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Emerging Roles of Thrombospondin Family Proteins in Pathogenesis and Risk Assessment of Atherosclerotic Vascular Disease

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ABSTRACT

***Background*:** Atherosclerotic vascular disease underpins a vast majority of cardiovascular morbidity and mortality, encompassing not only coronary artery disease but also cerebrovascular and peripheral arterial complications. Despite extensive knowledge of classical risk factors, there remains a critical need to understand the molecular mediators driving atherogenesis, plaque progression, and vascular complications. The thrombospondin (TSP) family of matricellular proteins—including TSP-1 through TSP-5—has recently emerged as a group of multifunctional regulators with distinct and overlapping roles in vascular biology. These glycoproteins mediate extracellular matrix remodeling, cellular adhesion, immune cell recruitment, angiogenesis, and the regulation of inflammatory and thrombotic responses, thereby influencing every stage of atherogenesis and vascular injury repair.

This review provides a comprehensive analysis of the molecular structure, regulation, and expression profiles of thrombospondin family proteins in vascular tissues. We examine experimental and clinical studies linking TSP-1, TSP-2, and less-studied isoforms (TSP-3, TSP-4, TSP-5) to key events in atherosclerotic plaque initiation, progression, and destabilization. Special attention is given to the interplay between thrombospondins, classical cardiovascular risk factors such as diabetes and hypertension, and their downstream effects on endothelial dysfunction and vascular smooth muscle cell migration.

Moreover, we assess the potential of circulating thrombospondin levels, particularly TSP-1 and TSP-2, as biomarkers for atherosclerotic disease severity and future cardiovascular events. We discuss recent data on genetic polymorphisms within TSP genes and their association with individual susceptibility to atherosclerosis and its complications. Finally, the therapeutic prospects of targeting thrombospondin-mediated pathways—either to inhibit maladaptive vascular remodeling or to modulate inflammatory and angiogenic responses—are reviewed.

In summary, thrombospondin family proteins are central players in the complex molecular networks underlying atherosclerotic vascular disease. Their dual role as mechanistic effectors and candidate biomarkers offers new opportunities for risk stratification and targeted therapy. Ongoing research into the specific contributions and regulation of each TSP isoform promises to advance precision cardiovascular medicine.

Keywords: Thrombospondin, Pathogenesis, Atherosclerotic Vascular Disease

INTRODUCTION

Atherosclerotic vascular disease remains the principal cause of morbidity and mortality in developed and developing countries alike, manifesting as coronary artery disease, stroke, and peripheral arterial disease [1]. While the contribution of traditional risk factors—such as hypertension, diabetes, hyperlipidemia, and smoking—to atherogenesis is well established, growing evidence underscores the importance of matricellular proteins as key modulators of vascular pathology. Among these, the thrombospondin (TSP) family has garnered particular interest due to its multifaceted involvement in vascular remodeling, immune responses, and cellular interactions within the arterial wall [2,3].

Thrombospondins comprise five structurally related glycoproteins—TSP-1 through TSP-5—each exhibiting tissue-specific expression and distinct, yet sometimes overlapping, biological functions [4]. Early research centered predominantly on TSP-1 as a regulator of platelet function and angiogenesis; however, recent advances reveal that other isoforms, notably TSP-2 and TSP-4, also contribute to vascular homeostasis and pathology. These proteins are secreted in response to diverse stimuli, including vascular injury, inflammation, and metabolic stress, and are implicated in processes such as extracellular matrix (ECM) remodeling, endothelial dysfunction, leukocyte recruitment, and smooth muscle cell migration—all pivotal events in the initiation and progression of atherosclerotic lesions [5,6].

Despite these insights, the precise mechanisms by which individual TSP family members modulate atherosclerotic disease remain incompletely defined. Contradictory results from animal models and human studies highlight a context-dependent role for each TSP isoform, influenced by the stage of disease, tissue environment, and interplay with other molecular mediators. Moreover, while TSP-1 and TSP-2 have been investigated as potential biomarkers for vascular risk assessment, data on the clinical significance of TSP-3, TSP-4, and TSP-5 are limited and warrant further exploration [7,8].

This review aims to provide a comprehensive synthesis of current knowledge regarding the thrombospondin family in atherosclerotic vascular disease. We address the structural and regulatory features of each isoform, summarize their biological actions in vascular tissues, and critically evaluate their emerging roles as biomarkers and therapeutic targets. In doing so, we highlight knowledge gaps and identify promising avenues for future research in the quest to refine risk stratification and develop novel interventions for atherosclerotic disease [9].

1: The Thrombospondin Family—Structure, Isoforms, and Expression

The thrombospondin family consists of five secreted glycoproteins—TSP-1, TSP-2, TSP-3, TSP-4, and TSP-5 (also known as cartilage oligomeric matrix protein, COMP)—that share conserved domains but exhibit unique structural features and expression patterns [1]. Structurally, these proteins are grouped into two subfamilies: subgroup A (TSP-1, TSP-2) forms trimers, while subgroup B (TSP-3, TSP-4, TSP-5) assembles as pentamers. All thrombospondins are characterized by a multi-domain architecture, including an N-terminal domain, procollagen-like region, type I/II/III repeats, and a C-terminal globular domain [2]. This complex structure enables interaction with diverse ligands, including extracellular matrix (ECM) proteins, integrins, growth factors, and cell surface receptors, which underpins their context-dependent functions [3].

TSP-1 and TSP-2 are widely expressed in the cardiovascular system, particularly in platelets, endothelial cells, vascular smooth muscle cells, and cardiac fibroblasts, where they are rapidly upregulated in response to injury, inflammation, or metabolic stress [4]. TSP-3, TSP-4, and TSP-5 have distinct tissue distributions; for instance, TSP-4 is prominent in the heart and vasculature under both physiological and pathological conditions, while TSP-5 is highly expressed in cartilage but is also implicated in vascular calcification and remodeling [5,6]. Differential gene expression and post-translational regulation of TSP isoforms add another layer of complexity, influencing their biological availability and activity within vascular tissues [7].

Emerging evidence from genetic and proteomic studies indicates that the expression of individual TSP isoforms may be dynamically regulated by mechanical stress, hypoxia, inflammatory cytokines, and metabolic factors such as glucose or lipids [8]. Understanding the precise regulation of thrombospondin expression in healthy and diseased vessels is crucial for deciphering their distinct and overlapping roles in vascular homeostasis and pathology [9].

2: Biological Functions of Thrombospondins in Vascular Homeostasis

Thrombospondins are now recognized as key modulators of cell-matrix and cell-cell interactions in the cardiovascular system. They play a vital role in orchestrating the dynamic remodeling of the ECM, which is essential for maintaining vascular structure,

elasticity, and repair following injury [10]. By binding to matrix components such as collagen, fibronectin, and proteoglycans, TSPs regulate ECM assembly and turnover, as well as the migration and adhesion of vascular smooth muscle cells and fibroblasts [11]. These properties are particularly relevant in the context of vascular injury, where rapid ECM reorganization is required to restore integrity and function [12].

In addition to their structural role, thrombospondins modulate growth factor availability and activity, notably transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), both central to vascular remodeling and angiogenesis [13]. For example, TSP-1 is a potent inhibitor of VEGF-mediated angiogenesis and can activate latent TGF-β, contributing to the balance between repair and fibrosis in vascular tissues [14]. TSP-4, conversely, has been shown to promote adaptive responses to cardiac stress, such as hypertrophy and angiogenesis, which may be protective in early heart disease but maladaptive in chronic conditions [15].

Thrombospondins also serve as regulators of vascular tone and endothelial function. By interacting with surface receptors such as CD36 and CD47, TSP-1 and TSP-2 can inhibit nitric oxide (NO) signaling pathways, leading to vasoconstriction and reduced endothelial-mediated relaxation [16]. This inhibition of NO bioavailability is a key mechanism underlying the development of endothelial dysfunction, a recognized precursor to atherosclerosis and vascular disease [17]. Collectively, the pleiotropic actions of the TSP family make them central players in the maintenance and adaptation of the vascular system [18].

3: Thrombospondins in Atherosclerotic Plaque Development

Atherosclerosis is fundamentally a process of maladaptive vascular remodeling, chronic inflammation, and progressive ECM alteration. Thrombospondins, particularly TSP-1 and TSP-2, have been extensively implicated in all phases of atherogenesis—from endothelial dysfunction and immune cell recruitment to plaque growth and destabilization [19]. TSP-1 promotes the adhesion and transmigration of monocytes and other leukocytes across the endothelial barrier, facilitating the inflammatory milieu required for plaque formation [20]. It also modulates matrix metalloproteinases (MMPs), which are essential for ECM degradation and smooth muscle cell migration during early plaque development [21].

Experimental studies in animal models have demonstrated that deficiency of TSP-1 or TSP-2 results in altered plaque composition, reduced collagen content, and increased plaque vulnerability, indicating their dual role in stabilizing and remodeling atherosclerotic lesions [22]. TSP-4, while less studied, has been linked to the recruitment and retention of inflammatory cells within the vascular wall, suggesting a pro-inflammatory function that may exacerbate lesion progression in certain settings [23]. Notably, the impact of each TSP isoform on plaque stability may differ depending on the stage of atherosclerosis, underlying metabolic conditions, and the presence of comorbidities such as diabetes or hypertension [24].

Beyond structural and inflammatory effects, TSPs influence angiogenesis within the plaque. TSP-1 acts as a negative regulator, suppressing intraplaque neovessel formation, whereas reduced TSP-1 expression has been associated with increased neovascularization, plaque instability, and intraplaque hemorrhage [25]. Thus, thrombospondins integrate multiple signaling pathways that converge on the control of plaque composition, stability, and the risk of clinical events [26].

4: Thrombospondins and Cardiovascular Risk Factors

The expression and function of thrombospondin family proteins are profoundly influenced by traditional cardiovascular risk factors, including diabetes mellitus, hypertension, and dyslipidemia. In the context of diabetes, elevated glucose levels stimulate TSP-1 and TSP-2 expression in vascular tissues, enhancing endothelial dysfunction, promoting inflammation, and inhibiting angiogenesis through the CD47 signaling pathway [27]. This mechanism is believed to underlie the heightened risk and severity of atherosclerotic complications observed in diabetic patients, where impaired vascular repair and increased thrombosis are prominent features [28]. Animal models support these findings, showing that deletion of TSP-1 improves endothelial function and mitigates vascular complications in diabetes [29].

Hypertension has also been linked to upregulation of TSP-1 and TSP-4, particularly in resistance arteries and the myocardium, where these proteins contribute to adverse vascular remodeling, fibrosis, and arterial stiffening [30]. Experimental data demonstrate that mechanical stress and angiotensin II stimulation both enhance TSP gene expression in vascular smooth muscle cells, promoting collagen deposition and increasing vascular resistance [31]. Similarly, TSPs mediate hypertensive heart disease progression through modulation of fibroblast activity and matrix accumulation, implicating them in the transition from compensated hypertrophy to heart failure [32].

Dyslipidemia, especially increased levels of oxidized low-density lipoprotein (oxLDL), is another potent stimulator of TSP-1 production by endothelial cells and macrophages [33]. TSP-1 binds to lipoproteins and facilitates their deposition in the vessel wall, further promoting local inflammation and foam cell formation—a central event in early atherogenesis [34]. Collectively, these interactions highlight thrombospondins as molecular links between classical risk factors and vascular disease progression, and as potential biomarkers reflecting cumulative risk exposure [35].

5: Genetic Polymorphisms and Thrombospondins as Clinical Biomarkers

Recent advances in genomics have identified several polymorphisms in TSP-1 and TSP-4 genes that may confer increased susceptibility to atherosclerotic vascular disease and its complications. For instance, the TSP-1 N700S variant has been associated with altered calcium binding, increased risk of myocardial infarction, and greater propensity for plaque instability [36]. Similarly, TSP-4 gene polymorphisms have been linked to higher incidence of coronary artery disease and adverse cardiac events, especially in individuals with metabolic syndrome [37]. These genetic variants may influence thrombospondin expression or function, contributing to interindividual differences in vascular risk and disease progression [38].

Clinically, circulating levels of TSP-1 and TSP-2 have been investigated as biomarkers of disease activity and severity in atherosclerosis, coronary artery disease, and acute coronary syndromes [39]. Elevated plasma TSP-1 correlates with the extent of coronary atherosclerosis, plaque burden, and adverse outcomes, while TSP-2 levels have shown prognostic value in patients with valvular and vascular diseases [40]. However, the specificity and predictive value of thrombospondin measurements remain to be fully established, with some studies reporting confounding influences from comorbidities, medications, and acute inflammatory states [41]. Nevertheless, ongoing large-scale studies aim to clarify their utility in risk stratification and monitoring therapeutic responses in vascular disease [42].

6: Therapeutic Perspectives and Future Directions

Given their central role in vascular remodeling, inflammation, and endothelial dysfunction, thrombospondins represent attractive therapeutic targets in atherosclerotic vascular disease. Preclinical studies have demonstrated that inhibition of TSP-1/CD47 signaling improves vascular function, promotes angiogenesis, and reduces fibrosis in models of diabetes, hypertension, and myocardial infarction [43]. Novel agents targeting the TSP-1/CD47 axis are under investigation for potential use in cardiovascular, fibrotic, and even oncologic disorders, highlighting the broad relevance of this pathway [44]. Additionally, strategies aimed at modulating TSP-2 or TSP-4 activity are being explored to enhance vascular repair and limit adverse remodeling following injury or revascularization procedures [45].

Despite these promising developments, several challenges remain. The multifunctional nature of thrombospondins means that broad inhibition could result in unintended effects on tissue repair, immunity, or tumor suppression. A more nuanced understanding of isoform- and tissue-specific actions will be crucial to designing effective therapies with favorable safety profiles [46]. Furthermore, integrating thrombospondin measurements into clinical practice for risk prediction and monitoring will require standardized assays, large prospective validation studies, and clear guidelines on interpretation [47].

Future research should continue to elucidate the context-dependent roles of individual TSP family members in human vascular disease, unravel the impact of genetic variation, and develop selective modulators as next-generation therapeutics. In this way, the thrombospondin family holds substantial promise for improving outcomes in patients with atherosclerotic vascular disease [48].

Conclusion

The thrombospondin family of matricellular proteins has emerged as a critical nexus in the pathogenesis, risk assessment, and potential treatment of atherosclerotic vascular disease. Acting through a combination of extracellular matrix remodeling, modulation of growth factor signaling, and regulation of immune and endothelial responses, thrombospondins influence every stage of atherogenesis, from endothelial dysfunction and plaque initiation to lesion progression and instability. The interplay of TSP-1, TSP-2, and other isoforms with classical cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia underscores their relevance as both effectors and indicators of vascular injury.

Advances in genetic and biomarker research support the clinical significance of thrombospondin polymorphisms and circulating protein levels as tools for risk stratification and prognosis in cardiovascular disease. However, challenges remain regarding their specificity and integration into routine clinical practice. Therapeutic targeting of TSP-mediated pathways—particularly the TSP-

1/CD47 axis—offers a promising avenue for novel interventions, though careful consideration of isoform- and tissue-specific effects is warranted.

Ongoing and future research should aim to clarify the distinct contributions of each thrombospondin isoform, refine biomarker utility, and develop targeted therapies that modulate these pathways for cardiovascular benefit. Ultimately, a deeper understanding of the thrombospondin family will enhance precision medicine approaches in the management and prevention of atherosclerotic vascular disease.

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REFERENCES

1. Tucker RP, Adams JC. Molecular evolution of the Thrombospondin superfamily. Semin Cell Dev Biol. 2024;155:12-21.
2. Murphy-Ullrich JE. Thrombospondin-1 signaling through the Calreticulin/LDL receptor related protein 1 Axis: functions and possible roles in Glaucoma. Front Cell Dev Biol. 2022;10:898772.
3. Zhang K, Li M, Yin L, Fu G, Liu Z. Role of thrombospondin-1 and thrombospondin-2 in cardiovascular diseases. Int J Mol Med. 2020;45(5):1275-1293.
4. Halper J. Basic components of connective tissues and extracellular matrix: fibronectin, fibrinogen, laminin, elastin, fibrillins, fibulins, matrilins, tenascins and thrombospondins. Progress in Heritable Soft Connective Tissue Diseases. 2021:105-126.
5. Dzobo K, Dandara C. The extracellular matrix: its composition, function, remodeling, and role in tumorigenesis. Biomimetics. 2023;8(2):146.
6. Forbes T, Pauza AG, Adams JC. In the balance: how do thrombospondins contribute to the cellular pathophysiology of cardiovascular disease? Am J Physiol Cell Physiol. 2021;321(5):C826-C845.
7. Spinale F. Myocardial Extracellular Matrix. Circ Res. 2014;114:872-888.
8. Pan H, Lu X, Ye D, Feng Y, Wan J, Ye J. The molecular mechanism of thrombospondin family members in cardiovascular diseases. Front Cardiovasc Med. 2024;11:1337586.
9. Farrugia BL, Melrose J. The glycosaminoglycan side chains and modular core proteins of heparan sulphate proteoglycans and the varied ways they provide tissue protection by regulating physiological processes and cellular behaviour. Int J Mol Sci. 2023;24(18):14101.
10. Song R, Zhang L. Cardiac ECM: its epigenetic regulation and role in heart development and repair. Int J Mol Sci. 2020;21(22):8610.
11. Oldenborg PA. CD47: a cell surface glycoprotein which regulates multiple functions of hematopoietic cells in health and disease. ISRN Hematol. 2013;2013:614619.
12. Rogers NM, Ghimire K, Calzada MJ, Isenberg JS. Matricellular protein thrombospondin-1 in pulmonary hypertension: multiple pathways to disease. Cardiovasc Res. 2017;113(8):858-868.
13. Lawler J. Counter regulation of tumor angiogenesis by vascular endothelial growth factor and thrombospondin-1. Semin Cancer Biol. 2022;86:126-135.

14. Bornstein P. Thrombospondins function as regulators of angiogenesis. J Cell Commun Signal. 2009;3:189-200.
15. Noroozi-Aghideh A, Kashanikhatib Z, Naderi M, Dorgalaleh A, Azad M, Alizadeh S. Expression and methylation status of vascular endothelial growth factor and thrombospondin-1 genes in congenital factor XIII-deficient patients with intracranial hemorrhage. Blood Coagul Fibrinolysis. 2021;32(5):317-322.
16. Singla B, Aithbathula RV, Pervaiz N, et al. CD47 activation by thrombospondin-1 in lymphatic endothelial cells suppresses lymphangiogenesis and promotes atherosclerosis. Arterioscler Thromb Vasc Biol. 2023;43(7):1234-1250.
17. Ma Z, Wang M, Xu X, et al. Thrombospondin-1 plasma levels associated with in-hospital major adverse cardiovascular events in patients with acute coronary syndrome. Int J Cardiol. 2023;375:98-103.
18. Kale A, Rogers NM, Ghimire K. Thrombospondin-1 CD47 signalling: from mechanisms to medicine. Int J Mol Sci. 2021;22(8):4062.
19. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko AV, Orekhov AN. Thrombospondins: a role in cardiovascular disease. Int J Mol Sci. 2017;18(7):1540.
20. Pathak AS, Stouffer GA. Differential responses to thrombospondin-1 and PDGF-BB in smooth muscle cells from atherosclerotic coronary arteries and internal thoracic arteries. Sci Rep. 2024;14(1):15847.
21. Sekhon BS. Matrix metalloproteinases–an overview. Res Rep Biol. 2010;1:1-20.
22. Ganguly R, Khanal S, Mathias A, Gupta S, Lallo J, Sahu S, et al. TSP-1 (Thrombospondin-1) deficiency protects ApoE−/− mice against leptin-induced atherosclerosis. Arterioscler Thromb Vasc Biol. 2021;41(2):e112-e127.
23. Baidildinova G, Nagy M, Jurk K, Wild PS, Ten Cate H, Van der Meijden PEJ. Soluble platelet release factors as biomarkers for cardiovascular disease. Front Cardiovasc Med. 2021;8:684920.
24. Kim CW, Pokutta-Paskaleva A, Kumar S, Timmins LH, Morris AD, Kang DW, et al. Disturbed flow promotes arterial stiffening through thrombospondin-1. Circulation. 2017;136(13):1217-1232.
25. Navneet S, Wilson K, Rohrer B. Müller glial cells in the macula: their activation and cell-cell interactions in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2024;65(2):42.
26. J. Zhang, C. Li, Y. Zheng, Z. Lin, Y. Zhang, Z. Zhang. Inhibition of angiogenesis by arsenic trioxide via TSP-1–TGF-β1-CTGF–VEGF functional module in rheumatoid arthritis. Oncotarget. 2017;8(43):73529.
27. Bitar MS. Diabetes impairs angiogenesis and induces endothelial cell senescence by up-regulating thrombospondin-CD47-dependent signaling. Int J Mol Sci. 2019;20(3):673.
28. Chen S, Shen Y, Liu Y-H, et al. Impact of glycemic control on the association of endothelial dysfunction and coronary artery disease in patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2021;20:1-9.
29. Krishna SM, Golledge J. The role of thrombospondin-1 in cardiovascular health and pathology. Int J Cardiol. 2013;168(2):692-706.
30. Saheera S, Krishnamurthy P. Cardiovascular changes associated with hypertensive heart disease and aging. Cell Transplant. 2020;29:0963689720920830.
31. Peters L, Kuebler WM, Simmons S. Sphingolipids in atherosclerosis: chimeras in structure and function. Int J Mol Sci. 2022;23(19):11948.
32. Caturano A, Vetrano E, Galiero R, Salvatore T, Docimo G, Epifani R, et al. Cardiac hypertrophy: from pathophysiological mechanisms to heart failure development. Rev Cardiovasc Med. 2022;23(5):165.
33. Kosmas CE, Rodriguez Polanco S, Bousvarou MD, et al. The triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio as a risk marker for metabolic syndrome and cardiovascular disease. Diagnostics. 2023;13(5):929.
34. Varaliová Z. Functional crosstalk between human adipose tissue and lymphatic system. 2023.
35. Wang K-Y, Zheng Y-Y, Wu T-T, Ma Y-T, Xie X. Predictive value of Gensini score in the long-term outcomes of patients with coronary artery disease who underwent PCI. Front Cardiovasc Med. 2022;8:778615.
36. Abdelmonem NA, Turky NO, Hashad IM, Abdel Rahman MF, El-Etriby A, Gad MZ. Association of thrombospondin-1 (N700S) and thrombospond in-4 (A387P) gene polymorphisms with the incidence of acute myocardial infarction in Egyptians. Curr Pharm Biotechnol. 2017;18(13):1078-1087.
37. Pan H, Lu X, Ye D, Feng Y, Wan J, Ye J. The molecular mechanism of thrombospondin family members in cardiovascular diseases. Front Cardiovasc Med. 2024;11:1337586.
38. Zhang K, Li M, Yin L, Fu G, Liu Z. Role of thrombospondin-1 and thrombospondin-2 in cardiovascular diseases. Int J Mol Med. 2020;45(5):1275-1293.
39. Elnoamany M, Dawood A, Momtaz NM, Abdou W. Thrombospondin-1 Levels in Patients with Coronary Heart Disease. World J Cardiovasc Dis. 2021;11(6):277-291.

40. Pohjolainen V, Mustonen E, Taskinen P, Näpänkangas J, Leskinen H, Ohukainen P, et al. Increased thrombospondin-2 in human fibrosclerotic and stenotic aortic valves. Atherosclerosis. 2012;220(1):66-71.
41. Menzel A, Samouda H, Dohet F, Loap S, Ellulu MS, Bohn T. Common and novel markers for measuring inflammation and oxidative stress ex vivo in research and clinical practice—which to use regarding disease outcomes? Antioxidants. 2021;10(3):414.
42. Yazdani AN, Pletsch M, Chorbajian A, Zitser D, Rai V, Agrawal DK. Biomarkers to monitor the prognosis, disease severity, and treatment efficacy in coronary artery disease. Expert Rev Cardiovasc Ther. 2023;21(10):675-692.
43. Rogers NM, Ghimire K, Calzada MJ, Isenberg JS. Matricellular protein thrombospondin-1 in pulmonary hypertension: multiple pathways to disease. Cardiovasc Res. 2017;113(8):858-868.
44. Kale A, Rogers NM, Ghimire K. Thrombospondin-1 CD47 signalling: from mechanisms to medicine. Int J Mol Sci. 2021;22(8):4062.
45. Plana E, Oto J, Medina P, Herranz R, Fernández-Pardo Á, Requejo L, Miralles M. Thrombospondins in human aortic aneurysms. IUBMB Life. 2022;74(10):982-994.
46. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko AV, Orekhov AN. Thrombospondins: a role in cardiovascular disease. Int J Mol Sci. 2017;18(7):1540.
47. Ma Z, Wang M, Xu X, et al. Thrombospondin-1 plasma levels associated with in-hospital major adverse cardiovascular events in patients with acute coronary syndrome. Int J Cardiol. 2023;375:98-103.
48. Pan H, Lu X, Ye D, Feng Y, Wan J, Ye J. The molecular mechanism of thrombospondin family members in cardiovascular diseases. Front Cardiovasc Med. 2024;11:1337586.