Review Article

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STRUCTURAL CHARACTERISTICS AND FUNCTIONAL INSIGHTS INTO TSP-4: IMPLICATIONS FOR CARDIOVASCULAR HEALTH

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ABSTRACT

Thrombospondin-4 (TSP-4) is a multidomain protein with unique functions within the thrombospondin family. It plays a works in tissue repair, cell-to-matrix conveying, and various physiological processes. TSP-4 differs structurally from other family members and is associated with a common single nucleotide polymorphism (SNP), A387P, linked to cardiovascular disorders. Its functions include tissue remodeling, regeneration, proliferation, adhesion, migration, angiogenesis, inflammation, and adipogenesis. The A387P SNP in TSP-4 increases the risk of these cardiovascular conditions and affects angiogenesis, inflammation, and adipogenesis. TSP-4 has clinical applications as a marker for various tissues and pathological disorders. Its expression levels differentiate cell origins, making it a biomarker for articular cartilage, tendon progenitor cells, and more. In heart-related conditions, TSP-4 serves as a marker for cardiac overload and coronary artery disease. Additionally, TSP-4 expression is associated with osteoarthritis severity, suggesting its potential as a biomarker for this condition. Overall, understanding TSP-4's diverse functions and its role in cardiovascular pathology provides insights into its clinical relevance and diagnostic potential, making it a promising target for further research and therapeutic interventions.

KEYWORDS: Thrombospondin-4 (TSP-4), Matricellular glycoprotein, Tissue repair, Cell-to-matrix communication, Cardiovascular disorders, Single nucleotide polymorphism (SNP), A387P, Tissue remodeling.

INTRODUCTION

A member of the TSP family, thrombospondin-4 (TSP-4) is a protein that is created by the human Thbs4 gene. TSP-4 performs various roles that are significantly different from those of other family members, and it even competes with them functionally. TSP-4, for instance, has the ability to stimulate angiogenesis (4), whereas TSP-1 and TSP-2 are anti-angiogenic (5). The actions of basement membranes in different tissues are regulated by TSP-4. TSP-4 has been identified in adult hearts (6), muscles of the skeleton (7), articular cartilage cells (8), and it builds up at the neuromuscular junction (9). TSP-4 is a crucial regulator of cell proliferation and remodeling, according to existing research.

Cardiac remodeling serves as a clinical indicator of genomic expression changes influenced by various factors such as cardiac strain, damage, hemodynamic load, and neurohormone activation. These factors contribute to modifications at the molecular, cellular, and extracellular levels, ultimately affecting heart size (10). The progression of heart failure (HF) is commonly attributed to cardiac remodeling (11) (12). Moreover, fluctuations in TSP-4 expression are frequently observed in conjunction with cardiovascular conditions like myocardial infarction (MI), heart failure, hypertension, arteriosclerosis.

In this review, we highlight the typical function of TSP-4, particularly in relation to heart disease. TSP-1 and TSP-2 are homotrimers in the TSP family, whereas TSP-3, TSP-4, and TSP-5 arehomopentamers in subgroup B (13). TSP-4 is a big central particle that can be detected in electron microscopy. It is made up of five subunits that are joined together by globular domains that are located near to the N-terminal (14). The appearance of TSP-4 subunits bears a resemblance to TSP-1 subunits; however, a notable difference lies in the smaller size of TSP-4 subunits (15-18). Notably, heparin is present in TSP-5 but not in TSP-4 (19). Heparin affinity chromatography allows for the enrichment of TSP-4 (20).

A prevalent single nucleotide polymorphism (SNP) linked to cardiovascular disorders within TSP-4 is A387P (22). This specific SNP substitution takes place in the third continuous type III, and it is recognized that this variant has the potential to enhance calcium binding (23).

Function

The majority of TSP-4's actions are intercellular because it is an intercellular protein. TSP-4 controls the extracellular matrix (ECM) composition in the majority of its enriched locations, which include the muscles and tendons. The fibril formation to the surface of cells may be mediated by TSP-4 (24). Additionally, TSP-4 deficiency alters the structure and physiological operation of tissues (25) and is a significant contributor to cardiovascular disease. Previous research has shown that TSP-4 is essential for migration, attachment, remodeling, recuperation, and inflammation as well as for promoting growth of the nervous system (26).

Renovation and regrowth

The TSP family, whose production is frequently stimulated, supports tissue regenerationthrough stress (27). The first and most frequently described function of TSP-4 is tissue remodeling and regeneration. During tissue injury, regeneration, and renovation, TSP-4 expression is frequently unregulated (28). TSP-4 is implicated in the remodeling process because it has the ability to change the composition of the matrix proteins (29). TSP-4 binds to and controls structural ECM proteins in heart cellstroma during tissue injury (30), which encourages adaptive ECM remodeling. Additionally, cardiac fibrosis is controlled by cardiomyocytes by transcriptionally modulating TSP-4, which in turn controls cardiac fibroblast activation (31). Additionally, through the Toll-like receptor 4 signaling system, TSP-4 can increase the production of the elastin gene and myofibroblast alteration, resulting in the fibrosis of the epidermis (32). In vivo limb regeneration is influenced by TSP (33). Additionally, the overexpression of TSP-4 induces non-hepatocytes in the vicinity of the injured liver's portal region to support liver regeneration (34).

Proliferation

Cell proliferation stands out as a fundamental function of TSP-4, particularly within the cardiovascular system, akin to activities such as tissue remodeling and tissue regeneration. The modulation of endothelial cell is crucial for vessel wall dynamics, is under the control of vascular cells producing TSP-4 (35). Through interactions with integrin 2 and gabapentin receptor 21, recombinant TSP-4 expedites the developement of vascular smooth muscle cells (36) and microvascular endothelial cells (37), while significantly impeding the growth of endothelial cells derived from TSP-4 knockout mice (38). The efficacy of TSP-4 in promoting endothelial cell proliferation undergoes substantial changes due to the single nucleotide polymorphism (SNP) in TSP-4 (39). Furthermore, the C-terminal peptide of TSP-4 (C21) exhibits the ability to enhance the proliferation of erythroid cells (40). C21 amplifies thymidine erythrocytes and fibroblasts from bovine skin (41).

Adhesion and migration

TSP-4 is implicated in cell adhesion and migration, according to numerous studies (42). TSP-4 is necessary for cellular adhesion (43). In the ECM, TSP-4 controls molecules that promote axonal development and adhesion (44). Fusion proteins including C21 promote myoblast adhesion, according to earlier research (26). (45). The ability of TSP-4 to facilitate endothelial cell adhesion is significantly altered by an SNP mutation (39). Additionally, it has been noted that suppressing the lncRNA TSP-4 prevents prostate cancer cells from migrating and invading (46).

Angiogenesis

Angiogenesis is a crucial process for growth and development, and the production of granulation tissue. The same time numerous endothelial cell-related responses are impacted by TSP-4, including the development of increased angiogenesis (37). For instance, TSP-4 enhances TGF-1's effect on angiogenesis (38). TSP-4 also improves endothelial cells' capacity to stimulate angiogenesis, which aids in the promotion of neovascularization (47). According to studies, TSP-4 knockdown and knockout (KO) suppress the angiogenesis caused by hepatocellular cancer (48) and TSP-4 KO mice have less angiogenesis (49).

Inflammation

The biological process of inflammation shields the body from damaging stimuli. TSP-4 has a crucial role in controlling vascular inflammation (50). Inflammation considerably increases the expression of TSP-4 (28). A glycoprotein implicated in the inflammatory response is encoded by Thbs4 . The inflammatory response to neuropathic pain is mediated by TSP-4 (51). Interleukin-8 and extra H2O2 are released by cells with the TSP-4 A387P mutation (52). Furthermore, TSP-4 suppression lowers other markers of arterial wall inflammation, inhibits endothelial cell activation, and greatly reduces the amount of macrophages in the lesion (45).

Adipogenesis

Pre-adipocytes differentiate into adipocytes through a process known as adipogenesis. In mice, TSP-4 is a putative myokine that is related with obesity and exercise (53). When compared to mature adipocytes, TSP-4 is upregulated in human pre-adipocytes (54). TSP-4 may therefore play a role in the early stages of adipogenesis. TSP-4 also facilitates the contact between muscle fibers and ECM (7).

Vascular conditions

Cardiovascular pathology is significantly impacted by TSPs and associated SNPs (50). It's interesting to note that whereas the N700S SNP in TSP-1 decreases Ca2+ binding production, the A387P SNP in TSP-4 increases Ca2+ binding (23). Cardiovascular illness is brought on by both TSP mutations, despite their divergent mechanisms.

Myocardial infarction

Research has demonstrated that TSP-4 promotes ER stress and specifically inhibits TGF- in myocytes, acting as a protective mechanism for cardiomyopathy and lowering early mortality after MI (55).

Following myocardial infarction (MI) in rats, elevated TSP-4 mRNA levels were observed (56), and a noteworthy correlation between the A387P variation of TSP-4 and MI was identified (57). Subsequent investigations revealed that the TSP-4 A387P variation plays a crucial role in the onset of MI across all age groups (58). Divergent research findings also exist. In one study, the TSP-4 A387P polymorphism, specifically in the female homozygous state, was exclusively associated with MI in females (22), whereas another study report homozygosity of the TSP-4 A387P variant to elderly women (59).Two separate studies underscore the substantial and independent association of the TSP-4 A387P genotype with MI risk in both American and Egyptian populations (60, 61).

Enlarged ventricles and cardiac failure

After hypertensive cardiac disease, TSP-4 is linked to myocardial remodeling (62), which may result in ventricular hypertrophy. In addition, abnormal ventricular hypertrophy frequently results in ventricular dilatation, which impairs the heart's ability to efficiently pump blood and causes HF. Additionally, TSP-4 is crucial in controlling HF remodeling (63). Thbs4(-/-) exhibits severe weaknesses in coping with chronic stress overload, according to animal investigations . Additionally, mice with end-stage dilated cardiomyopathy (6), monocrotaline-induced pulmonary hypertension (64,65) were found to have TSP-4 overexpression.

Hypertension

Persistent hypertension stands out as a prominent factor for various other cardiovascular ailments. Within the context of hypertension, the regulation of cardiac hypertrophy progression, influence on aortic aneurysm formation, and modification of endothelium-dependent resistance to arterial relaxation are orchestrated by TSP-4 (11).

Coronary artery disease

A decrease in the CAD, is brought on by a number of reasons. In the beginning, a study in the US population discovered a strong connection between CAD and the TSP-4 A387P SNP (66). More studies later supported this discovery and demonstrated that the A387P SNP of TSP-4 is linked to an elevated risk of CAD in the american population (67). In contrast, one study (9) found no connection between the TSP-4 A387P mutation and CAD in the target group.

Peripheral artery disease

At initially, atherosclerosis typically exhibits no symptoms, but in extreme circumstances, it cancause renal issues, CAD, stroke, and peripheral artery disease. TSP-4 is implicated in the formation of atherosclerosis and is concentrated in atherosclerotic lesions and regions prone to pathogenesis (68). As previously indicated, TSP-4 influences endothelial cells, which in turn modulates macrophage recruiting (45). The TSP-4 A387P SNP significantly alters the shape and prevents endothelial cells from adhering to one another and proliferating (35).The mutation is compatible with the phenotype that causes thrombosis and atherosclerosis (39), which suggests that atherosclerosis may be the result of the mutation. One of curcumin's potential mechanisms for preventing an low-density lipoprotein-induced decline in TSP is that it possesses anti-atherosclerotic properties. (69). On the other hand, in one investigation, atherosclerotic lesions showed a drop in TSP-4 levels (70).

Clinical benefit

The discernment of different cell origins can be achieved by assessing TSP-4 expression levels in tissues. TSP-4 serves as a distinctive marker for identifying articular cartilage (8) and distinguishing tendon progenitor cells from peritenon progenitors (71). TSP-4 is expressed at higher levels in SVZ astrocytes in mice than it is in cortical astrocytes (72). Additionally, TSP-4's differential regulation may be used as an biomarker for triggering signal transduction (73).

Specific pathological disorders and diseases can be recognized and diagnosed using TSP-4. TSP-4 is a recognized CAD marker (74) and an endothelial-specificmarkerfor cardiac overload (10). Currently, osteoarthritis can be diagnosed with the support of the finding of IgGisotype autoantibodies against TSP-4 (76). TSP-4 has also been mentioned as a possible biomarker for locoism (77) and the myopathy brought on by a lack of S-adenosylhomocysteine hydrolase (78). Similar to this, TSP-4 and the degree of methylation in it can be useful tumor indicators.

CONCLUSION

In conclusion, thrombospondin-4 (TSP-4) emerges as a multifaceted and pivotal player in various physiological and pathological processes, with a significant impact on cardiovascular health. TSP-4 distinguishes itself by exerting distinct functions compared to other family members, playing a crucial role in tissue remodeling, regeneration, angiogenesis, inflammation, adipogenesis, and cell proliferation. The intricate structure of TSP-4, characterized by homopentameric assembly and unique domains, underscores its versatility in mediating cell-matrix interactions and influencing diverse cellular activities. Notably, TSP-4's involvement in cardiovascular conditions, such cardiac failure, hypertension highlights its significance in maintaining cardiovascular homeostasis. The impact of single nucleotide polymorphisms (SNPs), particularly the A387P variant, underscores the genetic variability associated with TSP-4 and its role in cardiovascular disorders. This genetic variation can influence calcium binding and contribute to the pathogenesis of conditions like myocardial infarction, enlarging ventricles, and hypertension. Beyond its role in cardiovascular diseases, TSP-4 serves as a valuable marker in various clinical contexts, aiding in the diagnosis and understanding of diseases such as osteoarthritis, atherosclerosis, and myopathy.

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