Gene 587 (2016) 1–17

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Gene wiki review

TENOgenic MODULating INsider factor: systematic assessment on the functions of tenomodulin gene

Sarah Dex [a], Dasheng Lin [a], Chisa Shukunami [b], Denitsa Docheva [a,c,*]

[a] Experimental Surgery and Regenerative Medicine, Department of Surgery, Ludwig-Maximilians-University (LMU), Munich, Germany
[b] Department of Molecular Biology and Biochemistry, Division of Basic Life Sciences, Institute of Biomedical & Health Sciences, Hiroshima University, Hiroshima, Japan
[c] Department of Medical Biology, Medical University-Plovdiv, Plovdiv, Bulgaria

ARTICLE INFO

Article history:
Received 11 February 2016
Received in revised form 20 April 2016
Accepted 25 April 2016
Available online 26 April 2016

Keywords:
Tenomodulin
BRICHOS
Tendon
Eye
Chordae tendineae cordis
Vasculature
Periodontal ligament
Knockout mice
Tendon stem/progenitor cells
Cell differentiation
Gene marker
Single nucleotide polymorphism
Obesity
Metabolic syndrome

ABSTRACT

Tenomodulin (*TNMD*, *Tnmd*) is a gene highly expressed in tendon known to be important for tendon maturation with key implications for the residing tendon stem/progenitor cells as well as for the regulation of endothelial cell migration in chordae tendineae cordis in the heart and in experimental tumour models. This review aims at providing an encompassing overview of this gene and its protein. In addition, its known expression pattern as well as putative signalling pathways will be described. A chronological overview of the discovered functions of this gene in tendon and other tissues and cells is provided as well as its use as a tendon and ligament lineage marker is assessed in detail and discussed. Last, information about the possible connections between *TNMD* genomic mutations and mRNA expression to various diseases is delivered. Taken together this review offers a solid synopsis on the up-to-date information available about *TNMD* and aids at directing and focusing the future research to fully uncover the roles and implications of this interesting gene.

Abbreviations: 3D, three dimensional; Ad-EGFP, adenovirus vector encoding enhanced green fluorescent protein; APOE, apolipoprotein E; Aqp1, aquaporin 1; Arg, arginine; bHLH, basic helix-loop-helix; BMDSC, bone marrow-derived stem cell; BMP, bone morphogenetic protein; BMSCs, bone marrow stromal cells; C, cysteine; C2C12, mouse myoblast cell line;C57BL/6, C57 black 6; CA region, Cornu Ammonis region; cDNA, complementary deoxyribonucleic acid; Chm1, chondromodulin-1; Col, collagen; COMP, cartilage oligomeric matrix protein; COS-7, African green monkey fibroblast-like kidney cell line; CS, mutant with deleted cleavage site; CTC, chordae tendineae cordis; CTD, C-terminal domain deletion mutant; C-terminal, carboxyl-terminal; *cTnmd*, chicken tenomodulin; Cys, cysteine; DNA, deoxyribonucleic acid; E, embryonic day; EC domain, mutant with entire extracellular portion of Tnmd deleted; Egr, early growth response protein; Eya, eyes absent transcription factor; FCR, flexor carpi radialis; FGF, fibroblast growth factor; FL, full length tenomodulin; GSK-3, glycogen synthase-3; H5V, mouse embryonic heart endothelial cells; HH, Hamburger-Hamilton stage; hPDL, human periodontal ligament; *hTNMD*, human tenomodulin; Htra3, HtrA serine peptidase 3; HUVEC, human umbilical vein endothelial cell; I, isoleucine; ICC, immunocytochemistry; IFM, interfascicular matrix; IHC, immunohistochemistry; ISH, in situ hybridization; I-TASSER, iterative, threading assembly refinement; K, lysine; kb, kilo base; kDa, kilodalton; KO, knockout; MA, microarray; Mkx, Mohawk; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; MSC, mesenchymal stem cell; *mTnmd*, mouse tenomodulin; N, asparagine; NB, Northern blot; NIH3T3, mouse embryonic fibroblasts; OIR, oxygen-induced retinopathy; p53, tumour protein 53; PBS, phosphate-buffered saline; PCDH19, Protocadherin 19; PCR, polymerase chain reaction; PDL, periodontal ligament; PNGaseF, peptide-N-glycosidase F; Q, glutamine; qPCR, quantitative PCR; RCAS-cScx, replication-competent avian sarcoma-leukosis virus-copy Scleraxis; RNA, ribonucleic acid; rs, reference small nucleotide polymorphism; RT-PCR, reverse transcriptase-polymerase chain reaction; Sca-1, stem cells antigen-1; Scx, Scleraxis; SMA, smooth muscle actin; SNP, small nucleotide polymorphism; Sox, sex determining region Y; SUMO, small ubiquitin-like modifier; TGF, transforming growth factor; Thbs, thrombospondin; *TNMD*, *Tnmd*, tenomodulin; TSPC, tendon stem/progenitor cell; UTR, untranslated region; V, valine; VEGF, vascular endothelial growth factor; WB, western blot; WT, wildtype.

* Corresponding author at: Experimental Surgery and Regenerative Medicine, Department of Surgery, LMU, Nussbaumstr. 20, 80336, Munich, Germany.
E-mail address: denitsa.docheva@med.uni-muenchen.de (D. Docheva).

http://dx.doi.org/10.1016/j.gene.2016.04.051

Contents

1. Introduction

Tendons are dense connective tissues arranged in a hierarchical manner. Mature tendons are normally characterized by low cellular density and this is one of the most obvious features when looking at tendon histological preparations. About 90–95% of the cellular content of tendon comprises tendon-specific cell types described in the literature as tenoblasts and tenocytes, the latter being the terminally differentiated form (Kannus, 1997; Chuen et al., 2004). During development newborn tendons have a very high cell-to-matrix ratio with tenoblasts of various shapes and sizes aligned in long parallel chains. Following tendon maturation, the ratio between cells and matrix gradually decreases, with tenoblasts transforming from an ovoid to a spindle and elongated shape, specific for their differentiated counterparts, tenocytes (Ippolito et al., 1980).

Although the general knowledge about the differentiated cells residing in tendon tissue has been developing in the latest years, still little is known about their precursors. Stem/progenitor cells of mesenchymal origin, such as the tendon lineage, are of great interest in order to understand tendon development and healing processes. In 2007, Bi et al. (2007)demonstrated that human and mouse tendons harbour a unique cell population which has universal stem cell characteristics such as clonogenicity, self-renewal capacity and multipotency. Compared to bone marrow stromal stem cells, these tendon-derived cells expressed high levels of Scleraxis (*SCX*), cartilage oligomeric matrix protein (*COMP*), tenascin-C and tenomodulin (*TNMD*), all tendon-related factors, thus identifying their origin. Additionally, these isolated cells showed the ability to regenerate tendon-like tissue after extended expansion in vitro and transplantation in vivo. However, the fact that the cells of this population showed heterogeneity in their stem properties and the possibility of containing tendon progenitor cells as well, made the authors name them- tendon stem/progenitor cells (TSPCs).

The repair of musculoskeletal tissues often recapitulates the cellular and molecular events of development. Thus, understanding the process of tendon development can significantly help to develop novel repair strategies. So far, the knowledge on the ontogeny of the tendon lags far behind other mesodermal tissues due to both the lack of specific markers exclusive to the tendon lineage. However, the identification of the basic helix-loop-helix (bHLH) transcription factor *Scx* as a specific and early marker of tendon progenitors during embryonic development (Cserjesi et al., 1995; Schweitzer et al., 2001) and the study of mice harbouring genetic mutations leading to tendon phenotypes, reviewed in Tozer and Duprez (2005) and Liu et al. (2011), have provided some insights into the onset of the tendon lineage and the molecules involved in this process. Using knockout mouse models, further transcription factors were identified to be essential for tendon differentiation and development such as Mohawk (*Mkx*), *Egr1* and *Egr2* (Ito et al., 2010; Lejard et al., 2011; Guerquin et al., 2013).

Tenomodulin was discovered in 2001 by Brandau et al. (2001) and Shukunami et al. (2001) as a gene sharing high homology with chondromodulin-1 (CHM1, alternative names chondromodulin-1 and alternative abbreviations, CHM-I, LECT1, BRICD3 and MYETS1) (Hiraki et al., 1991). Both research groups described high expression in tendons, explaining the rationale behind its name. It was hinted to be useful as a tendon-specific marker, which later on became an established marker for the mature tendon and ligamentous lineage.

Despite great progress in deciphering tendon development, the exact molecular pathways orchestrating tendon progenitor specification and differentiation still remain largely unknown. Therefore, further studies are required to identify novel tendon-specific markers, to understand their roles and to elucidate the molecular cascades occurring during tendon development and maintenance.

In view of the above, the focus in this review is on *TNMD*, one of the best so far tendon-specific marker genes. We carried out a systematic review analysis on all available articles in the PubMed databank. The examination was performed by searching tenomodulin under its full name, but also by its alternative names and abbreviations (tendin and myodulin, *TNMD* and *TeM*). A summary of the selection of articles for this review is shown in Fig. 1.

2. Tenomodulin

2.1. Gene discovery and nomenclature

TNMD was found independently by Brandau et al. (2001) and Shukunami et al. (2001). Brandau's team named it tendin with the justification that it is highly expressed in tendons and ligaments. Shukunami's team, on the other hand named it tenomodulin, since it shares high homology to chondromodulin-I, but is expressed in tendons, hence postulating a similar modulatory function in these tissues. Tenomodulin also circulated around the literature very briefly under the name of myodulin (Pisani et al., 2004; Pisani et al., 2005). The authors gave the alternative name myodulin based on detecting *Tnmd* mRNA in Northern blot analysis of rat gastrocnemius muscles. As previously mentioned, its abbreviations in the literature are found under *TNMD* and *TeM*.

2.2. Gene and protein structure

TNMD, *Tnmd* belongs to the new family of type II transmembrane glycoproteins with a highly conserved cleavable C-terminal cysteine-rich domain (Brandau et al., 2001; Shukunami et al., 2001). The *TNMD*, *Tnmd* gene consists of seven exons localized on the X chromosome (Fig. 2) and accounts for an approximately 1.4 kb transcript and a predicted protein consisting of 317 amino acids (Brandau et al., 2001; Shukunami et al., 2001). Analysis of primary amino acid sequences