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Review Article

The role of thrombospondin-4 in cardiovascular diseases

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Abstract: Thrombospondin-4 is an extracellular matrix protein encoded by the human *Thbs4* gene. TSP-4 plays a significant role in tissue remodeling, tissue proliferation, cell migration, angiogenesis, and synaptogenesis, and so forth. TSP-4 has several different functions that act differently in different tissues because TSP-4 has multiple different functional domains and can participate in different signaling pathways. Moreover, TSP-4 has unique features not shared by other TSP family members. Also, many previous studies have found that TSP-4 also plays an important role in the pathogenesis of many cardiovascular diseases, such as myocardial infarction, heart failure, hypertension, atherosclerosis, coronary artery disease and peripheral arterial disease. As a biomarker, TSP-4 can help the diagnosis and differential diagnosis of diseases and can also be used to assess disease progression and prognosis. Targeted activation or targeted inhibition of TSP-4 can also be used for the treatment of disease. Here, we review previous research papers on TSP-4, summarizing the structure, function, signaling pathways of TSP-4 and its roles in disease, especially its role in cardiovascular disease and its potential therapeutic value.

Keywords: TSP-4, cardiovascular disease, function, clinical value

Introduction

Thrombospondin-4 (TSP-4) is a protein encoded by the *Thbs4* gene in humans and is a member of the TSP family. The TSPs are a family of five multidomain, calcium-binding matricellular glycoproteins that mediate cell-to-cell and cell-to-matrix interactions and are involved in tissue remodeling, which is associated with embryonic development [1-3], wound healing [3-6], synaptogenesis [1, 3, 7], and neoplasia [3, 8]. TSPs can be divided into two groups, subgroup A comprising TSP-1 and TSP-2 and subgroup B comprising TSP-3, TSP-4, and TSP-5. Compared with other family members, TSP-4 has some functions that are significantly different, even having functional antagonism with other family members. For example, TSP-4 can promote angiogenesis [3, 9-11], while TSP-1 and TSP-1 have potent anti-angiogenic effects [12, 13]. TSP-4 plays a role in the functions of basement membranes in various tissues. In adults, TSP-4 is detected in hearts [14-17], skeletal muscles [18, 19], and articular chondrocytes [20] and accumulates at the neuromuscular junction [1, 18]. Existing research indicates that TSP-4 is a critical regulator of tissue growth and remodeling.

Cardiac remodeling is a clinical manifestation of changes in related genomic expression that result in changes in molecular, cellular and interstitial changes and heart size, and is influenced by factors such as cardiac load or injury, hemodynamic load, and neurohormone activation [15, 21, 22]. Cardiac remodeling is generally accepted as a determinant of the clinical course of heart failure (HF) [21]. Previous research has shown that TSP-4 plays a very important role in myocardial remodeling and the cardiovascular system, it is expressed by endothelial cells and smooth muscle cells of large blood vessels, and it is expressed abundantly in capillaries [17, 23]. In addition, when there are cardiovascular diseases such as myocardial infarction (MI), HF, hypertension, arteriosclerosis, coronary artery disease (CAD) and peripheral arterial disease (PAD), they is often accompanied by changes in TSP-4 expression.

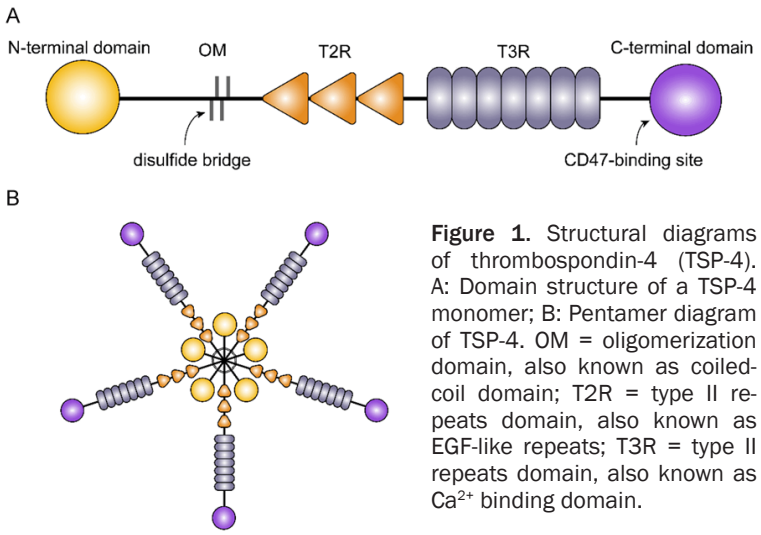

Figure 1. Structural diagrams of thrombospondin-4 (TSP-4). A: Domain structure of a TSP-4 monomer; B: Pentamer diagram of TSP-4. OM = oligomerization domain, also known as coiled-coil domain; T2R = type II repeats domain, also known as EGF-like repeats; T3R = type II repeats domain, also known as Ca^{2+} binding domain.

In this review, we sum up the common role of TSP-4, especially regarding cardiovascular disease.

Structure

In the TSP family, TSP-1 and TSP-2 of subgroup A are homotrimers, while TSP-3, TSP-4 and TSP-5 of subgroup B are homopentamers [24]. In electron microscopy, TSP-4 is seen as a large central particle and is composed of five subunits which are attached by globular domains close to the N-terminal [24, 25]. The subunits of TSP-4 are similar in appearance to the TSP-1 subunits, but there is an obvious difference in that the TSP-4 subunits are smaller [26, 27].

TSPs have a complex multidomain structure, including the C-terminal domain, type III (Ca^{2+} binding) repeats, type II (EGF-like) repeats, the oligomerization domain, and the N-terminal domain (**Figure 1A**). Compared with TSP-1 and TSP-2, TSP-4 lacks type I (CD36 binding MMP inhibition) repeats and Von Willebrand factor type C domain and has an additional type II repeat [24, 28-30]. The signature domain of a TSP is its C-terminal domain, type III repeats and type II repeats, which are highly conserved among all TSPs [24, 28, 29, 31]. Calcium-binding is associated with type III repeat regions and contributes to changes in major conformations and functions of TSP-4 [24, 29]. N-terminal is less conservative and regulates the structure and stability of the coiled-coil region and binds heparin, but it is absent in TSP-5 [32]. TSP-4 can be enriched by heparin affinity chromatography [33]. Moreover, TSPs are connected via disulfide bridges into homotrimers, homopentamers, and heterooligomers [34] (**Figure 1B**). In cardiovascular diseases, the most known single nucleotide polymorphism (SNP) in TSP-4 is A387P [35-40], and it is understood that the SNP substitution exists in the third type III repeat, and the mutant may increase calcium binding [38].

Function

As an intercellular protein, most of the functions of TSP-4 play a role in the intercellular substance. TSP-4 regulates the composition of the extracellular matrix (ECM) in its predominantly enriched sites, including muscles and tendons. TSP-4 may mediate the binding of the collagen fibril assembly to the cell surface [41]. Moreover, TSP-4 deficiency leads to changes in the composition and physiological function of these tissues [42] and plays a critical role in cardiovascular disease (**Figure 2**).

Previous studies have revealed that TSP-4 also plays an indispensable role in the migration, adhesion, remodeling, regeneration and inflammation, proliferation, and promotion of nervous system development [1, 4, 5, 43].

Remodeling and regeneration

The TSP family underlies tissue remodeling and regeneration, whose secretion is often induced by stress [44]. As a member of the TSP family, the earliest and most reported function of TSP-4 is tissue remodeling and regeneration.

The upregulation of TSP-4 expression often occurs during tissue damage, regeneration, and remodeling [45, 46]. TSP-4 can alter the composition of the matrix proteins and, as such, TSP-4 is involved in the remodeling process [47, 48]. In cardiac cell stroma, TSP-4 binds and regulates structural ECM proteins during tissue damage [49], a process that promotes adaptive ECM remodeling. Moreover, cardiomyocytes regulate cardiac fibrosis by transcriptionally controlling TSP-4, which in turn regulates the activation of cardiac fibroblasts [50]. Also, TSP-4 can stimulate collagen gene expression and myofibroblast transformation

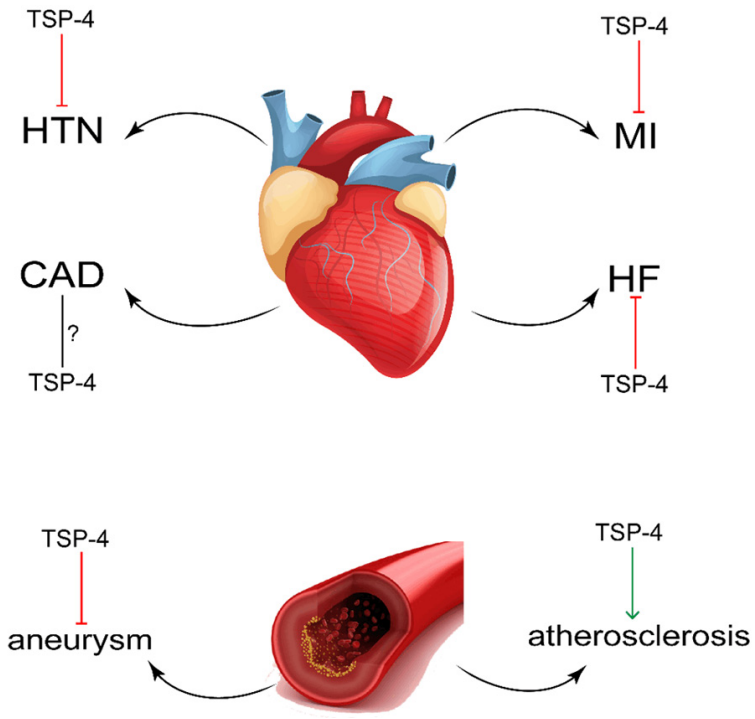

Figure 2. The role of thrombospondin-4 (TSP-4) in cardiovascular diseases. The green arrow defines the promoting effect, the red arrow defines the suppression effect, and the black straight line defines the unknown.

through the Toll-like receptor four signaling pathway, thereby promoting skin fibrosis [51]. TSP plays a role in limb regeneration in vivo [52]. Moreover, the overexpression of TSP-4 activates non-hepatocytes around the portal area of the damaged liver to promote liver regeneration [53].

Proliferation

As with tissue remodeling and tissue regeneration, proliferation is one of the main functions of TSP-4, especially in the cardiovascular system. The expression of TSP-4 by vascular cells regulates the proliferation of endothelial cells and smooth muscle cells, thereby affecting the vessel wall [23]. Recombinant TSP-4 binds to integrin α_2 and gabapentin receptor $\alpha_2\delta_1$ to accelerate the proliferation of vascular smooth muscle cells [54] and microvascular endothelial cells [9], and the proliferation of endothelial cells isolated from TSP-4 knockout (KO) mice is significantly slowed down [10]. The SNP of TSP-4 significantly alters its ability to support endothelial cell proliferation [55]. Moreover, the C-terminal peptide of TSP-4 (C21) can stimulate erythroid cell proliferation [56]. C21 stimulates thymidine erythrocytes and promotes the cell culture of cord blood erythrocytes and bovine skin fibroblasts [57].

Migration and adhesion

Many studies have shown that TSP-4 is involved in cell adhesion and migration [58-60]. TSP-4 is essential for cell adhesion and cell migration in neurons and vascular smooth muscle cells [61]. TSP-4 regulates adhesion molecules and axonal growth promoting molecules in ECM [2]. Previous studies have revealed that fusion proteins containing C21 support myoblast adhesion [43]. It was found that TSP-4 regulates the adhesion of macrophages to vascular smooth muscle cells [62] and the migration of vascular smooth muscle cells [54] by directly interacting with macrophages or by binding to integrin α_2 and gabapentin receptor $\alpha_2\delta_1$ [9]. TSP-4 with an SNP mutation also has a significant change in its capacity to support endothelial cell adhesion [55]. It has also been reported that the migration and invasion of prostate cancer cells are inhibited by silencing lncRNA TSP-4 [63].

Angiogenesis

Angiogenesis is an important process for growth and development as well as wound healing and granulation tissue formation. At the same time, it is also a basic step in the transition of a tumor from a benign state to a malignant state.

TSP-4 affects a variety of endothelial cell-associated responses, including the transformation into enhanced angiogenesis [9]. For example, TSP-4 upregulates the effect of TGF-β_1 on angiogenesis [10]. Moreover, TSP-4 enhances the angiogenesis-promoting function of endothelial cells, thereby promoting neovascularization [64]. It has been reported that the knockdown and KO of TSP-4 inhibit hepatocellular carcinoma-induced angiogenesis [11] and that TSP-4 KO mice exhibit reduced angiogenesis [65].

Inflammation

Inflammation is a complex biological response that protects the body from harmful stimuli. TSP-4 is important for the regulation of vascular inflammation [66].

The expression of TSP-4 is significantly upregulated in inflammation [45]. *Thbs4* encodes a glycoprotein involved in the inflammatory response [67]. TSP-4 is involved in the inflammatory response to neuropathic pain [68]. Cells with the TSP-4 A387P mutation release excess H_2O_2 and interleukin-8 [69]. Moreover, TSP-4 inhibition significantly reduces the number of macrophages in the lesion, inhibits endothelial cell activation, and reduces other markers of vascular wall inflammation [62].

Stabilization

TSP-4 has also been found to be stabilizing in muscle cells. TSP-4 has a protective effect on the heart and skeletal muscle. TSP-4 activates the adaptive endoplasmic reticulum (ER) stress response, induces ER expansion, and enhances muscle membrane stability [70]. In myofibers, TSP-4 selectively enhances partial vesicle trafficking to increase integrin and dystroglycan attachment complexes [31] to stabilize muscle fiber membranes [71]. Moreover, TSP-4 has been shown to maintain the stability of cartilage ECM by responding to substrate stiffness and mechanical changes in tendons and muscle tissue [72].

Adipogenesis

Adipogenesis is the process of cell differentiation by which pre-adipocytes become adipocytes. TSP-4 is a putative exercise-induced and obesity-associated myokine in mice [73]. The upregulation of TSP-4 in human pre-adipocytes is compared to mature adipocytes [74]. Therefore, TSP-4 may be involved in early adipogenesis events. Moreover, TSP-4 mediates the interaction between muscle fibers, fat cells, and ECM, so it promotes the spread of fat cells in muscle tissue [19].

Nervous system

The increased expression of TSPs during human brain evolution leads to changes in synaptic organization and plasticity, and contributes to human unique cognitive abilities and our special susceptibility to neurodegenerative diseases [7, 75].

TSP-4 accumulates in neuromuscular junctions and specific synaptic-rich structures in adults [1]. TSP-4 binds to the specific cell integrin receptors of ECM and activates intracellular signal transduction pathways leading to synaptogenesis [76]. In addition to synaptogenesis, TSP-4 increases dendritic dendrites and synaptic transmission to enhance synaptic connections [77], and TSP-4 is related to synaptic rearrangement and plasticity [78]. TSP-4 secreted by astrocytes promotes neuronal migration into the olfactory bulb [79]. When the TSP-4 of NG_2 cells is overexpressed, it can promote the spontaneous neuronal differentiation of NG_2 cells [80].

After a cortical injury, TSP-4 activates the subependymal ventricular zone (SVZ) notch to activate downstream signals, thereby promoting glial cell production [81]. The increased expression of TSP-4 in the spinal cord after spinal cord injury [82] and small joint injury [83] induces excitatory synapse development and promotes the transduction of articular stress in joints [84] and may lead to excessive spinal excitability in the development and maintenance of persistent neuropathic pain. Infraorbital nerve injury leads to the upregulation of TSP-4 in the trigeminal spinal complex, resulting in orofacial neuropathic pain [85]. After peripheral nerve injury, the expression of TSP-4 is increased in sensory neurons [86], and the appearance of hypersensitivity is promoted by the $\alpha_2\delta_1$ calcium subunit [87].

Signal pathway

ER stress response

The ER stress response is the most widely studied and reported TSP-4 signaling pathway. TSPs play a prominent role in the process of tissue remodeling of the disease, enhancing the ER function and ER protection by regulating the mechanism of action by activating transcription factor 6α (Atf6α) [88]. TSP-4 mediates pathological protection by up-regulating the Atf6α pathway, which is at least partially effective [49]. The transport of TSP-4 through the secretory pathway can increase cardiac and muscle fiber membrane stability [70]. The type III repeat and C-terminal domains of the wild-type

and calcium-binding mutant TSP-4 interact with Atf6α and then induce adaptive ER stress, which can cause intracellular vesicle expansion [44, 89].

TGF-β

In cardiomyocytes, the study revealed that levels of TSP-4 increased after stimulation with the TGF-β_1 ligand [6]. One study outlined a new pathway by which TGF-β_1 regulates angiogenesis. TSP-4 levels are up-regulated by SMAD3 from the TGF-β_1 signal in microvascular endothelial cells [10].

PI3K-Akt

Thbs4 is one of the leading genes that can enrich the PI3K-Akt pathway, and TSP-4 is also a product of activated fibroblasts, while TSP-4 can stimulate fibroblasts via the PI3K-Akt pathway in turn [51]. In the progression of gastric cancer, TSP-4 is down-regulated by fibroblast growth factor receptor two via the PI3K-Akt pathway [90].

ERK-MAPK

When TSP-4 is overexpressed, the ERK/MAPK signaling pathway is inhibited, which promotes the differentiation of polydendrocytes, while the level of neuronal markers in polydendrocytes increases significantly. This suggests that TSP-4 plays a role in the cell fate determination of polydendrocytes via the ERK-MAPK signaling pathway [80].

Cardiovascular diseases

TSPs and their SNPs play an important role in cardiovascular pathology [66]. Interestingly, the A387P SNP of TSP-4 promotes Ca^{2+} binding, but the N700S SNP of TSP-1 leads to decreased Ca^{2+} binding production [38]. Both TSP mutations, although different in mechanism, cause cardiovascular disease.

Myocardial infarction

Studies have shown that TSP-4 activates ER stress and selectively inhibits TGF-β in myocytes, which is a protective mode for cardiomyopathy and reduces early mortality after MI [6]. It was initially reported that elevated levels of TSP-4 mRNA in rats after MI [91] and the A387P variant of TSP-4 show a strong association of MI [92]. Later, some studies found that the A387P variant of TSP-4 is a determining factor in the development of MI at any age [36, 93]. There are also some research results that are different. A study shows that the TSP-4 A387P polymorphism is only associated with MI in females, especially female homozygous status [35], while another study has limited the homozygosity of the TSP-4 A387P variant to older women [39]. Moreover, the TSP-4 A387P SNP was also confirmed to be significantly associated with myocardial infarction in men [94]. For studies in specific countries, two studies suggest that the TSP-4 A387P polymorphism is a significant and independent risk factor for MI in Americans [95] and Egyptians [96]. Another study adds that existing evidence suggests that TSP-4 polymorphisms other than A387P in the study are not associated with MI [40]. There was an opposite finding that showed no significant association between the TSP-4 A387P polymorphism and MI in the population they studied [37].

Ventricular hypertrophy and heart failure

TSP-4 is associated with myocardial remodeling after hypertensive heart disease [97], which may lead to ventricular hypertrophy. Moreover, pathological ventricular hypertrophy often leads to ventricular dilatation, making the heart unable to effectively pump blood, leading to HF. Moreover, TSP-4 plays a vital role in regulating the remodeling of HF [22]. Animal experiments have revealed that *Thbs4*$^{(-/-)}$ has significant deficiencies in adapting to chronic stress overload [98]. Also, the overexpression of TSP-4 was also found in rats with monocrotaline-induced pulmonary hypertension [99], end-stage dilated cardiomyopathy [14], and volume overload HF caused by aorta-tubular heart [100].

Hypertension

Long-term hypertension is one of the key risk factors for CAD, HF, and other cardiovascular diseases. In hypertension, TSP-4 regulates the progression of cardiac hypertrophy, affects aortic aneurysm formation, and alters endothelium-dependent resistance to arterial relaxation [17]. Moreover, TSP-4 was identified as having a critical role in causing cardiac hypertrophy and aortic dissection in Ang II-induced hypertension [48]. TSP-4 is significantly increased in the small mesenteric arteries of hypertension

[15, 101]. Mice with specific destruction of TSP-4 in the heart significantly reduced the adaptation to pressure overload [49].

Coronary artery disease

CAD is caused by a decrease in myocardial blood flow due to various factors. Initially, a study found a significant association between CAD and the A387P SNP of TSP-4 in the US population [102]. Subsequently, more research confirmed this finding and showed that the A387P SNP of TSP-4 is associated with an increased risk of CAD in the US population [95, 103, 104]. In contrast, there was no significant relationship between the A387P mutations in TSP-4 and CAD in the target population in one study [37].

Peripheral artery disease

Atherosclerosis usually does not have any symptoms at first, but in severe cases, it can cause CAD, stroke, peripheral arterial disease, and kidney problems. TSP-4 is enriched in atherosclerotic lesions and areas prone to pathogenesis [105], and TSP-4 is also involved in the development of atherosclerosis [106]. As mentioned earlier, TSP-4 affects the recruitment of macrophages by affecting endothelial cells [62]. The A387P SNP of TSP-4 has a significant effect on the structure, and inhibits the adhesion and proliferation of endothelial cells [23]. The mutation is consistent with the phenotype that induces atherosclerosis and thrombosis [55], which may be responsible for atherosclerosis. Curcumin has anti-atherosclerotic effects, and one of its possible mechanisms is to prevent an oxidized low-density lipoprotein-induced decrease in TSP-4 expression [107]. Conversely, in one study, a decrease in TSP-4 levels was observed in atherosclerotic lesions [108].

One study found a significant increase in aneurysm formation rates in Thbs4$^{-/-}$ mice treated with ANG II, which was not observed in hypertensive WT mice or untreated Thbs4$^{-/-}$ mice [17]. It is speculated that TSP-4 has no obvious effect under physiological conditions, but it provides a major protective effect under pathological load conditions to prevent aortic aneurysms caused by hypertension [48]. Aortic aneurysms show significant differences in the etiology based on the location of the human abdominal aortic aneurysm, which exhibits a strong positive correlation with male gender [17, 65]. The protective effect of TSP-4 on aortic aneurysms needs to be further examined to determine the role of aneurysm location, age, gender and the effects of diabetes.

A recent study has found that TSP-4 levels are positively correlated with the severity of PAD and show an unknown correlation with diabetes [109], which may lead to arteriosclerosis. At present, related research on PAD other than atherosclerosis is still relatively lacking.

Clinical value

Biomarker

Different levels of TSP-4 expression in tissues can be used to distinguish between different cell sources. TSP-4 is one of the specific markers used to identify articular cartilage [20] and to distinguish between proper tendon progenitor cells and peritenon progenitors [110]. In mice, SVZ astrocytes express high levels of TSP-4 as opposed to cortical astrocytes expressing low levels of TSP-4 [81]. Furthermore, the differential regulation of TSP-4 has potential value as an in vitro biomarker for inducing signal transduction [111].

TSP-4 can be used for the identification and diagnosis of specific pathological conditions and diseases. TSP-4 is a known CAD marker [112] and a cardiac overload-specific endothelial-specific marker [15]. TSP-4 may be a new marker for atherosclerosis, especially in the subgroup of diabetic patients [109]. Another study found that TSP-4 expression was increased in osteoarthritis and correlated with the severity of osteoarthritis [46], suggesting that TSP-4 can be used as a biomarker for osteoarthritis. Currently, the detection of IgG isotype autoantibodies against TSP-4 can be used to support the diagnosis of osteoarthritis [113]. Also, TSP-4 was identified as a potential biomarker for locoism [114] and myopathy associated with S-adenosyl homocysteine hydrolase deficiency [115]. Similarly, TSP-4 and its degree of methylation can serve as important tumor markers.

Assessment

TSP-4-labeled innervated tendon, together with laminin labeled with the basement membrane, can assess the size and distribution of muscle

fibers [18]. The level of TSP-4 expression can be used to assess the mean of the phenotypic state of the meniscus cells [116]. The overexpression and polymorphism of TSP-4 are associated with vascular invasion in advanced cancer and can be used to assess the risk and prognosis of hepatic cancer [11] and gastric cancer [117].

Therapy

In addition to its use in diagnostics, TSP-4 can also be used as a therapeutic target for some diseases.

As an ECM scaffold at the tendon junction, TSP-4 may be used for tendon strengthening and repair [118, 119]. By targeting KLF6 to promote endothelial cell angiogenesis, TSP-4 contributes to the treatment of tendon lesions [120]. Also, TSP-4 has been identified as a potential therapeutic target for muscular dystrophy [71]. TSP-4 plays an important role in the progression of hepatic cancer [121], and targeting TSP-4 is a promising therapeutic strategy for the treatment of advanced hepatic cancer [11]. In a rat model, TSP-4 in bone marrow stromal cells promotes endothelial cell proliferation and migration as well as tube formation, and post-stroke injection can promote the recovery of neural function [64].

Understanding the timing and role of TSP-4 overexpression in persistent neuropathic pain after an injury is critical for designing TSP-4-based therapies [83]. Controlling the interaction between TSP4-mediated intracellular calcium signaling in peripheral sensory neurons [122] and blocking the EGF-like domain of TSP4 and Caαδ [32] may be targeted for the development of analgesic drugs for neuropathic pain.

Conclusion

According to this review, it is easy to find that the research on TSP-4 is still insufficient compared to the well-studied TSP-1 and TSP-2, especially in terms of specific molecular mechanisms associated with ligands and signaling pathways. In the cardiovascular system, TSP-4 inhibits MI, HF, hypertension, and promotes PAD, while its A387P mutation increases the risk of MI, CAD, and PAD. Moreover, the impact of TSP-4 on key etiological mechanisms such as inflammation and vascular remodeling in major aneurysms requires further investigation. Through further research on TSP-4, TSP-4 may become an effective therapeutic target for the aforementioned cardiovascular diseases.

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Disclosure of conflict of interest

None.

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References

[1] Arber S and Caroni P. Thrombospondin-4, an extracellular matrix protein expressed in the developing and adult nervous system promotes neurite outgrowth. J Cell Biol 1995; 131: 1083-1094.

[2] Dunkle ET, Zaucke F and Clegg DO. Thrombospondin-4 and matrix three-dimensionality in axon outgrowth and adhesion in the developing retina. Exp Eye Res 2007; 84: 707-717.

[3] Kazerounian S, Yee KO and Lawler J. Thrombospondins in cancer. Cell Mol Life Sci 2008; 65: 700.

[4] Whited JL, Lehoczky JA, Austin CA and Tabin CJ. Dynamic expression of two thrombospondins during axolotl limb regeneration. Dev Dyn 2011; 240: 1249-1258.

[5] McCart Reed AE, Song S, Kutasovic JR, Reid LE, Valle JM, Vargas AC, Smart CE and Simpson PT. Thrombospondin-4 expression is activated during the stromal response to invasive breast cancer. Virchows Arch 2013; 463: 535-545.

[6] Rainer PP, Hao S, Vanhoutte D, Lee DI, Koitabashi N, Molkentin JD and Kass DA. Cardiomyocyte-specific transforming growth factor β suppression blocks neutrophil infiltration, augments multiple cytoprotective cascades, and reduces early mortality after myocardial infarction. Circ Res 2014; 114: 1246-1257.

[7] Cáceres M, Suwyn C, Maddox M, Thomas JW and Preuss TM. Increased cortical expression of two synaptogenic thrombospondins in hu-

man brain evolution. Cereb Cortex 2007; 17: 2312-2321.
[8] Lawler J. Thrombospondin-1 as an endogenous inhibitor of angiogenesis and tumor growth. J Cell Mol Med 2002; 6: 1-12.
[9] Muppala S, Frolova E, Xiao R, Krukovets I, Yoon S, Hoppe G, Vasanji A, Plow E and Stenina-Adognravi O. Proangiogenic properties of thrombospondin-4. arterioscler. Thromb Vasc Biol 2015; 35: 1975-1986.
[10] Muppala S, Xiao R, Krukovets I, Verbovetsky D, Yendamuri R, Habib N, Raman P, Plow E and Stenina-Adognravi O. Thrombospondin-4 mediates TGF-β-induced angiogenesis. Oncogene 2017; 36: 5189-5198.
[11] Su F, Zhao J, Qin S, Wang R, Li Y, Wang Q, Tan Y, Jin H, Zhu F, Ou Y, Cheng Z, Su W, Zhao F, Yang Y, Zhou Z, Zheng J, Li Y, Li Z and Wu Q. Over-expression of Thrombospondin 4 correlates with loss of miR-142 and contributes to migration and vascular invasion of advanced hepatocellular carcinoma. Oncotarget 2017; 8: 23277-23288.
[12] Lawler J. The functions of thrombospondin-1 and -2. Curr Opin Cell Biol 2000; 12: 634-640.
[13] Adams JC and Lawler J. The thrombospondins. Int J Biochem Cell Biol 2004; 36: 961-968.
[14] Tan FL, Moravec CS, Li J, Apperson-Hansen C, McCarthy PM, Young JB and Bond M. The gene expression fingerprint of human heart failure. Proc Natl Acad Sci U S A 2002; 99: 11387-11392.
[15] Mustonen E, Aro J, Puhakka J, Ilves M, Soini Y, Leskinen H, Ruskoaho H and Rysä J. Thrombospondin-4 expression is rapidly upregulated by cardiac overload. Biochem Biophys Res Commun 2008; 373: 186-191.
[16] Frolova EG, Sopko N, Blech L, Popovic ZB, Li J, Vasanji A, Drumm C, Krukovets I, Jain MK, Penn MS, Plow EF and Stenina OI. Thrombospondin-4 regulates fibrosis and remodeling of the myocardium in response to pressure overload. FASEB J 2012; 26: 2363-2373.
[17] Palao T, Rippe C, van Veen H, VanBavel E, Swärd K and Bakker EN. Thrombospondin-4 knockout in hypertension protects small-artery endothelial function but induces aortic aneurysms. Am J Physiol Heart Circ Physiol 2016; 310: H1486-H1493.
[18] Kasprick DS, Kish PE, Junttila TL, Ward LA, Bohnsack BL and Kahana A. Microanatomy of adult zebrafish extraocular muscles. PLoS One 2011; 6: e27095.
[19] Albrecht E, Schering L, Liu Y, Komolka K, Kühn C, Wimmers K, Gotoh T and Maak S. Triennial growth and development symposium: factors influencing bovine intramuscular adipose tissue development and cellularity. J Anim Sci 2017; 95: 2244-2254.
[20] Jeschke A, Bonitz M, Simon M, Peters S, Baum W, Schett G, Ruether W, Niemeier A, Schinke T and Amling M. Deficiency of thrombospondin-4 in mice does not affect skeletal growth or bone mass acquisition, but causes a transient reduction of articular cartilage thickness. PLoS One 2015; 10: e0144272.
[21] Cohn JN, Ferrari R and Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000; 35: 569-582.
[22] Rysä J, Leskinen H, Ilves M and Ruskoaho H. Distinct upregulation of extracellular matrix genes in transition from hypertrophy to hypertensive heart failure. Hypertension 2005; 45: 927-933.
[23] Stenina OI, Desai SY, Krukovets I, Kight K, Janigro D, Topol EJ and Plow EF. Thrombospondin-4 and its variants: expression and differential effects on endothelial cells. Circulation 2003; 108: 1514-1519.
[24] Lawler J, McHenry K, Duquette M and Derick L. Characterization of human thrombospondin-4. J Biol Chem 1995; 270: 2809-2814.
[25] Narouz-Ott L, Maurer P, Nitsche DP, Smyth N and Paulsson M. Thrombospondin-4 binds specifically to both collagenous and non-collagenous extracellular matrix proteins via its C-terminal domains. J Biol Chem 2000; 275: 37110-37117.
[26] Mörgelin M, Heinegård D, Engel J and Paulsson M. Electron microscopy of native cartilage oligomeric matrix protein purified from the Swarm rat chondrosarcoma reveals a five-armed structure. J Biol Chem 1992; 267: 6137-6141.
[27] Oldberg A, Antonsson P, Lindblom K and Heinegård D. COMP (cartilage oligomeric matrix protein) is structurally related to the thrombospondins. J Biol Chem 1992; 267: 22346-22350.
[28] Selander-Sunnerhagen M, Ullner M, Persson E, Teleman O, Stenflo J and Drakenberg T. How an epidermal growth factor (EGF)-like domain binds calcium. High resolution NMR structure of the calcium form of the NH2-terminal EGF-like domain in coagulation factor X. J Biol Chem 1992; 267: 19462-19469.
[29] Misenheimer TM and Mosher DF. Biophysical characterization of the signature domains of thrombospondin-4 and thrombospondin-2. J Biol Chem 2005; 280: 41229-41235.
[30] Carlson CB, Bernstein DA, Annis DS, Misenheimer TM, Hannah B-lA, Mosher DF and Keck JL. Structure of the calcium-rich signature domain of human thrombospondin-2. Nat Struct Mol Biol 2005; 12: 910-4.

[31] Schips TG, Vanhoutte D, Vo A, Correll RN, Brody MJ, Khalil H, Karch J, Tjondrokoesoemo A, Sargent MA, Maillet M, Ross RS and Molkentin JD. Thrombospondin-3 augments injury-induced cardiomyopathy by intracellular integrin inhibition and sarcolemmal instability. Nat Commun 2019; 10: 76.

[32] Park JF, Yu YP, Gong N, Trinh VN and Luo ZD. The EGF-LIKE domain of thrombospondin-4 is a key determinant in the development of pain states due to increased excitatory synaptogenesis. J Biol Chem 2018; 293: 16453-16463.

[33] Hauser N, Paulsson M, Kale AA and DiCesare PE. Tendon extracellular matrix contains pentameric thrombospondin-4 (TSP-4). FEBS Lett 1995; 368: 370-310.

[34] Södersten F, Ekman S, Schmitz M, Paulsson M and Zaucke F. Thrombospondin-4 and cartilage oligomeric matrix protein form heterooligomers in equine tendon. Connect Tissue Res 2006; 27: 85-91.

[35] Cui J, Randell E, Renouf J, Sun G, Han FY, Younghusband B and Xie YG. Gender dependent association of thrombospondin-4 A387P polymorphism with myocardial infarction. Arterioscler. Thromb Vasc Biol 2004; 24: e183-e184.

[36] Wessel J, Topol EJ, Ji M, Meyer J and McCarthy JJ. Replication of the association between the thrombospondin-4 A387P polymorphism and myocardial infarction. Am Heart J 2004; 147: 905-909.

[37] Zhou X, Huang J, Chen J, Zhao J, Yang W, Wang X and Gu D. Thrombospondin-4 A387P polymorphism is not associated with coronary artery disease and myocardial infarction in the Chinese Han population. Clin Sci 2004; 106: 495-500.

[38] Stenina OI, Ustinov V, Krukovets I, Marinic T, Topol EJ and Plow EF. Polymorphisms A387P in thrombospondin-4 and N700S in thrombospondin-1 perturb calcium binding sites. FASEB J 2005; 19: 1893-1895.

[39] Cui J, Randell E, Renouf J, Sun G, Green R, Han FY and Xie YG. Thrombospondin-4 1186G>C (A387P) is a sex-dependent risk factor for myocardial infarction: a large replication study with increased sample size from the same population. Am Heart J 2006; 152: 543.e541-543.e545.

[40] Koch W, Hoppmann P, de Waha A, Schömig A and Kastrati A. Polymorphisms in thrombospondin genes and myocardial infarction: a case-control study and a meta-analysis of available evidence. Hum Mol Genet 2008; 17: 1120-1126.

[41] Södersten F, Ekman S, Niehoff A, Zaucke F, Heinegård D and Hultenby K. Ultrastructural immunolocalization of cartilage oligomeric matrix protein, thrombospondin-4, and collagen fibril size in rodent achilles tendon in relation to exercise. Connect Tissue Res 2007; 48: 254-262.

[42] Frolova EG, Drazba J, Krukovets I, Kostenko V, Blech L, Harry C, Vasanji A, Drumm C, Sul P, Jenniskens GJ, Plow EF and Stenina-Adognravi O. Control of organization and function of muscle and tendon by thrombospondin-4. Matrix Biol 2014; 37: 35-48.

[43] Adams JC and Lawler J. Cell-type specific adhesive interactions of skeletal myoblasts with thrombospondin-1. Mol Biol Cell 1994; 5: 423-437.

[44] Brody MJ, Schips TG, Vanhoutte D, Kanisicak O, Karch J, Maliken BD, Blair NS, Sargent MA, Prasad V and Molkentin JD. Dissection of thrombospondin-4 domains involved in intracellular adaptive endoplasmic reticulum stress-responsive signaling. Mol Cell Biol 2016; 36: 2-12.

[45] Niu J, Lin Y, Liu P, Yu Y, Su C and Wang X. Microarray analysis on the lncRNA expression profile in male hepatocelluar carcinoma patients with chronic hepatitis B virus infection. Oncotarget 2016; 7: 76169-76180.

[46] Maly K, Schaible I, Riegger J, Brenner RE, Meurer A and Zaucke F. The expression of thrombospondin-4 correlates with disease severity in osteoarthritic knee cartilage. Int J Mol Sci 2019; 20.

[47] De Groote MA, Sterling DG, Hraha T, Russell TM, Green LS, Wall K, Kraemer S, Ostroff R, Janjic N and Ochsner UA. Discovery and validation of a six-marker serum protein signature for the diagnosis of active pulmonary tuberculosis. J Clin Microbiol 2017; 55: 3057-3071.

[48] Palao T, Medzikovic L, Rippe C, Wanga S, Al-Mardini C, van Weert A, de Vos J, van der Wel NN, van Veen HA, van Bavel ET, Swärd K, de Waard V and Bakker EN. Thrombospondin-4 mediates cardiovascular remodelling in angiotensin II-induced hypertension. Cardiovasc Pathol 2018; 35: 12-19.

[49] Doroudgar S and Glembotski CC. ATF6 [corrected] and thrombospondin 4: the dynamic duo of the adaptive endoplasmic reticulum stress response. Circ Res 2013; 112: 9-12.

[50] Sawaki D, Hou L, Tomida S, Sun J, Zhan H, Aizawa K, Son BK, Kariya T, Takimoto E, Otsu K, Conway SJ, Manabe I, Komuro I, Friedman SL, Nagai R and Suzuki T. Modulation of cardiac fibrosis by Krüppel-like factor 6 through transcriptional control of thrombospondin 4 in cardiomyocytes. Cardiovasc Res 2015; 107: 420-430.

[51] Moon SJ, Bae JM, Park KS, Tagkopoulos I and Kim KJ. Compendium of skin molecular signatures identifies key pathological features asso-

ciated with fibrosis in systemic sclerosis. Ann Rheum Dis 2019; 78: 817-825.
[52] Whited JL, Lehoczky JA and Tabin CJ. Inducible genetic system for the axolotl. Proc Natl Acad Sci U S A 2012; 109: 13662-13667.
[53] Klaas M, Kangur T, Viil J, Mäemets-Allas K, Minajeva A, Vadi K, Antsov M, Lapidus N, Järvekülg M and Jaks V. The alterations in the extracellular matrix composition guide the repair of damaged liver tissue. Sci Rep 2016; 6: 27398.
[54] Lv L, Liang W, Ye M, Zhang J, Zhang H, Xue G and Zhang L. Thrombospondin-4 ablation reduces macrophage recruitment in adipose tissue and neointima and suppresses injury-induced restenosis in mice. Atherosclerosis 2016; 247: 70-77.
[55] Stenina OI, Byzova TV, Adams JC, McCarthy JJ, Topol EJ and Plow EF. Coronary artery disease and the thrombospondin single nucleotide polymorphisms. Int J Biochem Cell Biol 2004; 36: 1013-1030.
[56] Sadvakassova G, Dobocan MC, Difalco MR and Congote LF. Regulator of differentiation 1 (ROD1) binds to the amphipathic C-terminal peptide of thrombospondin-4 and is involved in its mitogenic activity. J Cell Physiol 2009; 220: 672-679.
[57] Congote LF, Difalco MR and Gibbs BF. The C-terminal peptide of thrombospondin-4 stimulates erythroid cell proliferation. Biochem Biophys Res Commun 2004; 324: 673-678.
[58] Kondo Y, Shen L, Yan PS, Huang TH and Issa JP. Chromatin immunoprecipitation microarrays for identification of genes silenced by histone H3 lysine 9 methylation. Proc Natl Acad Sci U S A 2004; 101: 7398-7403.
[59] Margagliotti S, Clotman F, Pierreux CE, Beaudry JB, Jacquemin P, Rousseau GG and Lemaigre FP. The Onecut transcription factors HNF-6/OC-1 and OC-2 regulate early liver expansion by controlling hepatoblast migration. Dev Biol 2007; 311: 579-589.
[60] Greco SA, Chia J, Inglis KJ, Cozzi SJ, Ramsnes I, Buttenshaw RL, Spring KJ, Boyle GM, Worthley DL, Leggett BA and Whitehall VL. Thrombospondin-4 is a putative tumour-suppressor gene in colorectal cancer that exhibits age-related methylation. BMC Cancer 2010; 10: 494.
[61] Ponda MP and Breslow JL. Serum stimulation of CCR7 chemotaxis due to coagulation factor XIIa-dependent production of high-molecular-weight kininogen domain 5. Proc Natl Acad Sci U S A 2016; 113: E7059-E7068.
[62] Frolova EG, Pluskota E, Krukovets I, Burke T, Drumm C, Smith JD, Blech L, Febbraio M, Bornstein P, Plow EF and Stenina OI. Thrombospondin-4 regulates vascular inflammation and atherogenesis. Circ Res 2010; 107: 1313-1325.
[63] Liu J, Cheng G, Yang H, Deng X, Qin C, Hua L and Yin C. Reciprocal regulation of long non-coding RNAs THBS4-003 and THBS4 control migration and invasion in prostate cancer cell lines. Mol Med Rep 2016; 14: 1451-1458.
[64] Zhang Q, Zhou M, Wu X, Li Z, Liu B, Gao W, Yue J and Liu T. Promoting therapeutic angiogenesis of focal cerebral ischemia using thrombospondin-4 (TSP4) gene-modified bone marrow stromal cells (BMSCs) in a rat model. J Transl Med 2019; 17: 111.
[65] Sure VN and Katakam PV. Janus face of thrombospondin-4: impairs small artery vasodilation but protects against cardiac hypertrophy and aortic aneurysm formation. Am J Physiol Heart Circ Physiol 2016; 310: H1383-H1384.
[66] Wilsgaard T, Mathiesen EB, Patwardhan A, Rowe MW, Schirmer H, Løchen ML, Sudduth-Klinger J, Hamren S, Bønaa KH and Njølstad I. Clinically significant novel biomarkers for prediction of first ever myocardial infarction: the Tromsø Study. Circ Cardiovasc Genet 2015; 8: 363-371.
[67] Cagliani R, Guerini FR, Rubio-Acero R, Baglio F, Forni D, Agliardi C, Griffanti L, Fumagalli M, Pozzoli U, Riva S, Calabrese E, Sikora M, Casals F, Comi GP, Bresolin N, Cáceres M, Clerici M and Sironi M. Long-standing balancing selection in the THBS4 gene: influence on sex-specific brain expression and gray matter volumes in Alzheimer disease. Hum Mutat 2013; 34: 743-753.
[68] Kuttapitiya A, Assi L, Laing K, Hing C, Mitchell P, Whitley G, Harrison A, Howe FA, Ejindu V, Heron C and Sofat N. Microarray analysis of bone marrow lesions in osteoarthritis demonstrates upregulation of genes implicated in osteochondral turnover, neurogenesis and inflammation. Ann Rheum Dis 2017; 76: 1764-1773.
[69] Pluskota E, Stenina OI, Krukovets I, Szpak D, Topol EJ and Plow EF. Mechanism and effect of thrombospondin-4 polymorphisms on neutrophil function. Blood 2005; 106: 3970-3978.
[70] Brody MJ, Vanhoutte D, Schips TG, Boyer JG, Bakshi CV, Sargent MA, York AJ and Molkentin JD. Defective flux of thrombospondin-4 through the secretory pathway impairs cardiomyocyte membrane stability and causes cardiomyopathy. Mol Cell Biol 2018; 38: e00114-00118.
[71] Vanhoutte D, Schips TG, Kwong JQ, Davis J, Tjondrokoesoemo A, Brody MJ, Sargent MA, Kanisicak O, Yi H, Gao QQ, Rabinowitz JE, Volk T, McNally EM and Molkentin JD. Thrombospondin expression in myofibers stabilizes muscle membranes. Elife 2016; 5: e17589.
[72] Islam A, Mbimba T, Younesi M and Akkus O. Effects of substrate stiffness on the tenoinduction of human mesenchymal stem cells. Acta Biomater 2017; 58: 244-253.
[73] Schering L, Hoene M, Kanzleiter T, Jähnert M, Wimmers K, Klaus S, Eckel J, Weigert C, Schür-

mann A, Maak S, Jonas W and Sell H. Identification of novel putative adipomyokines by a cross-species annotation of secretomes and expression profiles. Arch Physiol Biochem 2015; 121: 194-205.
[74] Urs S, Smith C, Campbell B, Saxton AM, Taylor J, Zhang B, Snoddy J, Jones Voy B and Moustaid-Moussa N. Gene expression profiling in human preadipocytes and adipocytes by microarray analysis. J Nutr 2004; 134: 762-70.
[75] Koh S, Kim N, Yin HH, Harris IR, Dejneka NS and Eroglu C. Human umbilical tissue-derived cells promote synapse formation and neurite outgrowth via thrombospondin family proteins. J Neurosci 2015; 35: 15649-15665.
[76] Campo C, da Silva Filho MI, Weinhold N, Mahmoudpour SH, Goldschmidt H, Hemminki K, Merz M and Försti A. Bortezomib-induced peripheral neuropathy: a genome-wide association study on multiple myeloma patients. Hematol Oncol 2018; 36: 232-237.
[77] Gan KJ and Südhof TC. Specific factors in blood from young but not old mice directly promote synapse formation and NMDA-receptor recruitment. Proc Natl Acad Sci U S A 2019; 116: 12524-12533.
[78] Andersson D, Wilhelmsson U, Nilsson M, Kubista M, Ståhlberg A, Pekna M and Pekny M. Plasticity response in the contralesional hemisphere after subtle neurotrauma: gene expression profiling after partial deafferentation of the hippocampus. PLoS One 2013; 8: e70699.
[79] Girard F, Eichenberger S and Celio MR. Thrombospondin 4 deficiency in mouse impairs neuronal migration in the early postnatal and adult brain. Mol Cell Neurosci 2014; 61: 176-186.
[80] Yang HJ, Ma SP, Ju F, Zhang YP, Li ZC, Zhang BB, Lian JJ, Wang L, Cheng BF, Wang M and Feng ZW. Thrombospondin-4 promotes neuronal differentiation of NG2 cells via the ERK/MAPK pathway. J Mol Neurosci 2016; 60: 517-524.
[81] Benner EJ, Luciano D, Jo R, Abdi K, Paez-Gonzalez P, Sheng H, Warner DS, Liu C, Eroglu C and Kuo CT. Protective astrogenesis from the SVZ niche after injury is controlled by Notch modulator Thbs4. Nature 2013; 497: 369-73.
[82] Zeng J, Kim D, Li KW, Sharp K, Steward O, Zaucke F and Luo ZD. Thrombospondin-4 contributes to spinal cord injury-induced changes in nociception. Eur J Pain 2013; 17: 1458-1464.
[83] Crosby ND and Winkelstein BA. Spinal astrocytic thrombospondin-4 induced by excitatory neuronal signaling mediates pain after facet capsule injury. Ann Biomed Eng 2016; 44: 3215-3224.
[84] Crosby ND, Zaucke F, Kras JV, Dong L, Luo ZD and Winkelstein BA. Thrombospondin-4 and excitatory synaptogenesis promote spinal sensitization after painful mechanical joint injury. Exp Neurol 2015; 264: 111-120.
[85] Li KW, Kim DS, Zaucke F and Luo ZD. Trigeminal nerve injury-induced thrombospondin-4 up-regulation contributes to orofacial neuropathic pain states in a rat model. Eur J Pain 2014; 18: 489-495.
[86] Pan B, Yu H, Park J, Yu YP, Luo ZD and Hogan QH. Painful nerve injury upregulates thrombospondin-4 expression in dorsal root ganglia. J Neurosci Res 2015; 93: 443-453.
[87] Pan B, Guo Y, Wu HE, Park J, Trinh VN, Luo ZD and Hogan QH. Thrombospondin-4 divergently regulates voltage-gated Ca^{2+} channel subtypes in sensory neurons after nerve injury. Pain 2016; 597: 3751-3768.
[88] Lynch JM, Maillet M, Vanhoutte D, Schloemer A, Sargent MA, Blair NS, Lynch KA, Okada T, Aronow BJ, Osinska H, Prywes R, Lorenz JN, Mori K, Lawler J, Robbins J and Molkentin JD. A thrombospondin-dependent pathway for a protective ER stress response. Cell 2012; 149: 1257-1268.
[89] Krawczyk KK, Ekman M, Rippe C, Grossi M, Nilsson BO, Albinsson S, Uvelius B and Swärd K. Assessing the contribution of thrombospondin-4 induction and ATF6α activation to endoplasmic reticulum expansion and phenotypic modulation in bladder outlet obstruction. Sci Rep 2016; 6: 32449.
[90] Huang T, Liu D, Wang Y, Li P, Sun L, Xiong H, Dai Y, Zou M, Yuan X and Qiu H. FGFR2 promotes gastric cancer progression by inhibiting the expression of thrombospondin4 via PI3K-Akt-Mtor pathway. Cell Physiol Biochem 2018; 50: 1332-1345.
[91] Jin H, Yang R, Awad TA, Wang F, Li W, Williams SP, Ogasawara A, Shimada B, Williams PM, de Feo G and Paoni NF. Effects of early angiotensin-converting enzyme inhibition on cardiac gene expression after acute myocardial infarction. Circulation 2001; 103: 736-742.
[92] Topol EJ, McCarthy J, Gabriel S, Moliterno DJ, Rogers WJ, Newby LK, Freedman M, Metivier J, Cannata R, O'Donnell CJ, Kottke-Marchant K, Murugesan G, Plow EF, Stenina O and Daley GQ. Single nucleotide polymorphisms in multiple novel thrombospondin genes may be associated with familial premature myocardial infarction. Circulation 2001; 104: 2641-2644.
[93] Hamsten A and Eriksson P. Thrombospondins and premature coronary artery disease: time to go beyond genotype-phenotype association studies. Arterioscler. Thromb Vasc Biol 2003; 23: 6-7.
[94] McCarthy JJ, Parker A, Salem R, Moliterno DJ, Wang Q, Plow EF, Rao S, Shen G, Rogers WJ, Newby LK, Cannata R, Glatt K and Topol EJ; GeneQuest Investigators. Large scale associa-

tion analysis for identification of genes underlying premature coronary heart disease: cumulative perspective from analysis of 111 candidate genes. J Med Genet 2004; 41: 334-341.
[95] Ye H, Zhou A, Hong Q, Chen X, Xin Y, Tang L, Dai D, Ji H, Xu M, Wang DW and Duan S. Association of seven thrombotic pathway gene CpG-SNPs with coronary heart disease. Biomed Pharmacother 2015; 72: 98-102.
[96] Abdelmonem NA, Turky NO, Hashad IM, Abdel Rahman MF, El-Etriby A and Gad MZ. Association of Thrombospondin-1 (N700S) and Thrombospondin-4 (A387P) gene polymorphisms with the incidence of acute myocardial infarction in egyptians. Curr Pharm Biotechnol 2017; 18: 1078-1087.
[97] Mustonen E, Leskinen H, Aro J, Luodonpää M, Vuolteenaho O, Ruskoaho H and Rysä J. Metoprolol treatment lowers thrombospondin-4 expression in rats with myocardial infarction and left ventricular hypertrophy. Basic Clin Pharmacol Toxicol 2010; 197: 709-717.
[98] Cingolani OH, Kirk JA, Seo K, Koitabashi N, Lee DI, Ramirez-Correa G, Bedja D, Barth AS, Moens AL and Kass DA. Thrombospondin-4 is required for stretch-mediated contractility augmentation in cardiac muscle. Circ Res 2011; 109: 1410-1414.
[99] Imoto K, Okada M and Yamawaki H. Expression profile of matricellular proteins in hypertrophied right ventricle of monocrotaline-induced pulmonary hypertensive rats. J Vet Med Sci 2017; 79: 1096-1102.
[100] Melenovsky V, Benes J, Skaroupkova P, Sedmera D, Strnad H, Kolar M, Vlcek C, Petrak J, Benes J, Papousek F, Oliyarnyk O, Kazdova L and Cervenka L. Metabolic characterization of volume overload heart failure due to aorto-caval fistula in rats. Mol Cell Biochem 2011; 354: 83-96.
[101] Palao T, Swärd K, Jongejan A, Moerland PD, de Vos J, van Weert A, Arribas SM, Groma G, van-Bavel E and Bakker EN. Gene expression and microRNA expression analysis in small arteries of spontaneously hypertensive rats. Evidence for ER stress. PLoS One 2015; 10: e0137027.
[102] Corsetti JP, Ryan D, Moss AJ, McCarthy J, Goldenberg I, Zareba W and Sparks CE. Thrombospondin-4 polymorphism (A387P) predicts cardiovascular risk in postinfarction patients with high HDL cholesterol and C-reactive protein levels. Thromb Haemost 2011; 106: 1170-1178.
[103] Corsetti JP, Salzman P, Ryan D, Moss AJ, Zareba W and Sparks CE. Plasminogen activator inhibitor-2 polymorphism associates with recurrent coronary event risk in patients with high HDL and C-reactive protein levels. PLoS One 2013; 8: e68920.
[104] Zhang XJ, Wei CY, Li WB, Zhang LL, Zhou Y, Wang ZH, Tang MX, Zhang W, Zhang Y and Zhong M. Association between single nucleotide polymorphisms in thrombospondins genes and coronary artery disease: a meta-analysis. Thromb Res 2015; 136: 45-51.
[105] Aissa AF, Amaral CLD, Venancio VP, Machado CDS, Hernandes LC, Santos PWDS, Curi R, Bianchi MLP and Antunes LMG. Methionine-supplemented diet affects the expression of cardiovascular disease-related genes and increases inflammatory cytokines in mice heart and liver. J Toxicol Environ Health Part A 2017; 80: 1116-1128.
[106] Chukkapalli SS, Rivera MF, Velsko IM, Lee JY, Chen H, Zheng D, Bhattacharyya I, Gangula PR, Lucas AR and Kesavalu L. Invasion of oral and aortic tissues by oral spirochete Treponema denticola in ApoE(-/-) mice causally links periodontal disease and atherosclerosis. Infect Immun 2014; 82: 1959-1967.
[107] Zhou ZY, Chen YQ, Wang FY, Tian N and Fan CL. Effect of curcumin on down-expression of thrombospondin-4 induced by oxidized low-density lipoprotein in mouse macrophages. Biomed Mater Eng 2014; 24: 181-189.
[108] Kristensen LP, Larsen MR, Mickley H, Saaby L, Diederichsen AC, Lambrechtsen J, Rasmussen LM and Overgaard M. Plasma proteome profiling of atherosclerotic disease manifestations reveals elevated levels of the cytoskeletal protein vinculin. J Proteomics 2014; 101: 141-153.
[109] Zierfuss B, Höbaus C, Herz CT, Pesau G, Koppensteiner R and Schernthaner GH. Thrombospondin-4 increases with the severity of peripheral arterial disease and is associated with diabetes. Heart Vessels 2020; 35: 52-58.
[110] Mienaltowski MJ, Cánovas A, Fates VA, Hampton AR, Pechanec MY, Islas-Trejo A and Medrano JF. Transcriptome profiles of isolated murine Achilles tendon proper- and peritenon-derived progenitor cells. J Orthop Res 2019; 37: 1409-1418.
[111] Berasi SP, Varadarajan U, Archambault J, Cain M, Souza TA, Abouzeid A, Li J, Brown CT, Dorner AJ, Seeherman HJ and Jelinsky SA. Divergent activities of osteogenic BMP2, and tenogenic BMP12 and BMP13 independent of receptor binding affinities. Growth Factors 2011; 29: 128-139.
[112] Jing L, Parker CE, Seo D, Hines MW, Dicheva N, Yu Y, Schwinn D, Ginsburg GS and Chen X. Discovery of biomarker candidates for coronary artery disease from an APOE-knock out mouse model using iTRAQ-based multiplex quantitative proteomics. Proteomics 2011; 11: 2763-2776.
[113] Ruthard J, Hermes G, Hartmann U, Sengle G, Pongratz G, Ostendorf B, Schneider M, Höllr-

iegl S, Zaucke F, Wagener R, Streichert T and Klatt AR. Identification of antibodies against extracellular matrix proteins in human osteoarthritis. Biochem Biophys Res Commun 2018; 503: 1273-1277.
[114] Jiao J, Wang S, Zhang R, Ma Z, Du G, Chen X, Tao D and Zhao J. iTRAQ-based quantitative proteomics discovering potential serum biomarkers in locoweed poisoned rabbits. Chem Biol Interact 2017; 268: 111-118.
[115] Sedic M, Kraljevic Pavelic S, Cindric M, Vissers JPC, Peronja M, Josic D, Cuk M, Fumic K, Pavelic K and Baric I. Plasma biomarker identification in S-adenosylhomocysteine hydrolase deficiency. Electrophoresis 2011; 32: 1970-1975.
[116] Grogan SP, Duffy SF, Pauli C, Lotz MK and D'Lima DD. Gene expression profiles of the meniscus avascular phenotype: a guide for meniscus tissue engineering. J Orthop Res 2018; 36: 1947-1958.
[117] Lin X, Hu D, Chen G, Shi Y, Zhang H, Wang X, Guo X, Lu L, Black D, Zheng XW and Luo X. Associations of THBS2 and THBS4 polymorphisms to gastric cancer in a southeast Chinese population. Cancer Genet 2016; 209: 215-222.
[118] Jelinsky SA, Archambault J, Li L and Seeherman H. Tendon-selective genes identified from rat and human musculoskeletal tissues. J Orthop Res 2010; 28: 289-97.
[119] Subramanian A and Schilling TF. Thrombospondin-4 controls matrix assembly during development and repair of myotendinous junctions. Elife 2014; 3: e02372.
[120] Ge Ha, Shrestha A, Liu C, Wu P and Cheng B. MicroRNA 148a-3p promotes Thrombospondin-4 expression and enhances angiogenesis during tendinopathy development by inhibiting Krüppel-like factor 6. Biochem Biophys Res Commun 2018; 502: 276-282.
[121] Wu H, Zhang G, Li Z, Ma J, Han X, Xiang T and Jiang X. Thrombospondin-4 expression as a prognostic marker in hepatocellular carcinoma. Gene 2019; 696: 219-224.
[122] Guo Y, Zhang Z, Wu HE, Luo ZD, Hogan QH and Pan B. Increased thrombospondin-4 after nerve injury mediates disruption of intracellular calcium signaling in primary sensory neurons. Neuropharmacology 2017; 117: 292-304.