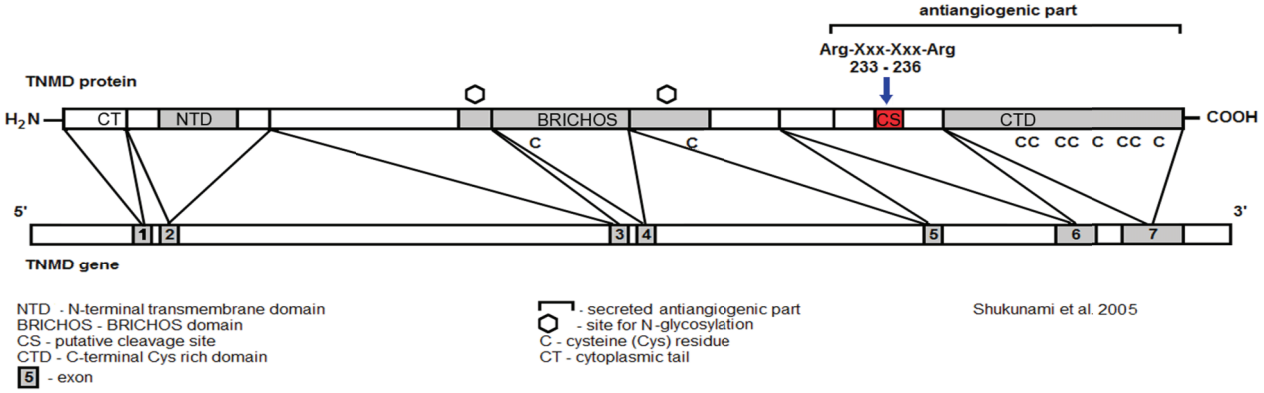

Figure 1. Genomic organization of the hTNMD gene and its translated product.[8]

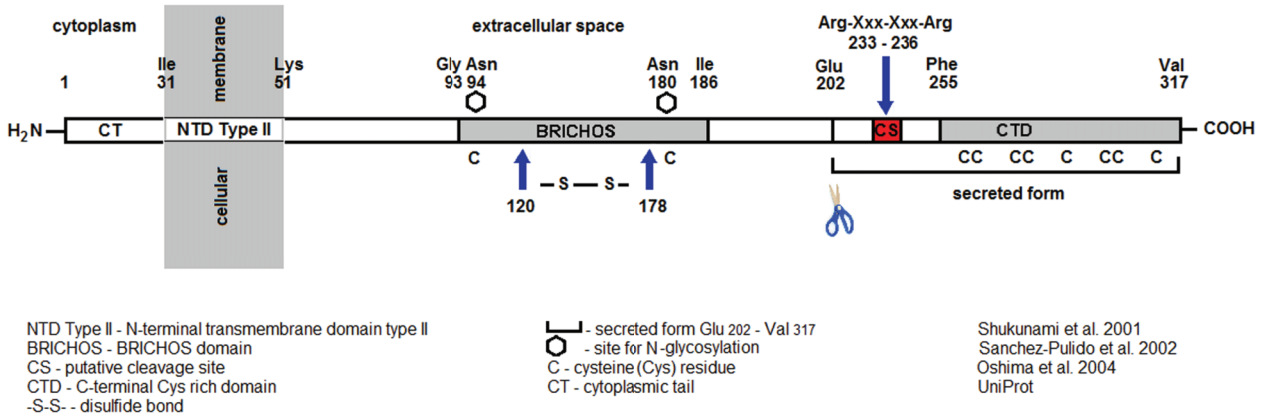

Figure 2. TNMD protein structure and cell location.[4,7,9]

The CTD is a highly conserved part across species.[10] It consists of a conservative sequence of 71 α-amino acids and 8 cysteine residues.[2-4] The CTD could be cleaved and released from the cells as a secreted soluble form with a strong antiangiogenic activity.[7] There is a potential cleavage site (Arg-Xxx-Xxx-Arg) located at positions 233 to 236.[7] Exons 3-7 code for the extracellular part of the protein. Exon 7 encodes the complete CTD with 8 cysteine residues.[2,8] Furthermore, the rabbit tenomodulin protein revealed 97.7%[10], while the mouse tenomodulin protein (Tnmd) shears 96% overall identity with TNMD.[4]

It has been shown that the TNMD protein can have different forms.[3,5,7,12] For example, TNMD has been detected as N-glycosylated and non-N-glycosylated form with molecular mass of 45 and 40 kDa, respectively.[3] The same forms are found in pigs, namely in pigs' *chordae tendineae cordis* (CTC) and pigs' eye.[12] These forms have been also found in mice.[5,7] More specifically, a 16-kDa secreted form cleaved in a tissue-specific manner has been detected in the porcine CTC, but not in the eye. N-terminal part of the protein has been presented in the CTC, as well.[12]

The UniProt data shows that TNMD has three isoforms containing: 317 α-amino acids (64 kDa), 207 α-amino acids (33k Da), and 254 α-amino acids (45 kDa), respectively. There is a disulfide bond between 120th and 178th α-amino acid in the polypeptide chain (Fig. 2). The mRNA processing and the post-transcriptional modifications of TNMD isoforms could differ in cultivated tenocytes *in vitro* and in tendon tissues *in vivo*.[13]

It has been shown that the TNMD molecule has different localizations in cells cultivated *in vitro*. For instance, in transfected COS-7 cells, TNMD isoforms I and II are localized in the nuclear envelope, while isoform III is in the cytoplasm.[13] The overexpressed TNMD is localized in Golgi apparatus, microtubules of the cytoskeleton and especially in the cell membrane of transfected NIH3T3 cells. TNMD is modified in the Golgi apparatus and then the protein is transported to the plasma membrane.[14]

STRUCTURAL HOMOLOGY BETWEEN TENOMODULIN AND CHONDROMODULIN

The similarities in the structural organization between TNMD and chondromodulin (ChM-I) proteins are discussed in this section. We also describe the functional activity of the proteins.

ChM-I has been identified and characterized as a functional matrix component in guanidine extracts of fetal cartilage.[15] That is a cartilage specific glycoprotein, stimulating chondrocyte growth and inhibiting the endothelial cell tube formation.[16] ChM-I is a part of the C-terminus of a larger transmembrane precursor (pre-ChM-I, 334 α-amino acids)[15] cleaved in a specific furin-like processing site. After cleavage from the pre-ChM-I, chondrocytes secrete mature ChM-I (120 α-amino acids) and the protein could be found in the extracellular matrix (ECM).[16] In contrast, TNMD protein is located on the cell surface.[3,5,7]

In fact, TNMD shares similarities in its structural configuration with the pre-ChM-I (Fig. 3). The overall amino acid sequence of TNMD shares only 34% identity with that of the human pre-ChM-I. Its C-terminal containing 63 residues (from Phe255 to Val317) was found to be 67% identical with the C-terminus of ChM-I (from Phe272 to Val334).[16] Both of the proteins ChM-I and TNMD have eight identically spaced cysteine residues with a conservative location. There is only one exception of the residue at position 291.[4] Besides the significant homology of Cys-rich domains at the C-termini[2-4], TNMD and pre-ChM-I proteins show structural similarity in the other domains, including NTD at the N-termini and BDs[9] (Fig. 3). BD has been supposed to have a chaperone function[9], but the functional role of BD remains totally unclear. Both proteins have a secreted part - 16 kDa for TNMD[6] and 25 kDa for pre-ChM-I.[15,16]

Recent data demonstrates that TNMD and pre-ChM-I are able to release their CTDs *in vitro* and *in vivo*. [7] Recombinant ChM-I protein effectively suppresses angiogenesis in colon adenocarcinoma and chondrosarcoma *in vivo*. The expression of hTNMD CTD also results in successful inhibition of tumor growth *in vivo*.[7] The CTD of TNMD suppresses tumor-induced angiogenesis as effectively as ChM-I and initiates antiangiogenic response in a similar way as the mature ChM-I.[5] ChM-I and TNMD form a unique class of anti-angiogenic molecules whose expression is closely associated with tissue avascularity.[8]

TENOMODULIN EXPRESSION IN TISSUES

The expression profile of TNMD shows that it could be found mainly in dense hypovascular connective tissues. Three-fold higher *TNMD* gene expression levels have been observed in adipocytes and adipose tissue as compared to other human tissues.[17]

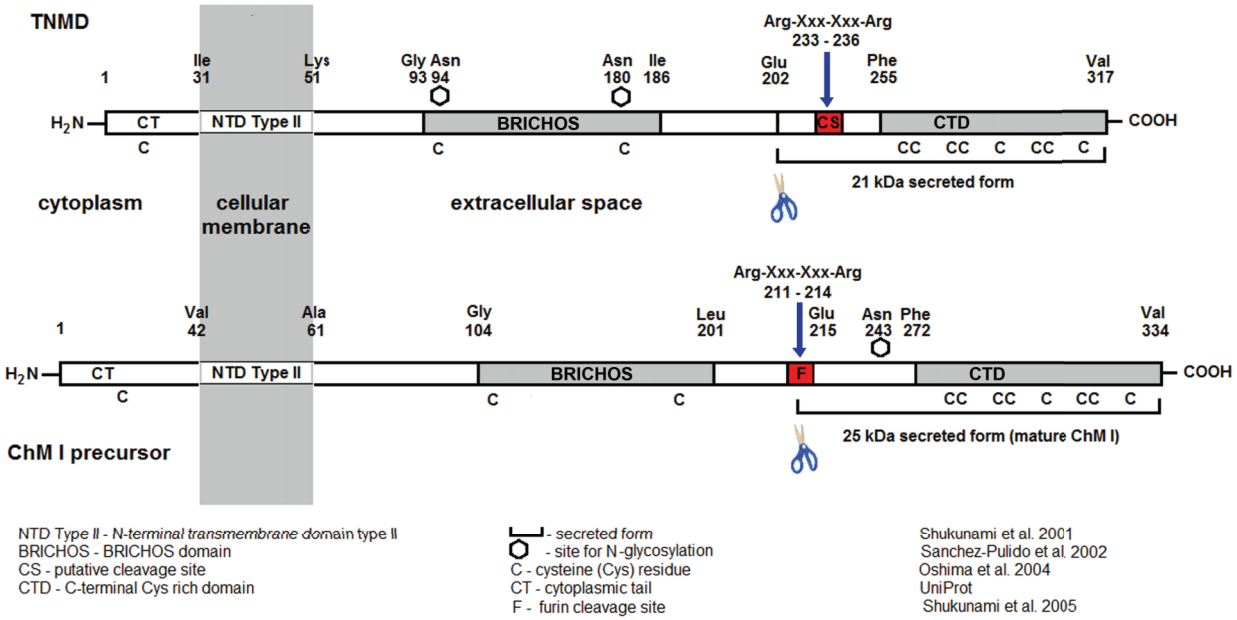

Figure 3. Structural features and similarities of the ChM-I precursor and TNMD proteins.[4,7-9]

Jelinsky et al.[18] reported that the *TNMD* expression was four times higher in tendons than in the adipose tissue. The *TNMD* is predominantly expressed in tendons, skeletal muscle, epimysium, ligaments[2,4,5] and CTC[10]. Moderate *TNMD* expression is demonstrated in cartilages and bones.[18]

A high level of *Tnmd* expression has been detected in skeletal muscles[1-4], epimysium[4,5,12], tendons[2,4], ligaments, diaphragm[2], whole rib[3], eye[2,3,5], cornea, lens fibers, sclera[5], periodontal ligament (PDL)[14]. Weak *Tnmd* signals have been found in the brain, heart, liver, lung, thymus, kidney, and skin.[2] Tenomodulin gene is reported to be abundantly expressed in normal rodent, porcine, and canine CTC.[12] These findings suggest that the expression during the vertebrate development spans the avascular area of mesenchymal tissues and depends on different factors.

REGULATION OF TENOMODULIN EXPRESSION

The tenocyte differentiation can be determined using two different protein markers: 1) Scleraxis (*SCX)* for the early tenocyte differentiation and 2) tenomodulin as a late tenocyte differentiation marker. Shukunami et al. (2006)[19] found a positive correlation between expression levels of *scleraxis* and *TNMD,* where *scleraxis* positively regulates tenomodulin expression in chicken. *scleraxis* expression precedes and stimulates tenomodulin expression *in vitro* in chick's tendon tenocytes. It also stimulates tenomodulin in tendons during the later stages of embryo development *in vivo.* Expression of *scleraxis* results in a significant upregulation of tenomodulin in cultured tenocytes, but not in chondrocytes.[19]

Another important regulator of the tendon development is *Mohawk (Mkx).* This is a homeobox gene that encodes a protein with a repressor activity during transcription. *Mkx* has an early effect on the tenocyte differentiation. For example, dramatically decreased *Tnmd* expression and disorders of tendon development have been observed in *Mkx*(-/-) mutant mice.[20]

A novel regulatory mechanism of tenomodulin expression has been recently described by Miyabara et al. (2014).[21] The researchers found that the presence of glycogen synthase kinase-3 inhibitors in cultivated equine bone marrow mesenchymal stem cells increases tenomodulin expression up to the level in the tendon and induces a tendon differentiation *in vitro*.[21] These results suggest that Wnt/β-catenin signalling mediates the expression of tenomodulin, and it does not depend on transcription factors *scleraxis* and *mohawk*.[21]

A large set of growth factors (e.g. GDF-8/Myostatin[22], TGF-β3[13]), different proteins (e.g. adiponectin[23], collagen[24]), and transcription factors (e.g. Scleraxis[19]) could upregulate tenomodulin expression. However, some factors (e.g. Elastin-A[24]) could inhibit tenomodulin expression. A putative negative feedback signal between *Tnmd* and both

scleraxis and myostatin has been found.[13] The reason could be the loss of *Tnmd* in knock-out mice which increases the expression of these genes.[22]

BIOLOGICAL FUNCTIONS OF TENOMODULIN

Tenomodulin has various biological functions and we have divided them into the following groups: anti-angiogenic activity, metabolism, diseases, cell processes and bone development, tenogenic function. The biological functions of TNMD are schematically presented in Fig. 4. Before providing more detailed information about the groups of functions, we discuss the putative role of the TNMD CTD and BD domains.

Both of the domains CTD and BD are supposed to play an important role in the TNMD functions. It has been suggested that BD has several functions: 1) in complex post-translational processing[11] 2) in targeting of mature proteins[11], and 3) an intramolecular chaperone-like function[9]. Several researchers suggested that the anti-angiogenic function of TNMD[5,7], and the suppression of cell-cell interaction, as well as the cell-matrix adhesion of endothelial cells can be assigned to the CTD domain of the protein. Additionally, it has been proposed that both the anti-angiogenic activity of the CTD and the function of BD in cell adhesion could maintain the properties of hypovascularized tissues as tendons, ligaments, and PDL.[14]

The CTD of the secreted TNMD is involved in the modulation and inhibition of the endothelial-cell proliferation, the morphogenesis of vascular endothelial cells and the tube formation *in vitro*[5] and tumorigenesis *in vivo* [7]. The overexpression and the subsequent secretion of the TNMD CTD in HUVECs and mouse endothelial MSS31 cells, leads to significant reduction of the cell tube-forming activity *in vitro*. The BL-6 melanoma cells transducted with CTD and then injected into C57BL/6 mice lead to a smaller tumor formation and a decreased vessel density *in vivo*.[7] CTD transducted in human retinal vascular endothelial cells has significantly decreased their growth and differentiation.[5]

Tnmd participates in the maintenance of avascular conditions in the eyes. For instance, Tnmd

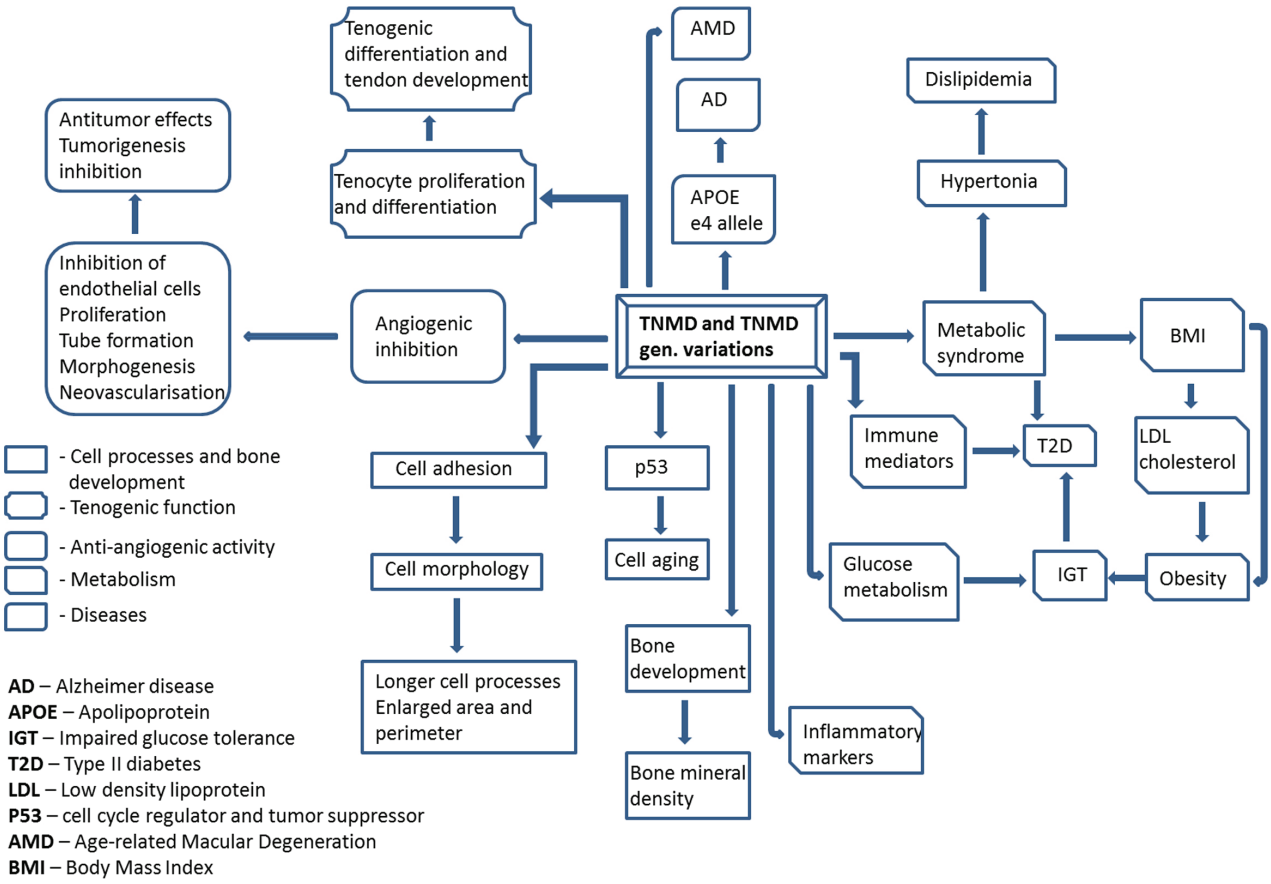

Figure 4. TNMD biological functions, summary.[5,6,8,14,19,28-30]

can be injected in the retina of C57BL/6 mice with an oxygen-induced retinopathy. Thus, the CTD cleaved from the Tnmd molecule effectively blocks the activity of the vascular endothelial growth factor (VEGF). It also prevents ischemic-induced retinopathy and pathological angiogenesis.[25]

TNMD has been found in cardiac valve tissues. It plays a crucial role in valve degeneration by control of the angiogenesis and the matrix metalloproteinase synthesis.[26] Additionally, local TNMD absence, angiogenesis and abnormal tube formation are associated with a CTC rupture.[12] In fact, the reduced expression of TNMD in calcified and rheumatoid cardiac valves leads to progressive pathological angiogenesis, CTC ruptures and valve degeneration.[27] *Tnmd* does not play a maintaining role in tendon angiogenesis *in vivo*.[6] Changes in tendon vessel density have not been found in *Tnmd*-deficient mice.[6]

TNMD expression in human adipose tissue indicates a putative role in its functions. Saiki et al. (2009) detected significantly increased *TNMD* expression in obese patients as compared to lean patients.[17] Their findings suggest that *TNMD* expression could be independently predicted by the Body Mass Index (BMI).[17] Additionally, it has been found that *TNMD* expression is downregulated during diet-induced weight loss.[17]

Also, the increased expression of *TNMD* gene could be associated with some symptoms of the metabolic syndrome, including type 2 diabetes (T2D), obesity, hypertonia, dyslipidemia. *TNMD* is one of the most downregulated genes in patients with metabolic syndrome symptoms, impaired fasting glycaemia and weight reduction intervention.[28] Additionally, body weight reduction modulates the expression of the genes regulating the ECM and the cell death.[28] Even though most of the *TNMD* regulatory mechanisms are unknown, we can summarize that *TNMD* has an important role in metabolic syndrome and related symptoms.

TNMD could have genetic associations with the central obesity, anthropometric measurements, body size, inflammations, serum level of system immune mediators, age-related macular degeneration, Alzheimer disease, type 2 diabetes, glucose and lipid metabolism. For a thorough review on these associations, see Tolppanen et al.[29]

TNMD-overexpressing NIH3T3 cells tended to have longer cell processes and an enlarged territory by significantly increasing in area and perimeter as compared to cells overexpressing GFP. Therefore, elevated levels of TNMD might change the cell morphology.[14] Additionally, it was supposed that an interaction between the TNMD and various proteins through BD could regulate cell adhesion.[14] The presence of *TNMD*, transfected in cells, enhances cell adhesion, while the loss of *TNMD* suppresses it. TNMD influences PDL cell adhesion to ECM. It was found that BD and the cleavage site region of TNMD are important for the cell adhesion enhancement. Cell adhesion capacity *in vitro* of cells originating from *Tnmd* knock-out mice is decreased compared to cells isolated from WT mice.[14]

Loss of *Tnmd* in tendon stem progenitor cells, isolated from knock-out mice, leads to increased expression of the p53 protein (cell cycle regulator and tumor suppressor), augmented senescence and reduced cell self-renewal.[30] Additionally, *Tnmd* plays a role as a remodeling factor in bone development *in vivo*. An indication of the latter is the significantly increased bone mineral density observed in adult knock-out mice deficient of *Tnmd*.[6]

Furthermore, *TNMD* has been described as a marker of tenocyte differentiation[4] and as a regulator of tenocyte proliferation and tendon development[6]. This is confirmed in various research experiments *in vitro* and *in vivo*. Lack of *TNMD* expression leads to weak tenocyte proliferation and reduces tenocyte density in tendons in knock-out mice.[6] *TNMD* is one of the most often used markers for tendon tissues together with *Scx*, *Smad8* and *Epha4*. One of the highest expression levels among tendon associated gene markers has been detected for *TNMD*.[18]

Additionally, *TNMD* has been used as a marker for other tenogenic processes. For instance, *TNMD* is a proven phenotypic marker for tenocyte differentiation *in vitro* and *in vivo*.[19]

POSSIBLE MEDICAL APPLICATIONS OF TENOMODULIN

Besides its role as a differentiation and proliferation marker, TNMD could have also possible medical applications. The expression level of *TNMD* mRNA in damaged tendons and ruptured tenocytes is higher than the level in healthy tendons and normal tenocytes. The increased *TNMD* level positively influences tenogenic differentiation and tendon recovery. A lot of growth factors provoke increase of *TNMD* expression in stem cells and lead to tenogenic differentiation. Different stem cells and cells isolated from tendon tissues with a tenogenic potential are cultivated on different substrates and scaffolds. All

these effects, leading to an increased *TNMD* expression level, are used in tendon tissue engineering and treatment of ruptured tendons.

Additionally, TNMD isoforms could be used as new biomarkers and therapeutic targets in tendon injury and diseases, given the effect on cell proliferation.[13] A stimulation of *TNMD* expression by adiponectin could play a role in the treatment of diabetes patients with tendinopathia.[23] Also, TNMD could be involved in the remodeling of ECM.[28]

Furthermore, TNMD has a unique therapeutic potential. For instance, CTD plays a central role in the anti-angiogenic properties of TNMD, thus providing an opportunity to design a therapeutic target for tumor angiogenesis and other angiogenic disorders. However, a better understanding of the binding mechanisms of anti-angiogenic molecules in ECM will be crucial not only to maintain the angiogenic balance for normalization, but also to enable a later shift to an anti-angiogenic state during therapy. Finally, CTD effectively inhibits pathological angiogenesis in mouse eyes and it could have a potential role in prevention and treatment of eye neovascularization.[25]

Both the growth and the persistence of solid tumors are dependent on angiogenesis. It has been shown that the inhibition of angiogenesis is an effective strategy for tumor treatment. Therefore, CTD presented in TNMD might be a useful target for an anti-tumor drug.[7] Further investigation of the role of proteolytically processed TNMD in local CTC angiogenesis could provide a better understanding of the mechanisms underlying the sudden chordal disruption on a new molecular level.[12]

CONCLUSIONS

The *TNMD* gene and the translated protein have an unrevealed potential. TNMD has a variety of different functions and plays a role in tenocyte differentiation, tendon development, angiogenesis inhibition, adipose tissue, cell adhesion, cell morphology, cell aging, and bone mineral density. Still, most of the interactions of the molecule in tissues and ECM are unknown. A better understanding of the TNMD activity mechanisms and its biological functions will contribute to the application of TNMD in tendon tissue engineering, tendon healing and recovery, tumor treatment and anti-angiogenic therapy in the future.

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Проспект теномодулина

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Теномодулин представляет собой трансмембранный гликопротеин II типа, который может регулировать рост сухожилий. Ген, кодирующий теномодулин человека, сопоставляется с X-хромосомой и кодирует полипептид в размере 317 альфа-аминокислот. Белок находится на поверхности клетки, как N-гликозилированный или не-N-гликозилированный полипептид с молекулярной массой 45 и 40 кДа, соответственно. Молекула состоит из трех доменов и короткого цитоплазматического концевого сегмента на N-конце. Теномодулин в основном экспрессирован в плотных соединительных гипо-васкуляризированных тканях, таких как сухожилия, скелетные мышцы, эпимизий и связки. Кроме того, теномодулин является эффективным маркером дифференциации теноцита и играет важную роль в регуляции пролиферации теноцита, развития сухожилий и ингибирования ангиогенеза. В последнее время число полиморфизмов генов теномодулина соотносится с ожирением, риском диабета, системными иммунными медиаторами, уровнем холестерина, болезнью Альцгеймера, возрастной макулярой дегенерацией. Теномодулин участвует в клеточной адгезии, определении морфологии клеток, старении клеток и минеральной плотности костной ткани. Предполагается, что он играет важную роль в восстановлении сухожилий, тканевой инженерии сухожилий, противоопухолевой терапии, лечении хордальных нарушений, ремоделировании внеклеточного матрикса.

Ключевые слова: Теномодулин