Heart Surgery Forum 2024; 27(11): E1360–E1366
doi: 10.59958/hsf.7927

Review

Research Progress of Transcription Factor RUNX1 Mediating Inflammatory Response in the Pathogenesis of Aortic Dissection

Mingrui Zou[1], Baohui Liu[1], Yuexin Han[1], Xin Guo[1], Yujiu Wang[1,*]

[1]Cardiovascular Surgery Department, Binzhou Medical University Hospital, 256603 Binzhou, Shandong, China
*Correspondence: yujiuwang0543@126.com (Yujiu Wang)

Submitted: 24 July 2024 Revised: 18 August 2024 Accepted: 18 September 2024 Published: 25 November 2024

Abstract

Aortic dissection is a highly lethal condition of the major vessels of the heart, with its pathogenesis still not fully understood. This review explores the critical role of transcription factor Runx-related transcription factor-1 (RUNX1) in the pathogenesis of aortic dissection, particularly its involvement in mediating inflammatory responses through various signaling pathways such as nuclear factor kappa-B (NF-κB), interleukin-6 (IL-6), and matrix metalloproteinase-9 (MMP-9). The review covers studies detailing RUNX1's impact on endothelial cell damage, smooth muscle cell phenotypic changes, and extracellular matrix degradation. Potential therapeutic strategies targeting RUNX1 are discussed, highlighting the need for further research to translate these findings into clinical practice.

Keywords

transcription factor; RUNX1; aortic dissection; inflammatory response; therapeutic target

Introduction

Aortic Dissection (AD) occurs when blood infiltrates the aortic media through a tear in the intimal layer, leading to a separation and expansion of the media along the aortic axis, forming two distinct aortic cavities. This condition is characterized by rapid progression and a high mortality rate, primarily due to the destruction of the aortic wall's structure and function. The key pathological features of AD include the abnormal structure and function of the aortic wall, marked by inflammatory factor infiltration, collagen deposition, degradation of the Extracellular Matrix (ECM), depletion of Vascular Smooth Muscle Cells (VSMC), and the rupture of elastic fibers. During the onset of AD, a significant infiltration of inflammatory cells occurs, compromising the integrity of the aortic wall and precipitating acute AD. Inflammation is widely recognized as an independent risk factor for AD, playing a pivotal role in its pathogenesis [1].

Runx-related transcription factor-1 (RUNX1) has emerged as a critical "key molecule" in cardiovascular diseases, with numerous studies affirming its essential role in the inflammatory processes underlying various cardiovascular pathologies. Historically, RUNX1 research within the cardiovascular field has predominantly focused on conditions such as myocardial hypertrophy, acute myocardial infarction, and diabetic cardiomyopathy, all of which are linked to stress-induced load. However, recent studies have increasingly highlighted RUNX1's significant involvement in aortic dissection [2]. In previous investigations, we observed high RUNX1 expression in the perivascular adipose tissue (PVAT) of both AD patients and mouse models. Notably, in AD models developed using RUNX1-specific PVAT knockout mice, the expression of inflammatory mediators such as NF-κB, IL-6, and MMP-9 was significantly reduced, alongside a marked decrease in AD incidence in these mice. These findings strongly suggest RUNX1's involvement in the inflammatory processes associated with PVAT in aortic dissection [3]. This review, therefore, focuses on the role of RUNX1 in the pathogenesis of aortic dissection, aiming to pave the way for new approaches in disease prevention, diagnosis, and treatment.

Overview of Transcription Factor RUNX1

RUNX1 is a member of the RUNX family, functioning as a transcription factor that directly binds to DNA, playing a crucial role in hematopoiesis, bone formation, and tumor biology. Initially discovered on the long arm of human chromosome 21, RUNX1 consists of three main domains: the runt homology domain at the N-terminal, the trans-activation domain at the C-terminal, and the repression domain. During embryonic development, RUNX1 is the most widely expressed of all RUNX proteins, manifesting across a range of tissues, including the heart and major blood vessels. RUNX1 encodes proteins that bind to DNA to form heterodimeric transcription factors with core factor β, which are integral to various cellular developmental processes such as proliferation, differentiation, tissue growth, and DNA damage response. Like many transcription factors, RUNX family proteins undergo post-translational modifications—methylation, phosphory-

lation, glycosylation, acetylation, and ubiquitination—that influence their localization, stability, DNA-binding affinity, and interactions with other proteins. The function of RUNX proteins is context-dependent, influenced by cellular background, and regulated by key signaling pathways such as transforming growth factor-β (TGF-β), bone morphogenetic protein (BMP), hedgehog, notch, receptor tyrosine kinase-6, and yesrelated protein1 (YAP1), all of which are linked to major developmental pathways [4]. RUNX1 also has the ability to bind to and activate condensed chromatin, recruiting other transcription factors and regulatory proteins through its transactivation domain (TAD), PY motif, VWRPY motif, and other structural elements, thereby exerting robust transcriptional regulatory functions [5,6]. In cardiovascular diseases, RUNX1 was first noted for its upregulation in patients with ischemic cardiomyopathy. Subsequent research has reinforced the role of RUNX1 as a key regulator in cardiovascular diseases, implicating it in the renin-angiotensin-aldosterone system's regulation of angiotensin expression, the activation of hypoxia-inducing factor HIF-1α, leading to hypoxia and ischemia in vascular endothelial cells, and in the activation of fibroblasts that promote aortic wall fibrosis [7].

Inflammatory Factors Participate in the Remodeling of the Aortic Wall and Destroy its Structure and Function

The aortic wall is composed of four layers: the inner layer (vascular endothelial cells), the middle layer (smooth muscle cells), the outer layer (fibroblasts), and perivascular adipocytes. The key pathological features of aortic dissection stem from changes in the structure and function of the middle aorta, which include damage to vascular smooth muscle cells, infiltration of inflammatory cells, and degradation of the extracellular matrix. Inflammatory responses play a critical role in these processes.

Vascular Endothelial Cells

AD-related intimal lacerations are primarily associated with the destruction of vascular endothelial cell structure and function during inflammation. Aortic endothelial cells secrete chemotactic and adhesion molecules that mediate inflammatory processes. Sayed *et al*. [8] found that inflammatory regulation of endothelial cells could trigger neovascularization within the media, promote extracellular matrix degradation, and facilitate endothelial cell migration, leading to aortic wall remodeling and the formation of dissection ruptures. In mouse aortic tissues, Kurihara *et al*. [9] observed significant neutrophil infiltration in the intimal layer, suggesting that this infiltration may be linked to the formation of intimal lacerations in AD.

Macrophages

Macrophages, as the most prevalent inflammatory cells within the aortic wall, play a pivotal role in vascular remodeling. Following aortic injury, bone marrow-derived progenitor cells are induced to migrate to the injury site, differentiating into macrophages or fibroblasts to participate in the immune-inflammatory response. Macrophages gradually infiltrate the media, contributing to aortic wall remodeling [10]. M1-type macrophages secrete pro-inflammatory factors such as IL-6, TNF-α, nitric oxide synthase, and MMPs, which disrupt the aortic wall structure. Conversely, M2-type macrophages exert anti-inflammatory effects by transforming growth factor-β (TGF-β) and IL-10 expression, stabilizing the structure and function of the aortic wall. Related studies have shown that RUNX1 interacts with the NF-κB subunits p50 and p65 in macrophages, regulating their participation in the inflammatory response. RUNX1 and its mediated signaling pathways play a significant regulatory role in this process, including the induction of inflammatory factors such as NF-κB, IL-6, and TNF-α, all major contributors to the inflammatory response [11].

Smooth Muscle Cells

VSMCs, when subjected to injury, oxidative stress, or inflammatory stimuli, activate various signaling pathways, including apoptosis, necroptosis, and pyroptosis. For instance, adiponectin inhibits the phenotypic transformation of VSMCs and pyroptosis by upregulating miR-133a, thus delaying disease progression. This mechanism may involve inhibiting the NLRP3/Caspase-1/GSDMD pathway and reducing the synthesis of inflammatory mediators in pyroptotic cells. Other studies indicate that vascular endothelial cells can regulate VSMC phenotypic changes in response to hypoxia, inflammation, or mechanical stress, thereby maintaining vascular homeostasis. For example, endothelial cell-specific Nox2 knockout mice revealed that endothelial cells secrete reactive oxygen-dependent cyclophilin A, which activates VSMCs and triggers their phenotypic transformation, contributing to the progression of AD [12].

Fibroblasts

The outer layer of the aorta is primarily composed of elastic fibers produced by adventitial fibroblasts (AF). Under pathological conditions, fibroblasts can transform into myofibroblasts, which migrate from the outer membrane to the media and participate in new membrane formation. AF can also migrate to the aortic media under inflammatory stimuli, transforming into VSMCs and contributing to aortic remodeling. Numerous studies have demonstrated that IL-6 can reduce the structural stability of the aortic outer membrane, facilitating dissection by regulating the release of pro-inflammatory factors from fibroblasts and recruiting macrophages. Furthermore, RUNX1 can upregulate PI3K

in the AKT pathway, promoting fibroblast transformation by binding to the TGF-β receptor promoter, thereby contributing to aortic wall degradation [13].

Perivascular Adipose Tissue

Traditionally, the outer layer of blood vessels was believed to support and protect the vascular wall. However, recent studies suggest that aortic dissection progresses "from the outside in", with the inflammatory response initiating in the aortic outer membrane and surrounding adipose tissue (PVAT). The outer vascular layer functions as a signaling hub, regulating vascular structure and function. By mediating inflammation within the aortic wall, nourishing vessels in the outer and middle aortic layers transport inflammatory factors, leading to the accumulation of inflammatory cells in the affected regions and triggering inflammatory responses [14,15].

The cumulative effects of vascular endothelial cell injury, inflammatory cell infiltration, VSMC phenotypic changes, ECM degradation, and elastic fiber breakdown culminate in aortic dissection. Consequently, the inflammatory response, mediated by various inflammatory factors, is intricately linked to the onset, progression, and clinical outcomes of AD. Additionally, this inflammatory response offers potential guidance for clinical interventions.

RUNX1 Mediates Inflammation and Participates in the Occurrence and Development of Aortic Dissection

Recent research has demonstrated that RUNX1 can regulate matrix metalloproteinase-9 (MMP-9) expression, exacerbating the inflammatory response in AD. Sun *et al.* [16] constructed a ceRNA network and identified, through GO functional enrichment analysis, that RUNX1 is involved in inflammatory response pathways, accelerating the development of AD. Current evidence suggests that aortic dissection is closely associated with aortic wall inflammation, ECM degradation, VSMC phenotypic transformation, and apoptosis, all of which lead to dysfunction and structural compromise of the aortic wall.

RUNX1 orchestrates multiple inflammatory pathways, serving as a target gene for various miRNAs and lncRNAs, and modulating inflammatory cell activity through mechanisms such as the TGF-β, Angiotensin II (AngII), HIF-1α, and Toll-like receptor (TLR) signaling pathways [17]. RUNX1's activation can mediate the TGF-β pathway, regulating cell proliferation and differentiation to maintain homeostasis. Upon binding to Smad4, TGF-β translocates to the nucleus to activate or inhibit target genes, while simultaneously promoting inhibitory Smad protein transcription to maintain TGF-β signaling balance. The TGF-β pathway is integral to ECM synthesis and plays a significant role in the early stages of aortic development. Studies have found that TGF-β is markedly activated in acute AD, contributing to AD progression by upregulating MMP-2 and MMP-9, both involved in ECM degradation [18,19]. Similarly, RUNX1's modulation of AngII affects cytokine release, impacting vascular permeability and inflammatory cell infiltration. AngII regulates the release of adhesion molecules, cytokines, chemokines, and pro-fibrotic substances, thereby modulating inflammatory processes [20]. Research confirms AngII's role in regulating endothelial function and vascular structure, with its interaction with cell adhesion molecules (such as integrin and VE-cadherin) altering vascular permeability and inducing inflammatory cell infiltration [21]. This study further validated the reliability of AngII and β-aminopropionitrile (BAPN) as a mouse model for aortic dissection. Additionally, RUNX1 has been shown to regulate the expression of angiotensin-converting enzyme 2 (ACE2). Inhibition of RUNX1 in mice resulted in decreased ACE2 expression in both *in vivo* and *in vitro* settings, suggesting RUNX1's involvement in the RAAS system, which is crucial to AD pathogenesis [22,23]. HIF-1α is a central pathway in cellular ischemia and hypoxia. RUNX1 interacts with HIF-1α, leading to ischemia and hypoxia in cells involved in aortic wall formation. RUNX1 has been shown to promote HIF-1α signaling in various cell types, including hematopoietic cells, cardiomyocytes, and glioblastoma cells, enhancing the expression of its downstream target genes [24]. TLRs are key pattern recognition receptors involved in detecting pathogen-associated molecular patterns, with their activation promoting the inflammatory response in AD [25]. The TLR-mediated signaling pathway activates the AP-1 transcription factor and the TAK1/TAB complex via MAPK, thereby enhancing NF-κB kinase complex activity and mediating the NF-κB inflammatory pathway. Increased TLR4 expression has been observed in both AD patients and mouse models, accompanied by upregulated RUNX1 expression, although the precise interaction mechanisms warrant further exploration [26]. RUNX1 also modulates inflammatory responses in various aortic wall cells. RUNX1 influences endothelial cell migration and proliferation through inflammation, regulates angiogenesis, and maintains blood supply to the aortic wall, all of which are linked to vascular remodeling. Zhang *et al.* [27] discovered that CXCL1 and granulocyte colony-stimulating factor (G-CSF) in the vascular outer membrane recruit and activate local neutrophils, inducing extravascular inflammation through increased IL-6 production, leading to acute aortic dissection rupture. Wang *et al.* [28] observed increased ERK1/2 phosphorylation and α-smooth muscle actin (α-SMA) expression in the outer aortic membrane of AD patients. The elevated α-SMA expression suggests that AF may undergo phenotypic transformation, promoting aortic vascular remodeling and AD formation through proliferation, migration, secretion of inflammatory

factors, and MMPs. Myofibroblasts are essential in maintaining the physiological structure and function of the aortic wall. Aghagolzadeh *et al*. [29] identified high expression of the Fixer/Lox complex in cardiovascular disease, with RUNX1 functioning downstream of this complex to regulate myofibroblast expression. The Fixer/CBX4/RUNX1 axis was shown to control the fibrogenic gene program in myofibroblasts, affecting aortic wall structure. The phenotypic transformation of VSMCs is critical in driving aortic disease formation, and understanding the mechanisms underlying this transformation could identify potential therapeutic targets for major artery diseases [29]. Luo *et al*. [30] first elucidated the key role and molecular mechanism of solute carrier family 44 member 2 (SLC44A2) in regulating VSMC phenotypic transformation and aortic disease. Their study also found that SLC44A2 expression is regulated by RUNX1, with the drug lenalidomide promoting SLC44A2 expression via RUNX1 to modulate VSMC phenotypic transformation. Macrophages are pivotal in the inflammatory phase of vascular disease and are recognized as significant therapeutic targets [31]. RUNX1 mediates IL-6 and monocyte chemokine-1 (MCP1) to accelerate macrophage-driven vascular inflammation, leading to AD in mice. Analysis of increased chromatin open areas in AD mice revealed a close association with inflammatory pathways. Further investigation identified these open chromatin regions as RUNX1 binding sites, confirming that RUNX1-enriched target genes are involved in AD development [32]. Moreover, RUNX1 is implicated in the formation of atherosclerotic plaques. Studies have demonstrated high RUNX1 expression in monocyte-derived macrophages in patients with familial hypercholesterolemia, with RUNX1 interacting with the NF-κB subunits p50 and p65 to enhance lipopolysaccharide-induced macrophage inflammation, suggesting that it may promote atherosclerosis through inflammatory amplification [33,34]. In RUNX1-deficient mice, McCarroll *et al*. [35] demonstrated that the aortic wall's thickness and physiological function were maintained, offering protective effects against AD. Additionally, RUNX1 was shown to promote the high expression of smooth muscle cells and collagen fibers, which, through collagen deposition in the aortic wall, increased wall fragility and predisposed to AD. Research has detected RUNX1 transcription in long non-coding RNAs associated with AD, with RUNX1 overexpressed in both AD patients and mouse models. Further studies [36–39] have linked AD to the overactivation of the sympathetic nervous system, with hypertension being significantly correlated with AD incidence, where RUNX1 plays a key role in activating adrenergic receptors such as β2AR. RUNX1 can also mediate phospholamban (PLN) phosphorylation, regulating Ca^{2+} concentrations in the sarcoplasmic reticulum and affecting intracellular calcium homeostasis, potentially leading to aortic wall calcification and damage [40].

RUNX1: Potential Therapeutic Targets for Aortic Dissection?

Currently, it is widely acknowledged that the onset and progression of aortic dissection are closely linked to endothelial injury, VSMC phenotypic changes, ECM degradation, elastic fiber rupture, and inflammatory responses [41]. Our research group posits that aortic dissection progresses "from the outside in", suggesting that restoring the stability of the outer vascular membrane's structure and function may be key to preventing and treating aortic dissection, thereby underscoring the crucial role of transcription factor RUNX1. Thus far, RUNX1 has been confirmed to be intricately involved in the inflammatory response processes of AD in both *in vivo* and *in vitro* models, offering reasonable scientific feasibility and a robust theoretical foundation for potential clinical trials. RUNX1 may therefore represent a promising therapeutic target for aortic dissection in clinical practice.

In recent years, there has been growing interest among domestic and international researchers in the role of RUNX1 in cardiovascular diseases, given its ability to mediate inflammation and influence the course, outcome, and prognosis of cardiovascular conditions. Diverse intervention strategies targeting RUNX1 and its multifaceted effects continue to emerge. However, challenges remain in understanding the upstream regulation and downstream targets of RUNX1, the signal transduction pathways of RUNX1 concerning inflammatory factors, and the impact of post-translational modifications on the expression levels of other related proteins. Both basic and clinical research affirm that RUNX1 holds promise as a therapeutic target for cardiovascular diseases, with practical intervention methods and significant clinical value.

It is important to note, however, that RUNX1 is essential for growth factor-mediated signaling, protein folding, normal cell function, and other physiological processes. Misregulation of RUNX1, whether through overexpression or deficiency, may result in protein misfolding or non-specific expression of related proteins, leading to various diseases [42]. Therefore, careful dose determination will be critical in maintaining a therapeutic balance if RUNX1-targeted therapies advance to clinical application.

While numerous studies have confirmed the role of RUNX1 in aortic dissection, many rely on animal models, which may not fully replicate human disease pathology. Additionally, sample sizes in some studies are small, limiting the generalizability of the findings. Future research should focus on large-scale, multi-center clinical trials to validate these findings in human populations. Targeting RUNX1 offers promising therapeutic potential, particularly through the use of specific inhibitors like Ro5-3335, which have shown efficacy in reducing RUNX1 activity. However, challenges remain, such as ensuring specificity and

minimizing off-target effects. Ongoing clinical trials are exploring the use of these inhibitors in cardiovascular diseases, and preliminary results are encouraging. Further research is needed to optimize dosing and delivery methods.

Summary and Outlook

In recent years, significant breakthroughs have been made in the treatment of aortic dissection, with continuously evolving treatment protocols. However, these advancements also impose certain challenges on societal development. Understanding the pathophysiology and pathogenesis of this disease holds the potential to unlock new avenues for its prevention, clinical diagnosis, and treatment. RUNX1 has emerged as a promising therapeutic target for aortic diseases, with an increasing body of research suggesting that early intervention targeting RUNX1, especially when its levels are elevated at the onset of the disease, could positively influence treatment outcomes. As society advances, the role of RUNX1 in cardiovascular health has garnered heightened attention. Continuous discoveries of diverse interventions targeting RUNX1 and their varied effects are contributing to a broader understanding of its therapeutic potential. Nevertheless, current research on RUNX1 in the context of aortic dissection remains in its exploratory stages. The complete spectrum of RUNX1's upstream and downstream targets and its regulatory mechanisms has yet to be fully elucidated. Despite these gaps, this research opens up novel perspectives for disease prevention and treatment. With ongoing research and deepening understanding, RUNX1 is likely to continue to be explored as a therapeutic target for aortic dissection, holding considerable promise for future clinical applications.

RUNX1 plays a pivotal role in the pathogenesis of aortic dissection through its regulation of inflammatory pathways. Targeting RUNX1 presents a potential therapeutic avenue, although further research is necessary to translate these findings into clinical practice. Future studies should focus on large-scale clinical trials and exploring the molecular mechanisms in greater detail to develop effective RUNX1-targeted therapies.

RUNX1, a transcription factor, has been found to be associated with various cardiovascular diseases, including aortic dissection. Aortic dissection is a life-threatening condition in which the inner layer of the aorta tears, causing blood to flow between the layers of the aortic wall. RUNX1 plays a significant role in regulating hematopoiesis, but it has also been implicated in vascular biology. Recent studies suggest that RUNX1 may contribute to the development of aortic dissection through its influence on vascular smooth muscle cells (VSMCs) and endothelial cells. RUNX1 is involved in processes such as inflammation, cell proliferation, and apoptosis—all of which are important factors in the weakening of the aortic wall that leads to dissection. Furthermore, elevated expression of RUNX1 has been linked to increased vascular inflammation, which may exacerbate the progression of aortic dissection.

However, the exact mechanisms by which RUNX1 contributes to the pathology of aortic dissection are still under investigation. Understanding these mechanisms could provide insights for potential therapeutic targets to prevent or treat this condition.

Author Contributions

MZ was responsible for experimental design and implementation, data collation and analysis, and the first draft of the paper. YW, BL, YH and XG were responsible for experimental guidance, paper design and review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Zhang H, Lun Y, Zhang J. Advances in molecular biological mechanisms of acute aortic dissection. Chinese Journal of Vascular Surgery. 2019; 8: 226–231. (In Chinese)

[2] Wang A, Zou M, Han Y, Wang Y. Research progress of inflammation of perivascular adipose tissue involved in the occurrence and development of aortic dissection. International Journal of Medicine and Health. 2019; 30: 1590–1593. (In Chinese)

[3] Wang A, Dong S, Liu B, Liu D, Zou M, Han Y, *et al*. The role of RUNX1/NF-κB in regulating PVAT inflammation in aortic dissection. Scientific Reports. 2024; 14: 9960.

[4] Lu C, Yang Z, Yu D, Lin J, Cai W. RUNX1 regulates TGF-β induced migration and EMT in colorectal cancer. Pathology, Research and Practice. 2020; 216: 153142.

[5] Seo W, Nomura A, Taniuchi I. The Roles of RUNX Proteins in

Lymphocyte Function and Anti-Tumor Immunity. Cells. 2022; 11: 3116.
[6] Roy A, Chauhan S, Bhattacharya S, Jakhmola V, Tyagi K, Sachdeva A, *et al*. Runt-related transcription factors in human carcinogenesis: a friend or foe? Journal of Cancer Research and Clinical Oncology. 2023; 149: 9409–9423.
[7] Yang N, Yu JM, Zhu HJ. Research progress of the role of RUNX1 in heart failure. Chinese Journal of Clinical & Pathology. 2019; 43: 1289–1294. (In Chinese)
[8] Sayed S, Choke E, Helme S, Dawson J, Morgan R, Belli A, *et al*. Endovascular stent graft repair of mycotic aneurysms of the thoracic aorta. The Journal of Cardiovascular Surgery. 2005; 46: 155–161.
[9] Kurihara G, Ujihara Y, Nakamura M, Sugita S. Delamination Strength and Elastin Interlaminar Fibers Decrease with the Development of Aortic Dissection in Model Rats. Bioengineering. 2023; 10: 1292.
[10] Guo Y, Che Y, Zhang X, Ren Z, Chen Y, Guo L, *et al*. Cannabidiol protects against acute aortic dissection by inhibiting macrophage infiltration and PMAIP1-induced vascular smooth muscle cell apoptosis. Journal of Molecular and Cellular Cardiology. 2024; 189: 38–51.
[11] Gao D, Zhang XX, Han H, Yan XC. Research progress on the mechanism of vascular endothelial cells regulating the phenotype of vascular smooth muscle cells and its role in arterial vascular diseases. Journal of PLA Medical College. 2019; 45: 100–105. (In Chinese)
[12] Gao D, Zhang XX, Han H, Yan XC. Research progress on the mechanism of vascular endothelial cells regulating the phenotype of vascular smooth muscle cells and its role in arterial vascular diseases. Journal of PLA Medical College. 2019; 45: 100–105. (In Chinese)
[13] Xu L, Su Y, Yang X, Bai X, Wang Y, Zhuo C, *et al*. Gramine protects against pressure overload-induced pathological cardiac hypertrophy through Runx1-TGFBR1 signaling. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2023; 114: 154779.
[14] Humphrey JD. Mechanisms of Vascular Remodeling in Hypertension. American Journal of Hypertension. 2021; 34: 432–441.
[15] Tinajero MG, Gotlieb AI. Recent Developments in Vascular Adventitial Pathobiology: The Dynamic Adventitia as a Complex Regulator of Vascular Disease. The American Journal of Pathology. 2020; 190: 520–534.
[16] Sun J, Chen G, Jing Y, He X, Dong J, Zheng J, *et al*. LncRNA Expression Profile of Human Thoracic Aortic Dissection by High-Throughput Sequencing. Cellular Physiology and Biochemistry. 2018; 46: 1027–1041.
[17] Liu M, Cao Y, Hu Y, Zhang Z, Ji S, Shi L, *et al*. MiR-199a-3p Restrains Foaming and Inflammation by Regulating RUNX1 in Macrophages. Molecular Biotechnology. 2022; 64: 1130–1142.
[18] Takeda N, Hara H, Fujiwara T, Kanaya T, Maemura S, Komuro I. TGF-β Signaling-Related Genes and Thoracic Aortic Aneurysms and Dissections. International Journal of Molecular Sciences. 2018; 19: 2125.
[19] Tzavlaki K, Moustakas A. TGF-β Signaling. Biomolecules. 2020; 10: 487.
[20] Bekassy Z, Lopatko Fagerström I, Bader M, Karpman D. Crosstalk between the renin-angiotensin, complement and kallikrein-kinin systems in inflammation. Nature Reviews. Immunology. 2022; 22: 411–428.
[21] Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of Angiopoietin-2 in Vascular Physiology and Pathophysiology. Cells. 2019; 8: 471.
[22] Glinsky GV. Tripartite Combination of Candidate Pandemic Mitigation Agents: Vitamin D, Quercetin, and Estradiol Manifest Properties of Medicinal Agents for Targeted Mitigation of the COVID-19 Pandemic Defined by Genomics-Guided Tracing of SARS-CoV-2 Targets in Human Cells. Biomedicines. 2020; 8: 129.
[23] O'Hare M, Amarnani D, Whitmore HAB, An M, Marino C, Ramos L, *et al*. Targeting Runt-Related Transcription Factor 1 Prevents Pulmonary Fibrosis and Reduces Expression of Severe Acute Respiratory Syndrome Coronavirus 2 Host Mediators. The American Journal of Pathology. 2021; 191: 1193–1208.
[24] Bogoch Y, Friedlander-Malik G, Lupu L, Bondar E, Zohar N, Langier S, *et al*. Augmented expression of RUNX1 deregulates the global gene expression of U87 glioblastoma multiforme cells and inhibits tumor growth in mice. Tumour Biology. 2017; 39: 1010428317698357.
[25] Fitzgerald KA, Kagan JC. Toll-like Receptors and the Control of Immunity. Cell. 2020; 180: 1044–1066.
[26] Li T, Liu X, Ning H, Li X, Yang J, Ma C. Association of Toll-Like Receptor 4 Gene Polymorphisms with Acute Aortic Dissection in a Chinese Han Population. BioMed Research International. 2020; 2020: 8306903.
[27] Zhang X, Peng Y, Li G, Li J, Luo M, Che Y, *et al*. Elongation of the proximal descending thoracic aorta and associated hemodynamics increase the risk of acute type B aortic dissection. Technology and Health Care. 2024; 32: 765–777.
[28] Wang Z, Ren Z, Hu Z, Hu X, Zhang H, Wu H, *et al*. Angiotensin-II induces phosphorylation of ERK1/2 and promotes aortic adventitial fibroblasts differentiating into myofibroblasts during aortic dissection formation. Journal of Molecular Histology. 2014; 45: 401–412.
[29] Aghagolzadeh P, Plaisance I, Bernasconi R, Treibel TA, Pulido Quetglas C, Wyss T, *et al*. Assessment of the Cardiac Noncoding Transcriptome by Single-Cell RNA Sequencing Identifies *FIXER*, a Conserved Profibrogenic Long Noncoding RNA. Circulation. 2023; 148: 778–797.
[30] Luo Y, Luo J, An P, Zhao Y, Zhao W, Fang Z, *et al*. The activator protein-1 complex governs a vascular degenerative transcriptional programme in smooth muscle cells to trigger aortic dissection and rupture. European Heart Journal. 2024; 45: 287–305.
[31] Song T, Zhao S, Luo S, Chen C, Liu X, Wu X, *et al*. SLC44A2 regulates vascular smooth muscle cell phenotypic switching and aortic aneurysm. The Journal of Clinical Investigation. 2024; 134: e173690.
[32] Liu M, Tao G, Cao Y, Hu Y, Zhang Z. Silencing of IGF2BP1 restrains ox-LDL-induced lipid accumulation and inflammation by reducing RUNX1 expression and promoting autophagy in macrophages. Journal of Biochemical and Molecular Toxicology. 2022; 36: e22994.
[33] Edgar L, Akbar N, Braithwaite AT, Krausgruber T, Gallart-Ayala H, Bailey J, *et al*. Hyperglycemia Induces Trained Immunity in Macrophages and Their Precursors and Promotes Atherosclerosis. Circulation. 2021; 144: 961–982.
[34] Escate R, Mata P, Cepeda JM, Padreó T, Badimon L. miR-505-3p controls chemokine receptor up-regulation in macrophages: role in familial hypercholesterolemia. FASEB Journal. 2018; 32: 601–612.
[35] McCarroll CS, He W, Foote K, Bradley A, Mcglynn K, Vidler F, *et al*. Runx1 Deficiency Protects Against Adverse Cardiac Remodeling After Myocardial Infarction. Circulation. 2018; 137: 57–70.
[36] Li SP, Liu LP, Zhou R. Research progress on the role of long noncoding RNA in the pathogenesis of aortic dissection. Journal of Practical Cardio-Cerebral Pulmonary Vascular Diseases. 2019; 31: 121–127. (In Chinese)
[37] Wu J, Liu L, Huang Z, Wang L, Cai F, Li A, *et al*. Long daytime napping: A silent danger for hypertensive individuals. European Journal of Neurology. 2024; 31: e16382.

[38] Boisset JC, van Cappellen W, Andrieu-Soler C, Galjart N, Dzierzak E, Robin C. In vivo imaging of haematopoietic cells emerging from the mouse aortic endothelium. Nature. 2010; 464: 116–120.
[39] Dimri M, Joshi J, Chakrabarti R, Sehgal N, Sureshbabu A, Kumar IP. Todralazine protects zebrafish from lethal effects of ionizing radiation: role of hematopoietic cell expansion. Zebrafish. 2015; 12: 33–47.
[40] Pan Z, Zhou X, Cao Z, Pan J. Latest Findings on the Role of RUNX1 in Bone Development and Disorders. Journal of Sichuan University. Medical Science Edition. 2024; 55: 256–262.
[41] Brunet J, Pierrat B, Badel P. Review of Current Advances in the Mechanical Description and Quantification of Aortic Dissection Mechanisms. IEEE Reviews in Biomedical Engineering. 2021; 14: 240–255.
[42] Gonzalez Galofre ZN, Kilpatrick AM, Marques M, Sá da Bandeira D, Ventura T, Gomez Salazar M, *et al*. Runx1+ vascular smooth muscle cells are essential for hematopoietic stem and progenitor cell development in vivo. Nature Communications. 2024; 15: 1653.