ETS-1/ETS-2 transcription factors in CVD (Review)

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Abstract. Cardiovascular diseases remain the leading cause of global morbidity and mortality, imposing a significant burden on families and societies. E26 transformation-specific (ETS)-1 and ETS-2, members of the ETS family of transcription factors (also known as proto-oncogenes), are increasingly recognized for their roles in tumor progression. Recent studies highlight their importance in normal coronary artery development, myocardial homeostasis and the regulation of vascular inflammation and remodeling. Emerging evidence suggests that ETS-1/ETS-2 are critical in the pathogenesis of atherosclerosis, myocardial ischemia-reperfusion injury, cardiac remodeling and heart failure. The present review summarized the research progress of ETS-1/ETS-2 in cardiovascular diseases, discusses the relevant challenges encountered in the translational process of ETS-1/ETS-2-targeted therapy for cardiovascular diseases and provides novel strategies for the treatment of cardiovascular diseases targeting ETS-1/ETS-2.

Contents

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1. Introduction

In the 21st century, cardiovascular disease (CVD) has become one of the leading causes of mortality worldwide. Statistics from the World Economic Forum show that CVD causes >50% of non-communicable disease deaths and it is expected that CVD will cause >22.2 million mortalities by 2030 (1). In China, the incidence and lethality of CVD top the list, with cardiovascular-induced deaths accounting for 46.74-44.26% of the total causes of death in rural and urban areas, respectively, in 2019 (2). Since 1990, the health burden imposed by CVD has been continuously escalating across most countries worldwide, a trend closely linked to changes in the exposure level to harmful risk factors, population growth and the accelerated aging of the population. The Global Burden of Disease Study 2023 provided updated insights into the epidemiological profile of cardiovascular diseases worldwide (3). Data from this study indicate that the global disability-adjusted life years (DALYs) of cardiovascular diseases in 2023 reached 401-465 million, a 1.4-fold escalation relative to the 1990 level (292-344 million). Among the various cardiovascular conditions, ischemic heart disease, intracerebral hemorrhage, ischemic stroke and hypertensive heart disease accounted for the majority of the disease burden in terms of DALYs. Regional disparities in the disease burden were evident: The age-standardized DALY rate of cardiovascular diseases was the highest in low and low-middle Socio-demographic Index (SDI) regions and the lowest in high-SDI regions. In parallel with the growing DALY burden, global mortality from cardiovascular diseases surged from 12.2-14 million in 1990 to 17.4-20.4 million in 2023, underscoring the persistent and worsening threat of cardiovascular diseases to global public health (3,4). The study projected that from 2025-2050, the global prevalence of cardiovascular diseases would increase by 90.0%, the crude mortality rate by 73.4% and the crude DALYs by 54.7%. Specifically, the number of mortalities attributable to cardiovascular diseases was estimated to reach 35.6 million in 2050, representing a marked increase from the 20.5 million recorded in 2025 (5). CVD brings a heavy burden to society and the study of the pathophysiological mechanism of its development may help to improve the effectiveness of CVD diagnosis and treatment. CVD includes atherosclerosis (AS), hypertension, myocardial ischemia-reperfusion injury (MIRI), myocardial remodeling and heart failure (HF) (6). Despite the significant improvement

in the treatment of CVD patients, there is still no effective drug available for the cure of CVD. The pathogenesis of CVD is complex and involves a variety of cytopathic processes such as cell migration, proliferation, apoptosis, hypertrophy, regeneration, endothelial cell dysfunction, cellular oxidative stress injury, inflammatory response and myocardial fibrosis (7,8).

Members of the E26 transformation-specific (ETS) transcription factor family share a highly conserved DNA-binding domain and are involved in the regulation of a variety of biological processes, including oncogenic transformation, angiogenesis, differentiation and apoptosis (9,10). ETS-1/ETS-2 belongs to a subgroup of ETS family members that can be expressed in different cell types and tissues and play a variety of roles in both physiological and pathological conditions play various roles (11). Currently, most of the ETS-1/ETS-2 studies are focused on tumor invasion and other aspects and relatively few studies have been conducted in the field of the cardiovascular system, but they have received more and more attention from cardiovascular system researchers in recent years because they are closely related to angiogenesis and cardiac development and they can also promote cardiac remodeling and vascular remodeling and other pathological processes. Therefore, the present study hoped to elucidate the possible mechanisms of the role of ETS-1/ETS-2 in related CVD, to provide new ideas for the treatment of cardiovascular system diseases.

2. ETS family

ETS was originally discovered in the avian leukemia retrovirus E26, which was transduced from a homologous gene in the chicken genome and encodes a portion of a hybrid viral protein (12). The ETS transcription factor has long been thought to be associated with tumorigenesis and its expression level correlates with tumor progression in leukemia (13), thyroid cancer (14), pancreatic cancer (15), gastric cancer (16), hepatocellular carcinoma (17), prostate cancer (18), colon cancer (19), lung cancer (20) and breast cancer (21) and definitive evidence for its role in human malignancies was initially discovered through the discovery of recurrent translocations between the EWSR1 gene on chr22 and the FLI1 gene on chr11 in Ewing's sarcoma (22). The ETS family is encoded by 28 genes and acts as transcriptional activators or repressors to regulate target genes (23). The ETS family proteins all contain a conserved sequence region known as the ETS domain, which is a winged helix-turn-helix DNA-binding domain composed of highly conserved 85 amino acids. This domain forms three α-helices and a four-stranded β-sheet. It can bind to the purine-rich GGAA/T core motifs present in the promoters and enhancers of different target genes by interacting with other transcription factors, cofactors and cis-elements close to the ETS binding site (24-26). In *Drosophila*, the ETS family of transcription factors consists of eight proteins: Ecdysone-induced protein 74EF (EIP74EF), ETS-21c, ETS65A, ETS96B, ETS97D, ETS98B, Pointed (PNT) and Anterior Open (Yan). Of these, PNT and Yan are the most widely studied ETS factors (27). Among them, the PNT gene encodes three isoforms, including PNT.P1, PNT.P2 and PNT.P3, all of which share an ETS structural domain and exhibit similar DNA binding activity (28). Human ETS factors are divided into 11 subgroups: ETS (ETS-1/2), ERG, FLI1, ETV (PEA3, ETV1/4/5), TEL (ETV6/7), ELG (GABPα), TCF (ELK1/3/4), ELF (ELF1/2/4), SPI1 (SPI1/B/C), ERF (ERF, ETV3, ETV3L) and FEV (29), all contain a conserved PNT structural domain, which are involved in protein-protein interactions (Fig. 1). During early vertebrate embryogenesis, at least 13 ETS genes were found to be expressed in hematopoietic or endothelial cells, including ETS-1, ETS-2, Etv2, Etv6, Fli1, Erg, Fev, Gabpa, Elf1, Elf2, Spi1, Spib and Elk4 (30,31). Moreover, ETS proteins regulate various processes in embryonic development, such as mediating cell proliferation, differentiation, transformation, apoptosis, angiogenesis, or mediating the development of the hematopoietic or cardiovascular system, by binding to the DNA-bound GGAA/T core (32) (Fig. 2).

Different signaling pathways and protein chaperones can regulate the ETS factor, which is upregulated and activated by various signaling pathways, including the Ras/mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, in response to stimulation by a variety of growth factors (33). ETS-1 and ETS-2 are representative members of the ETS family of transcription factors, which are identified on chromosomes 11 and 21, respectively and are downstream effectors of the RAS/RAF/extracellular signal-regulated kinase (ERK) pathway that enhance the expression of ETS-1 target genes (34-37). Overexpression of dominant-negative forms of ETS-1 or ETS-2 blocks Ras translation (38), suggesting that members of the ETS family play an essential role in this process.

3. ETS-1 and ETS-2

ETS-1 belongs to the ETS family of transcription factors, also known as ETS proto-oncogene 1, and is the founding member of the ETS family and was first identified as a fusion protein expressed in conjunction with the E26 avian erythropoietic virus GAG and MYB genes, which recognizes the conserved GGAA/T motifs and binds to DNA through the winged helix-turn-helix motifs known as ETS structural domains (39). In humans, the ETS-1 gene is located on chromosome 11 (11q24.3). The human ETS-1 gene without TATA contains eight exons, called exon A (the first exon) and exons III-IX (the last seven exons) (40) and its product is the major isoform of ETS-1 with 441 amino acids. The ETS-1 mRNA undergoes selective splicing to produce three isoforms of the protein-full-length protein (termed p51 or p54), a protein lacking the sequence encoded in exon VII (termed p42) and a protein lacking the sequence encoded in exons III-VI (termed p27) (41). A total of three different targeting alleles of ETS-1 have been reported. The first was reported by the BORIES laboratory, which produced an allele that deleted the last two exons of the gene, which encode the DNA-binding structural domain and are null alleles (42). Second, the allele reported by the MUTHUSAMY laboratory is missing exon IV and part of the exon (43). The last allele was developed by HIGUCHI and targets the exon VII of the gene. This targeting allele produces only the p42 isoform of ETS-1, which lacks a self-repressor sequence and is therefore more active than full-length ETS-1 (44). ETS-1 is a 54 kDa nuclear protein that primarily acts as a transcriptional activator but also represses gene transcription (45). The

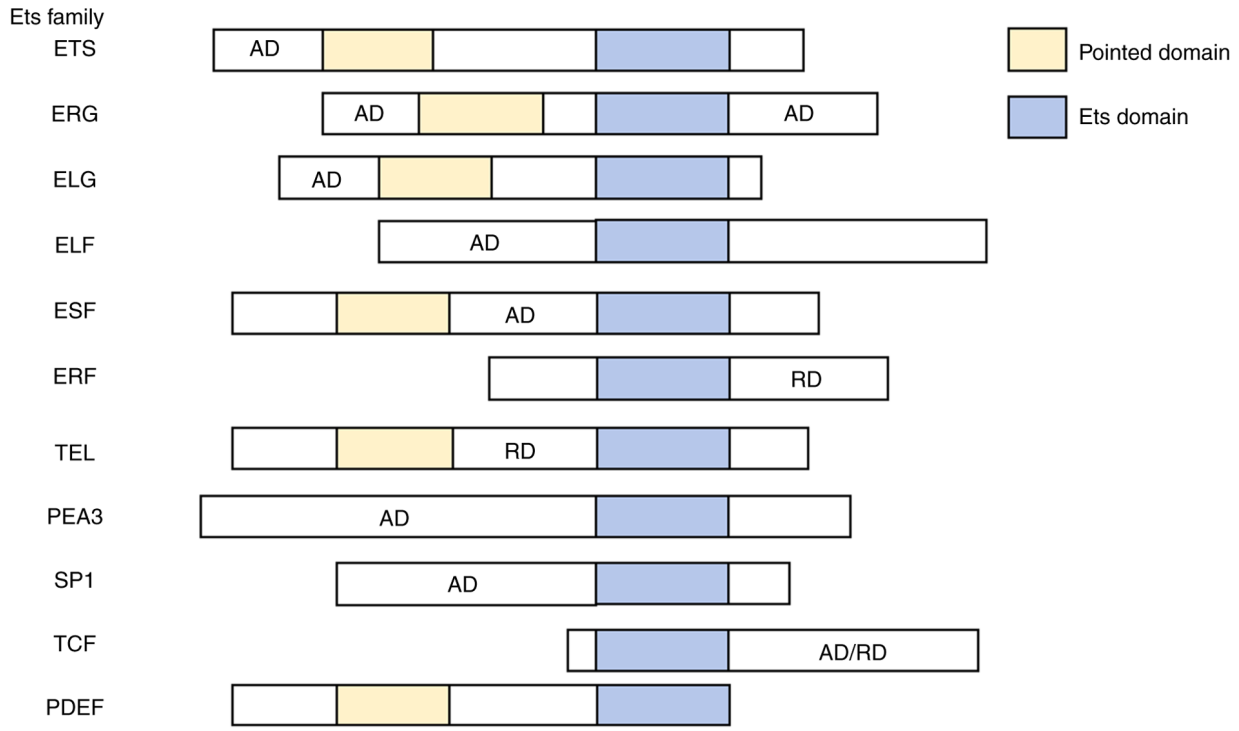

Figure 1. List of the members of the ETS family and their domains. AD, activation domain; RD, repression domain; ETS, E26 transformation-specific; ERG, ETS transcription factor; ELG, ETS-like gene; ELF, eukaryotic translation release factor 3; ESE, epithelial-specific ETS; ERF, ETS2 repressor factor; TEL, translocation ETS leukemia; PEA3, polyomavirus enhancer activator 3; SP1, specificity protein 1; TCF, T-cell factor/lymphoid enhancer factor; PDEF, prostate-derived ETS factor.

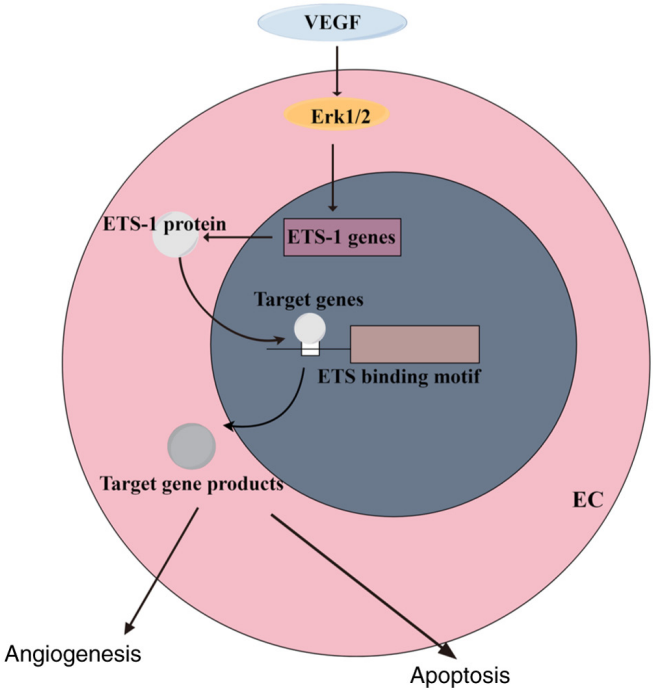

Figure 2. Mechanism of ETS-1 protein in angiogenesis and apoptosis: VEGF activates the ETS-1 gene through the ERK1/2 signaling pathway, leading to the production of ETS-1 protein. This protein binds to the ETS binding motifs in the promoters of target genes, thereby regulating the expression of these genes. Once activated, the target genes produce corresponding gene products that influence the function of ECs, resulting in changes in the balance between angiogenesis and apoptosis (The diagram was drawn using Figdraw 2.0; https://www.figdraw.com). ETS, E26 transformation-specific; VEGF, vascular endothelial growth factor; ERK, extracellular signal-regulated kinase; ECs, endothelial cells.

transcriptional activity of the transcriptional activity of ETS can be regulated by post-translational modifications (including phosphorylation, ubiquitination, acetylation and sumoylation), transcription factors and nuclear translocation (46). ETS-1 is expressed in a variety of cells, including lymphocytes, endothelial cells, vascular smooth muscle cells and epithelial cells, but it is predominantly expressed in lymphocytes and, as such, it plays a key role in immunity (47-49). In addition, it mediates extracellular matrix degradation, cell migration, angiogenesis and drug resistance (50).

ETS-2, like its closely related homolog ETS-1, is a member of the ETS family of DNA-binding transcription factors encoded in a 56 kDa nuclear protein containing 469 amino acids and is also a downstream regulator of RAS-mediated transformation.ETS-2 is located on human chromosome 21q22.3 and has been reported to be overexpressed in the brain and fibroblasts of subjects with Down syndrome (DS) (51-53). The common core binding sequence of ETS-2 is 5'-GGAA/T-3' and when combined with this core sequence, ETS-2 supports a variety of cellular functions, such as cell proliferation, adhesion, migration, survival and angiogenesis and plays an important role in a variety of human diseases (54). Currently, previous studies have demonstrated that the ETS-2 protein is associated with the development of a variety of tumors and is an oncogene (55-57).

4. Relationship between ETS-1/ETS-2 and CVD

Currently, CVD remains one of the leading causes of mortality and morbidity in the global population. Despite the many efforts made in the last few decades, the number of patients

with CVD is still high. Therefore, the need for the development of new therapeutic strategies is crucial for a better understanding of the biology of the cardiovascular system.

Traditionally, cancer and CVD have been viewed as separate pathological entities. The only established association between them was that cancer treatment could increase the risk of cardiotoxicity and subsequent cardiovascular complications. Nevertheless, mounting clinical evidence has demonstrated that cancer patients are at a higher risk of developing CVD (58). Moreover, cancer and CVD share a multitude of common risk factors and underlying pathogenic mechanisms (59), including diabetes mellitus, dyslipidemia, cachexia and impaired immune function. Notably, the widely used 10-year risk score for atherosclerotic cardiovascular disease is also predictive of cancer incidence (60). Similarly, cancer is a systemic disease that affects the cardiovascular system through multiple mechanisms, including the release of small molecules, modulation of immune cell activity and metastatic lesions (61), thereby exacerbating the progression of adverse outcomes and elevating the risk of mortality in patients with CVD. A previous study based on the Surveillance, Epidemiology and End Results (SEER) database, which included more than 3.23 million U.S. cancer patients, clearly demonstrated that CVD accounted for ~11.3% of all mortalities among cancer patients (62). The CVD-related mortality risk and all-cause mortality risk were both markedly increased in this population. Such survival disadvantages have been observed across multiple types of cancer, including esophageal cancer, hepatocellular carcinoma, gastrointestinal cancer, ovarian cancer, breast cancer, prostate cancer and lung cancer (63-66). Wang *et al* (67) conducted a population-based cohort study using data from the SEER program of the U.S. National Cancer Institute. The authors reported that the incidence rate ratios (IRR) of cardiovascular disease mortality among patients with lung cancer were higher than those in the general population [IRR 1.74; 95% confidence interval (CI) 1.71-1.77]. Lung cancer in patients aged 30-79 years was markedly associated with an increased risk of cardiovascular disease mortality (IRR 2.61; 95% CI 2.55-2.66) and this association was most pronounced in individuals aged 30-34 years (IRR 48.93; 95% CI 21.98-108.92). In 2025, Sabaté-Tormos *et al* (68) performed a retrospective cohort study enrolling 3,626 patients admitted to the emergency department for suspected acute coronary syndrome between 2012 and 2013. Using univariate and multivariate Cox regression models, the authors analyzed the associations of clinical variables and a history of cancer with all-cause mortality over a 4-year follow-up period. The results demonstrated that all-cause mortality was markedly higher in cancer patients with myocardial infarction (68.8%) than in cancer patients without myocardial infarction (32.4%) and in non-cancer patients either with or without myocardial infarction (11.3%). Multivariate analysis revealed that a diagnosis of cancer was an independent predictor of mortality, particularly in patients with concomitant myocardial infarction. Although the link between cancer and cardiovascular-related mortality has been well established, the core regulatory molecules underlying cardiovascular system injury, imbalanced inflammatory responses and abnormal tissue remodeling during the comorbidity of cancer and cardiovascular disease remain to be elucidated.

Recently, ETS-1/ETS-2 has been recognized as a major regulator of cardiovascular system development, playing an important role in normal coronary artery and myocardial development as well as in regulating vascular inflammation and remodeling (69,70). For example, Wang *et al* (71) demonstrated that endothelial and/or endocardial ETS-1 is essential for the regulation of ventricular cardiomyocyte proliferation and homeostasis, as well as coronary vascular growth during cardiac development. The data from this study showed that deletion of ETS-1 in endothelial cells resulted in ventricular noncompactification, recapitulating the phenotype caused by the overall deletion of ETS-1. Endothelial-specific deletion of ETS-1 reduces the levels of six important angiogenesis-related genes, Alk1, Cldn5, Sox18, Robo4, Esm1 and KDR, in endothelial cells, resulting in defective development of the coronary vasculature system, which is associated with reduced proliferation of cardiomyocytes in the dense zone. Notably, defects in the coronary vasculature system cause the development of congenital heart defects that can progress to early heart failure. Therefore, further understanding of the important mediating mechanisms of ETS-1/ETS-2 in related CVD is crucial and provides promising therapeutic targets for the treatment of CVD.

Est-1/ETS-2 and vascular inflammation/vascular remodeling. Transient inflammation and its resolution after vascular injury are necessary for wound healing and repair, whereas prolonged excessive inflammation leads to pathological vascular remodeling manifested as neointimal hyperplasia (72). Among other things, vascular inflammation induces endothelial dysfunction and confers a pro-adhesive and pro-thrombotic phenotype to endothelial cells, which has a significant effect on the development and progression of various CVDs, most notably AS, thrombosis and congestive HF (73). Vascular remodeling is a complex pathological process that is a fundamental pathological process characterized by abnormal changes in vascular cell morphology, structure and function in various diseases, such as migration, proliferation, hypertrophy and apoptosis and is mostly caused by vascular endothelial injury, medial smooth muscle proliferation, extracellular matrix remodeling, oxidative stress and vascular inflammation, which in turn leads to increased vascular tone and thus the development of vascular disease (74,75). Currently, studies have confirmed that the role of ETS factors in regulating endothelial-specific gene expression (76-78) and studies support a role for several ETS family members in the regulation of vascular inflammation and vascular remodeling, including endothelial activation in response to inflammatory mediators, recruitment of inflammatory cells to the vascular wall and proliferation and migration of vascular smooth muscle cells (VSMCs) (79-81) (Fig. 3).

Angiotensin II (Ang II) is a central mediator of vascular inflammation and remodeling and Zhan *et al* (82) found in vascular smooth muscle and endothelial cells from mouse thoracic aorta that the transcription factor ETS-1 was rapidly induced in response to systemic Ang II infusion and that compared with control mice, ETS-$1^{-/-}$ mice had markedly reduced arterial wall thickening, perivascular fibrosis and cardiac hypertrophy. Also, cell cycle-dependent kinase inhibitor p21CIP (associated with cell hypertrophy, cell cycle arrest, apoptosis and endothelial dysfunction), plasminogen

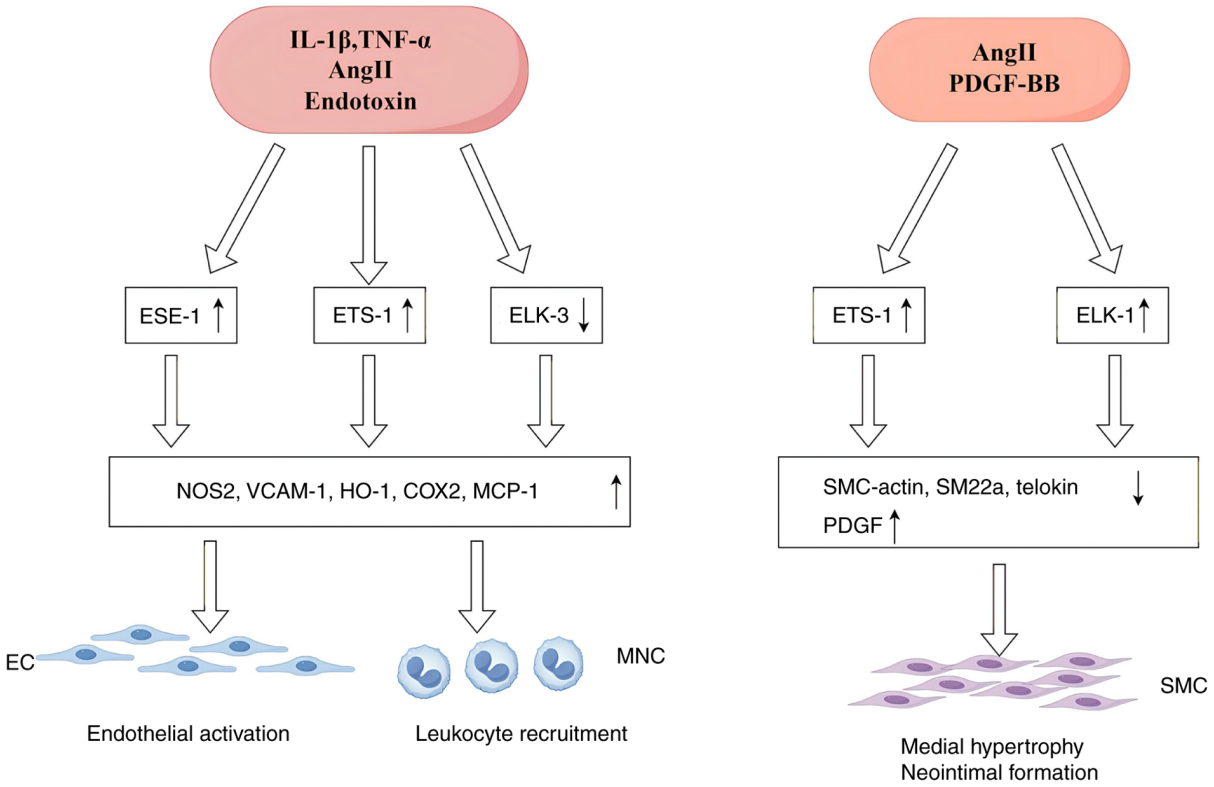

Figure 3. Role of ETS transcription factors in the regulation of vascular inflammation: members of the ETS family of transcription factors play a crucial role in the regulation of vascular inflammation. Transcription factors such as ESE-1, ETS-1 and Elk-3 regulate the expression of related genes, thereby influencing the activation of endothelial cells, the recruitment of leukocytes and the proliferation and migration of vascular smooth muscle cells (VSMCs). These processes are essential components of the vascular inflammatory response (The diagram was drawn using Figdraw 2.0; https://www.figdraw.com). ETS, E26 transformation-specific; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; Ang II, angiotensin II; PDGF-BB, platelet-derived growth factor-BB; EC, endothelial cell; SMC, smooth muscle cell; ESE-1, epithelial-specific ETS 1; ELK-1, ETS-like protein 1; NOS2, nitric oxide synthase 2; VCAM-1, vascular cell adhesion molecule 1; HO-1, heme oxygenase 1; COX2, cyclooxygenase 2; MCP-1, monocyte chemoattractant protein 1; SMC-actin, smooth muscle cell actin; SM22α, smooth muscle 22α; PDGF, platelet-derived growth factor.

activator inhibitor-1 (PAI-1; which promotes the development of perivascular fibrosis) and monocyte chemotactic protein-1 (MCP-1; a central mediator of inflammatory responses in hypertensive vascular disease) were identified in the study as ETS-1 targets, all of which were reduced in expression in ETS-1$^{-/-}$ mice in response to Ang II and resulted in a significant reduction in T cell and macrophage recruitment to the vessel wall compared with control mice. This suggests that ETS-1 plays a key role in Ang II-induced vascular inflammation and remodeling. Vascular inflammation plays an important role in the pathogenesis of hypertension, atherosclerosis, restenosis and other forms of vascular disease. In particular, carotid balloon injury is a model of vascular injury characterized by increased expression of inflammatory mediators and marked leukocyte infiltration, which leads to a process of vascular remodeling and neointimal formation after luminal injury (83,84). Feng *et al* (85) found that the expression of ETS-1 was markedly increased after balloon injury, which mediated the increased expression of pro-inflammatory molecules and adhesion molecules in carotid balloon injury, including MCP-1, P-selectin and E-selectin and that the blockade of ETS-1 before balloon injury not only reduced leukocyte infiltration but also prevented the development of neointima after balloon injury. Taken together, ETS-1 plays a key role as a transcriptional mediator of inflammation and neointima formation induced by intraluminal vascular injury and has the potential to be a new strategy for the treatment and prevention of diseases associated with vascular injury.

Est-1/ETS-2 and angiogenesis. Angiogenesis is a complex event that requires endothelial cell germination, lumen formation and tubulogenesis and is regulated by the coordinated action of different transcription factors. Angiogenesis is involved in a variety of biological processes, including atherosclerosis and cancer. Many transcription factors have been implicated in vascular development and angiogenesis and their interactions lead to endothelial cell differentiation and the acquisition of arterial, venous and lymphatic properties (86). For example, Di *et al* (87) found that miR33a-5p/ETS-1/Dickkopf1 (DKK1) signaling was pro-angiogenic in ox-LDL-induced HUVECs.

Endothelial cells (ECs) are located in the innermost layer of blood vessels and form the vascular lining, which is important for maintaining vascular homeostasis and normal circulation (88). In response to endothelial dysfunction caused by stimulation by pathological (hyperbaric or hypoxic) and chemical (oxidized low-density lipoprotein or infection) factors, ECs are activated, increasing their permeability, releasing cytokines to promote inflammation and thrombosis and increasing adhesion molecule recruitment and adhesion to inflammatory factors (89). Endothelial dysfunction and endothelial activation are thought to play a key role in the initiation of the atherosclerotic process and the progression of advanced

AS (90). AS is a chronic vascular inflammatory disease and is one of the leading causes of cardiovascular morbidity and mortality (91). The development of AS is associated with structural vascular lesions and the pathologic process involves endothelial damage, lipid deposition, inflammatory cell infiltration, foam cell formation and plaque formation, leading to the formation of atherosclerotic plaques (92). These plaques narrow the lumen of the coronary arteries, leading to episodic or persistent angina. If the plaque ruptures, it can lead to thrombus formation, myocardial infarction and even death (93). AS involves complex interactions between various cell types, including macrophages, ECs and smooth muscle cells (SMC) (94). AS is a complex disease involving multiple factors. Currently, it has been demonstrated that ETS-1/ETS-2 plays a role in the regulation of vascular inflammation in AS, including endothelial activation in response to inflammatory mediators, recruitment of inflammatory cells to the vascular wall and proliferation and migration of VSMCs (79). ETS-1 is upregulated *in vitro* upon exposure to agonists such as serum and is expressed in damaged vessels and it is also expressed in SMCs in human carotid atherosclerotic lesions (95). Similarly, it has been shown that in $ApoE^{-/-}$ mice experiments using a vulnerable plaque model, ETS-2 expression is increased under atherogenic conditions and is specifically enhanced in vulnerable plaques compared to stable plaques. ETS-2 levels are associated with microvessel formation within the plaque and proinflammatory in human vulnerable atherosclerotic plaques ETS-2 levels correlate with intraplaque microvessel formation and proinflammatory cytokine levels in human susceptible atherosclerotic plaques and overexpression of ETS-2 promotes lesion growth with neovascularization, hemorrhage and plaque destabilization (96).

Currently, it has been shown that ETS-2 is critical for a variety of inflammatory functions in human macrophages and that macrophage activation, cytokine production, reactive oxygen species (ROS) production, phagocytosis and migration are induced by overexpression of ETS-2 in a dose-dependent manner and that overexpression of ETS-2 increases the secretion of pro-inflammatory cytokines. RNA sequencing of ETS-2 edited and unedited inflammatory macrophages from multiple donors reveals that disruption of ETS-2 results in extensive transcriptional changes and reduced expression of many inflammatory genes. This suggests that macrophage ETS-2 signaling may play a central role in a variety of inflammatory diseases (97). Moreover, Jiang *et al* (80) found that ETS-1 promotes hyperglycemia-mediated endothelial inflammation by upregulating protein tyrosine phosphatase 1B (PTP1B) expression, which is involved in high glucose-induced elevation of endothelial cell inflammatory factor levels). In addition, it was found that hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF) and ETS-1 coexist in the deeper layers of plaques in carotid atherosclerosis, with significant angiogenesis. Notably, the major lesions of plaques exhibit markedly elevated levels of HIF-1α, VEGF and ETS-1. This suggests that HIF-1α induces angiogenesis through the expression of VEGF and ETS-1 (98). In addition, Katsume *et al* (99) also found that the early inflammatory response in atherosclerosis is mediated by proline-rich tyrosine kinase/reactive oxygen species, which induces the release of tumor necrosis factor α (TNF-α) and promotes the expression of TNF-α-dependent pro-inflammatory molecules through the $p21^{Cip1}$/ETS-1/p300 transcriptional regulatory system. Endothelial dysfunction represents the initial step of AS. Endothelial dysfunction is the initial step of AS (100). 17β-estradiol (E2) can delay atherosclerosis formation by improving lipid levels, accelerating endothelial repair by promoting endothelial proliferation and migration, inhibiting the proliferation and migration of vascular smooth muscle cells and modulating the function of immune cells to alleviate the vascular inflammatory response (101-103). Li *et al* (104) demonstrated the effect of E2 on miR-126-3p expression (which is critical in the proliferation, migration and tube formation) in a cellular model by utilizing human venous umbilical cord endothelial cells. Using human venous umbilical cord endothelial cells, Li *et al* (104) demonstrated the effect of E2 on microRNA (miRNA/miR) 126-3p expression (which plays a critical role in endothelial cell proliferation, migration and tube formation), which prevents endothelial cell apoptosis and slows down atherogenesis in a cellular model and identified the key role of ETS-1, a transcription factor for miR-126-3p. It was found that E2 increased the expression level of miR-126 through ETS-1 in HUVEC and then miR-126-3p bound to its targets Spred1 and vascular cell adhesion molecule-1 (VCAM-1) mRNA, leading to their degradation and silencing of protein expression and finally promoted endothelial proliferation, atherogenesis and atherosclerosis. In addition, Nie *et al* (105) showed that the ETS-2 transcription factor is a potent regulator of angiogenesis and mediates immune activation of the endothelium in the late stages of AS. miR-203 promotes the proliferation of vascular smooth muscle cells and was found to be involved in the process of atherosclerotic plaque formation through the regulation of ETS-2. Immediately after, Nie *et al* (105) found that shangou, a common traditional aromatic herb, reduced atherosclerotic plaque area and serum antioxidant low-density lipoprotein (LDL) autoantibodies in endogenous high angiotensin II $ApoE^{-/-}$ mice by increasing miR-203 expression and decreasing ETS-2 expression, which was beneficial in preventing or treating the onset and progression of AS. In addition, it has been demonstrated that tyrosine kinase receptor B (TrkB) plays an important role in protecting the integrity of the endothelial barrier during the process of atherogenesis and Jiang *et al* (106) found that TrkB can promote VE-calmodulin expression in endothelial cells by inducing and activating the expression of ETS-1, which binds to two ETS binding sites in the promoter of the VE-calmodulin gene in endothelial cells. ETS-1 promotes VE- cadherin expression by binding to two ETS binding sites in the VE- cadherin promoter in endothelial cells to protect endothelial integrity during atherogenesis.

Inflammation is observed in all stages of atherosclerosis, the initial phase of which is characterized by leukocyte recruitment to activated ECs. Zhu *et al* (107) used bioinformatics analysis to show that ETS-1 is a key endothelial transcription factor in inflammation and tube formation and is a candidate target for the miR-155 and miR-221/222 clusters and that miR-155 and miR-221 are highly expressed in human umbilical vein endothelial cells (HUVECs) and VSMCs, confirming that angiotensin II type 1 receptor (AT1R) is a target of miR-155 in HUVECs. It was found that HUVEC with high miR-155 expression may co-target AT1R and ETS-1, while miR-221/222 targets ETS-1, which indirectly regulates

the expression of several inflammatory molecules in ECs, thereby attenuating the adhesion of Jurkat T-cells to activated HUVECs and decreasing the migration of HUVECs and thus reducing the inflammation of endothelial cells and ameliorating atherosclerosis.

ETS-1/ETS-2 and MIRI. Ischemic heart disease has become the leading cause of morbidity and mortality worldwide (108). Myocardial cell death plays a central role in the pathogenesis of ischemic heart disease; therefore, timely restoration of coronary blood flow, that is, reperfusion, is the best method to reduce myocardial cell loss induced by ischemic injury (109). However, myocardial reperfusion can lead to further damage to the heart, termed MIRI (110). MIRI leads to myocardial dysfunction, cardiomyocyte loss and fibrosis. The process of myocardial ischemia/reperfusion can lead to several types of cardiomyocyte death, including necrosis, apoptosis, autophagy and iron death (111). These new forms of regulated cell death lead to cardiomyocyte loss and exacerbate MIRI by influencing ROS production, calcium stress and inflammatory cascade responses, which subsequently mediate adverse remodeling, cardiac insufficiency and HF. Therefore, prevention of cardiac apoptosis and fibrosis has been the goal of some therapies that interfere with MIRI.

Lee *et al* (112) found that adipose-derived stem cell conditioned medium (ADSC-CM) had a significant effect on apoptosis and fibrosis in MIRI-treated hearts and hypoxia/reoxygenation (H/R)-treated cardiomyocytes. ADSC-CM attenuates cardiac apoptosis and fibrosis by downregulating the expression of p53 upregulated modulator of apoptosis (PUMA) and ETS-1 via the miR-221/222/p38/NF-κB pathway, thereby alleviating MIRI. The approximate mechanisms are as follows: i) ADSC-CM treatment markedly reduced the expression of apoptosis-related proteins, such as PUMA, phosphorylated (p-)p53 and B-cell lymphoma 2 (Bcl2), as well as the fibrosis-related proteins, ETS-1, fibronectin and collagen 3, and markedly attenuated the cardiac injury and fibrosis in both MIRI-treated mice and H/R-treated cardiomyocytes. ii) ADSC-CM is abundant in miR-221/222, which can target and regulate the protein levels of PUMA or ETS-1. Knockout of PUMA and ETS-1 reduced the induction of apoptosis and fibrosis, respectively, and overexpression of miR-221/222 achieved similar results. Furthermore, MIRI significantly increased apoptosis and fibrosis in miR-221/222 knockout (KO) mice, whereas ADSC-CM attenuated these effects. iii) Increased phosphorylation of p38 and NF-kB not only mediates myocardial apoptosis through the PUMA/p53/Bcl2 pathway, but also regulates fibrosis through the ETS-1/fibronectin/collagen 3 pathway. In addition, Lai *et al* (113) also found that both PUMA and ETS-1 are target genes of miR-221/222. The addition of H_2O_2 to cultured cardiomyocytes increases the levels of PUMA and ETS-1 and treatment with adipose-derived stem cell exosomes markedly inhibits the levels of PUMA and ETS-1 and reduces apoptosis and hypertrophy through the miR-221/miR-222/PUMA/ETS-1 pathway, thereby preventing cardiac I/R injury.

Apoptosis, ROS and inflammation-induced myocardial injury are the most critical factors in MIRI (114). It has been demonstrated that the lysine (K)-specific demethylase 3A (KDM3A), plays a key role in MIRI. Guo *et al* (115) found that KDM3A knockdown exacerbated myocardial dysfunction and cardiomyocyte injury *in vivo* and *in vitro*, while worsening mitochondrial apoptosis, ROS and inflammation were observed. By contrast, KDM3A overexpression was ameliorated in MIRI. At the same time, it was found that KDM3A, which is known to target ETS-1, directly regulates ETS-1 expression by binding to its promoter region. KDM3A overexpression leads to higher ETS-1 transcription, resulting in reduced apoptosis, ROS and inflammation, which plays a protective role during myocardial injury. Thus, the data from this study suggest that the protective effect of KDM3A on MIRI is partially attributable to epigenetic transactivation of ETS-1.

Thus, it is clear that targeting ETS-1 plays a critical role in preventing MIRI-induced apoptosis and hypertrophy. However, there is no experimental data to analyze whether ETS-2 can prevent MIRI through certain mechanisms.

ETS-1/ETS-2 and cardiac remodeling. Cardiac remodeling, defined as genomic, molecular, cellular and interstitial alterations clinically manifested as changes in cardiac size, shape and function in response to cardiovascular injury and pathogenic risk factors, is at the core of most CVD and persistent cardiac remodeling almost always ends in HF and mortality (116). Cardiac remodeling is categorized as physiological (in response to growth, exercise and pregnancy) and pathological (in response to inflammation, ischemia, MIRI, biomechanical stress, excessive neurohormonal activation and pressure overload). Among these, pathological cardiac remodeling is the process of structural and functional changes in the left ventricle as a result of internal or external cardiovascular injury or pathogenic risk factors (117,118). Pathological changes in pathological cardiac remodeling include cardiomyocyte apoptosis, cardiac hypertrophy and cardiac fibrosis and persistent adverse remodeling can lead to HF (119,120). Therefore, it is crucial to understand the mechanisms leading to cardiac remodeling and to prevent adverse remodeling. Research has demonstrated the critical role of ETS-1/ETS-2 in the development of cardiac remodeling.

The process of diabetic cardiomyopathy involves a series of sequential and interrelated steps, including myocardial apoptosis, hypertrophy and fibrosis. Cardiomyocyte apoptosis is key to this process and to myocardial remodeling. Wang *et al* (121) found that elevated levels of high mobility group box 1 (HMGB1) may promote cardiomyocyte apoptosis induced by high glucose (HG) or hyperglycemia. HG can activate ETS-1; however, inhibition of HMGB1 can attenuate HG-induced ETS-1 activation through ERK1/2. However, inhibition of HMGB1 attenuates HG-induced ETS-1 activation through ERK1/2 signaling. In addition, inhibition of ETS-1 markedly reduces HG-induced cardiomyocyte apoptosis. In conclusion, inhibition of HMGB1 may prevent HG-induced cardiomyocyte apoptosis by downregulating ERK-dependent activation of ETS-1.

The two major cellular signaling pathways that drive cardiac hypertrophy are the calcineurin/nuclear factor of activated T-cells (NFAT) pathway and the MAPK/ERK pathway and sustained activation of either of these pathways causes myocardial hypertrophy (122,123). Luo *et al* (124) found that ETS-2 is activated during hypertrophic myocardial growth,

and ETS-2 deficiency attenuates cardiac hypertrophy induced by pressure overload. In addition to this, ETS-2 was observed to be activated by Erk1/2 in hypertrophic mouse hearts and in human dilated cardiomyopathy tissues in this study. ETS-2 is also required for pressure overload and calmodulin-induced cardiac hypertrophy and, as a transcription factor, ETS-2 is able to bind to the promoters of hypertrophic hallmark genes, such as atrial natriuretic peptide, brain natriuretic peptide and Rcan1.4, which is an established downstream target of NFAT. ETS-2 forms a complex with NFAT, stimulating transcriptional activity by enhancing NFAT binding to the promoters of at least two hypertrophy-stimulating genes: Rcan1.4 and miR-223 (which are downstream targets of ETS-2 and NFAT in cardiomyocytes). Inhibiting miR-223 in cardiomyocytes suppresses calcineurin-mediated cardiac hypertrophy, revealing that microRNA-223 is a novel pro-hypertrophic target of the calcineurin/NFAT and Erk1/2-ETS-2 pathways. In conclusion, ETS-2 plays a critical role in cardiac hypertrophy driven by the calmodulin/NFAT pathway and reveals a molecular link between the Erk1/2 activation of ETS-2 and the expression of NFAT/ETS-2 target genes. Furthermore, Zhan *et al* (82) demonstrated that ETS-1 is a key mediator of vascular remodeling and inflammation in response to Ang II. The authors showed that vascular proliferation, perivascular fibrosis and cardiac hypertrophy, were markedly reduced in ETS-1$^{-/-}$ mice in response to systemic administration of Ang II compared to control mice.

ETS-1, as a prototypical member of the ETS family of transcription factors, has now been demonstrated in several studies to play an important role in myocardial fibrosis. Hao *et al* (125) identified a role for ETS-1 in the pro-fibrotic effects of Ang II in cardiac fibroblasts (CFs) and in the heart *in vivo*. In the left ventricle of Ang II-infused rats, ETS-1, plasminogen activator inhibitor-1 (PAI-1) and connective tissue growth factor (CTGF) protein levels were concomitantly upregulated, while activation of ERK and c-Jun NH2-terminal kinase was increased. Knockdown of ETS-1 by short interfering RNA markedly inhibits the induction of cell proliferation and CTGF and PAI-1 expression by Ang II. Thus, ETS-1 may mediate Ang II-induced cardiac fibrotic effects. These findings point for the first time to the potential role of ETS-1 in cardiac fibrosis *in vitro* and *in vivo*, contributing to a fundamental understanding of the molecular mechanisms underlying myocardial fibrosis as a pathological process and laying the foundation for further studies. Subsequently, it was suggested that endothelial-mesenchymal transition (EMT) promotes Ang II-mediated cardiac fibrosis and that ETS-1 has a potential role in Ang II-mediated myocardial fibrosis. Xu *et al* (126) found that endothelial ETS-1-deficient mice exhibited markedly reduced cardiac fibrosis and hypertrophy after Ang II infusion, accompanied by decreased expression of fibrotic stromal genes, EMT (which is a possible source of myofibroblasts and has been shown to cause myocardial fibrosis) as well as its downstream transcription factors (including Snail family transcriptional repressor 1, Snail family transcriptional repressor 2, Twist-related protein 1 and Zinc finger E-box binding homeobox 1), as well as reduced expression of cardiac hypertrophy and hypertrophy-related genes. Moreover, *in vitro* studies using cultured H5V cells further demonstrated that ETS-1 knockdown inhibited TGF-β1-induced EMT. Thus, it is evident that deletion of endothelial ETS-1 attenuates Ang II-induced myocardial fibrosis through inhibition of EMT and that inhibition of ETS-1 may be a potential therapeutic strategy for delaying myocardial fibrosis.

Aldosterone plays an important role in the pathophysiology of cardiac remodeling and recently, spironolactone (an aldosterone receptor antagonist) has been found to improve cardiac structure, function and prognosis and delay the progression of myocardial fibrosis in patients with HF. Wang *et al* (127) found that spironolactone reduced the levels of inflammatory cytokines in the myocardial tissues of autoimmune myocarditis (EAM) and had a positive effect on experimental myocardial fibrosis in EAM mice. This study found that ETS-1 was activated through the TGF-β1/Smad-2/3 signaling pathway and is involved in EAM-induced cardiac fibrosis in EAM mice and the use of spironolactone markedly inhibited the activation of ETS-1 and the phosphorylation of TGF-β1/Smad2/3 and suppressed ETS-1-mediated myocarditis-induced myocardial fibrosis. In addition, inhibition of ETS-1 also reduced the expression and activity of matrix metalloproteinase (MMP)-2 and MMP-9 in EAM mice, which reduced myocardial fibrosis. The results of this study suggest that the improvement of myocardial fibrosis by spironolactone may be related to the TGF-β1/Smad-2/3/ETS-1 signaling pathway in EAM mice.

In addition, abnormal levels of chitinase-3-like protein 1 (CH3L1) and long non-coding RNA (lnc)TUG1 are associated with myocardial fibrosis. Sun *et al* (128) found that CH3L1 upregulated the expression of lncTUG1 and lncTUG1 weakened the inhibitory effect on ETS-1 through sponge adsorption of miR -495-3p, which promoted the process of myocardial fibrosis. Similarly, Li *et al* (129) isolated exosomes from MSC and administered them *in vitro* to CFs and male infarcted Sprague-Dawley rat hearts *in vivo* with vericiguat-treated mesenchymal stem cell-derived exosomes (MSCVER-Exos) and found that MSCVER-Exo was able to inhibit the proliferation of CFs. MSCVER-Exo was found to inhibit CFs proliferation, migration and pro-fibrotic gene expression. Meanwhile, miR-1180-3p was found to be enriched in MSCVER-Exo and ETS-1 was a downstream target of miR-1180-3p. miR-1180-3p could be delivered to CFs through Exo and attenuate TGF-β1-induced fibrosis by inhibiting ETS-1 signaling. Thus, miR-1180-3p targeting ETS-1 plays an important role in anti-fibrosis.

ETS-1/ETS-2 and Jacobsen syndrome (JS). JS is a rare syndrome caused by partial chromosomal deletions in the 11q23 region between sub-band 11q23.3 and telomeres, ranging from approximately 7 Mb to 20 Mb (130). The condition was first described in 1973 by Dr Jacobsen, in which multiple members of a family inherited an unbalanced 11;21 translocation from parents who carried a balanced translocation chromosome (131). Since Jacobsen's first report, more than 200 cases have been noted (132). In cases of JS diagnosed after birth in the neonatal period, the majority of children with JS have prolonged hospitalizations, most commonly due to feeding difficulties, heart problems, or bleeding problems. Of these children, ~20% succumb within the first two years of life, most commonly related to complications of congenital heart disease, most of which require surgical intervention. Of patients with heart defects, ~1/3 have membranous ventricular

septal defects, another third have left ventricular outflow tract defects with varying degrees of hypoplasia or obstruction of the mitral valve, left ventricle, aortic valve, or aorta and the final third present with a variety of heart defects, including right ventricular double outlet, transposition of the great arteries, atrioventricular septal defect, ostium secundum atrial septal defect, dextrocardia, anomalous right subclavian artery, patent ductus arteriosus, persistent left superior vena cava, tricuspid atresia, interrupted aortic arch type B, persistent truncus arteriosus and pulmonary valve stenosis (133,134). It has been shown that ETS-1 transcription factors play an important role in mammalian heart development, thus providing important insights into some of the most common congenital heart diseases. For example, Ye *et al* (135) identified an ~7 megabase (Mb) cardiac critical region distal to the long arm of chromosome 11 that contained a gene for congenital heart disease, ETS-1, which is a candidate for causing congenital heart disease in at least some of the patients with 11q- JS. In addition, phenotypic analysis of gene-targeted ETS-1 KO mice by Ye *et al* (135) showed that deletion of ETS-1 in a pure C57/B6 background resulted in a high prevalence of ectopic, large membranous ventricular septal defects and frequently abnormal ventricular morphology characterized by a bifid apex. Thus, in summary, these results suggest a role for ETS-1 in ventricular development and a gene in the critical region of Jacobsen syndrome, the deletion of which leads to ventricular septal defects and abnormal ventricular morphology in mice.

Ventricular septal defects, including double outlet right ventricle, are one of the most common congenital heart diseases (CHDs) in JS. One possible mechanism for CHDs and other problems in Jacobsen syndrome is a defective function of neural crest cells (cNCCs), which are required for normal mouse cardiac development to accurately regulate the differentiation of cNCCs. Ye *et al* (136) again found that ETS-1 is strongly expressed in mouse cNCCs and that the expression of Sox10, a key regulator of the gene regulatory network of neural crest cells and an early marker of NCCs, helps to analyze the function of cNCCs during embryonic development. However, this study found that deletion of ETS-1 leads to a decrease in migrating cells expressing Sox10 in E10.5 C57/B6 mouse embryos, which results in impaired cardiac NCC function and causes congenital heart defects.

ETS-1/ETS-2 and HF. HF has become a rapidly growing global health problem affecting more than 37.7 million people worldwide. The prevalence of HF has been increasing in this decade as the population over the age of 65 increases (137). Although many different approaches have been investigated to help manage HF, including medical devices, medications and telemonitoring, the clinical management of HF remains relatively poor (138). Therefore, there is an urgent need for clinicians to investigate new therapies for the treatment of HF.

Dysregulation of gene expression is a common mechanism in HF and transcription factors (TFs) are thought to play an important role in the regulation of gene expression. Li *et al* (139) analyzed the expression levels of miR-155, G protein-coupled receptor 18 (GRP18) and ETS-2 in clinical HF samples through the use of bioinformatics and experimental analysis and functional validation was performed in H9c2 cells. A total of three miRNAs and eight TFs were identified in the TF/miRNA target network. clinical validation showed that the expression level of miR-155 was markedly reduced in HF samples, whereas the expression levels of ETS-2 and GPR18 were markedly increased in HF samples and GPR18 was found to be targeted by both ETS-2 and miR-155. Thus, the data suggest that miR-155 and ETS-2 may play a key role in the development of HF by targeting GPR18 and this finding may help to provide new information for understanding and treating HF. In addition to this, Tan *et al* (140) found that ETS-2 could promote cardiomyocyte apoptosis and autophagy in HF by regulating the lncRNA TUG1/miR-129-5p/ATG7 axis. In this experiment, it was found that H_2O_2 stimulation increased the expression of ETS-2, TUG1 and ATG7 and decreased the expression of miR-129-5p in AC16 cells, which stimulated cardiomyocyte apoptosis and autophagy, whereas the absence of ETS-2, the silencing of TUG1, or the upregulation of miR-129-5p reversed this phenomenon.

DNA methyltransferase 1 (DNMT1) expression is rapidly upregulated in cardiac tissues of mice with pressure overload and adriamycin-induced HF, which promotes the development of HF (141). In addition to this, dysregulation of mitochondrial autophagy has been associated with the progression of HF and aging (142). Deng *et al* (143) pointed out that upregulation of miR-152-3p plays a protective role in cardiomyocytes and the STRING database predicted that there is an interaction between ETS-1 and Ras homologous gene family member H (RhoH) and that ETS-1/RhoH may inhibit mitochondrial autophagy and exacerbate HF. Therefore, targeting the ETS-1/RhoH axis may be a potential therapeutic approach. Meanwhile, Deng *et al* (143) found that DNMT1 may inhibit miR-152-3p expression by promoting the methylation of miR-152-3p and enhancing the expression of ETS-1, which induces RHOH transcriptional activation and inhibits mitochondrial autophagy and ultimately promotes the development of HF.

5. Treatment

ETS-1 and ETS-2, key members of the ETS transcription factor family, play a central role in regulating cell proliferation, angiogenesis, inflammatory responses and fibrosis, which renders them potential therapeutic targets for various diseases, including cardiovascular diseases, cancer and autoimmune disorders (144). However, the translational potential of ETS-1/ETS-2 has been disproportionately explored in the field of oncology, whereas research targeting non-neoplastic diseases (e.g., cardiovascular lesions) has been mainly confined to preclinical basic studies with limited translational progress. To date, a large number of mechanistic studies, preclinical models and even early exploratory trials have elucidated the therapeutic value of modulating ETS-1/ETS-2 activity for cancer intervention, covering diverse strategies such as small-molecule inhibitors. By contrast, the therapeutic targeted application of ETS-1/ETS-2 in cardiovascular and other non-malignant diseases is still in its infancy. Given the significant discrepancy in research maturity, this section will focus specifically on the current status of ETS-1/ETS-2-targeted therapeutic strategies in tumorigenesis, summarizing key advances, challenges and directions for future clinical translation.

Table I. Link between cardiovascular diseases and ETS-1/ETS-2.

Authors, year	Cardiovascular disease	Models	Target	Effects	(Refs.)
Jiang *et al*, 2022	AS	Diabetic rat model	ETS-1	ETS-1 promotes hyperglycemia-mediated endothelial inflammation and facilitates the development of AS by upregulating PTP1B expression.	(80)
Zhan *et al*, 2005	Vascular inflammation and remodeling	Use of the male ETS-1$^{-/-}$mouse model	ETS-1	Arterial wall thickening and perivascular fibrosis were markedly reduced in ETS-1$^{-/-}$ mice. Meanwhile, reduced expression of p21CIP, PAI-1 and MCP-1 were all found in ETS-1$^{-/-}$ mice, leading to a significant reduction in the recruitment of T cells and macrophages to the vessel wall.	(82)
Feng *et al*, 2010	Vascular inflammation and remodeling	A mouse model of balloon injury to the right common carotid artery	ETS-1	Blockade of ETS-1 before carotid balloon injury not only reduced leukocyte infiltration but also prevented the development of neointima after balloon injury.	(85)
Cheng *et al*, 2011	AS	ApoE$^{-/-}$ mouse model	ETS-2	ETS-2 levels correlate with intraplaque microvessel formation and proinflammatory cytokine levels in human vulnerable atherosclerotic plaques and overexpression of ETS-2 promotes lesion growth with neovascularization, hemorrhage and plaque instability.	(96)
Li *et al*, 2017	AS	ApoE$^{-/-}$ mouse model	ETS-1	E2 increased the expression level of miR-126 through ETS-1 in HUVEC and subsequently miR-126-3p bound to its targets Spred1 and VCAM-1 mRNA, leading to their degradation and silencing of protein expression and finally promoting endothelial proliferation, migration and tube formation and inhibiting monocyte adhesion as a means of improving endothelial function and delaying the onset of AS.	(104)
Nie *et al*, 2016	AS	ApoE$^{-/-}$ mouse model	ETS-2	Xiaoxianggou reduced atherosclerotic plaque area and serum antioxidant LDL autoantibodies in endogenous high AngII ApoE$^{-/-}$ mice by increasing miR-203 expression and decreasing ETS-2 expression, which were beneficial in preventing or treating the occurrence and progression of AS.	(105)
Jiang *et al*, 2015	AS	/	ETS-1	TrkB can protect endothelial integrity during atherogenesis by inducing and activating ETS-1 expression.	(106)
Zhu *et al*, 2011	AS	*In vivo* MIRI mouse model	ETS-1	HUVEC highly expressing miR-155 co-targeted AT1R and ETS-1, miR-221/222 targeted ETS-1 and indirectly regulated the expression of several inflammatory molecules in ECs, thereby attenuating the adhesion of Jurkat T cells to activated HUVEC and decreasing HUVEC migration as a means to reduce endothelial cell inflammation and ameliorate atherosclerosis.	(107)

Table I. Continued.

Authors, year	Cardiovascular disease	Models	Target	Effects	(Refs.)
Lee *et al*, 2021	MIRI	*In vivo* MIRI mouse model	ETS-1	ADSC-CM reduces cardiac apoptosis and fibrosis by decreasing the expression of PUMA and ETS-1 mediated by miR-221/222/p38/NF-kB pathway, thereby attenuating myocardial ischemia-reperfusion injury.	(112)
Lai *et al*, 2020	MIRI	The MIRI rat model	ETS-1	Treatment with ADSC-Exo prevented MIRI by markedly inhibiting the levels of PUMA and ETS-1 through the miR-221/miR-222/PUMA/ETS-1 pathway, reducing apoptosis and hypertrophy.	(113)
Guo *et al*, 2022	MIRI	The MIRI rat model		KDM3A overexpression leads to higher ETS-1 transcription, resulting in reduced apoptosis, ROS, and inflammation, which plays a protective role during myocardial injury.	(115)
Wang *et al*, 2014	Cardiomyocyte apoptosis	Diabetic mouse model	ETS-1	Inhibition of HMGB1 may prevent hyperglycemia-induced cardiomyocyte apoptosis by downregulating ERK-dependent activation of ETS-1.	(121)
Zhan *et al*, 2005	Myocardial hypertrophy	ETS-$1^{-/-}$ mouse model	ETS-1	Vascular proliferation, perivascular fibrosis and cardiac hypertrophy in ETS-$1^{-/-}$ mice were markedly reduced in response to systemic administration of Ang II.	(82)
Luo *et al*, 2021	Myocardial hypertrophy	Severe transverse aortic constriction mouse model	ETS-2	ETS-2 deficiency attenuated cardiac hypertrophy in response to pressure overload, while ETS-2 was found to play a key role in cardiac hypertrophy driven by the calmodulin phosphatase/NFAT pathway.	(124)
Hao *et al*, 2015	Myocardial fibrosis	Myocardial fibrosis rat model	ETS-1	Knockdown of ETS-1 by siRNA markedly inhibited the induction of cell proliferation and CTGF and PAI-1 expression by Ang II.	(125)
Xu *et al*, 2019	Myocardial fibrosis and myocardial hypertrophy	Endothelium-specific ETS-1 knockout mice bind Ang II-induced cardiac fibrosis model	ETS-1	Deletion of endothelial ETS-1attenuates Ang II-induced myocardial fibrosis by inhibiting EMT and inhibition of ETS-1 may be a potential therapeutic strategy to delay myocardial fibrosis.	(126)
Wang *et al*, 2022	Myocardial fibrosis	Autoimmune myocarditis mouse model	ETS-1	The use of spironolactone markedly inhibited ETS-1 activation and TGF-β1/smad2/3 phosphorylation and suppressed ETS-1-mediated myocarditis-induced myocardial fibrosis. In addition, inhibition of ETS-1 also reduced myocardial fibrosis by decreasing the expression and activity of MMP-2 and MMP-9 in EAM mice.	(127)
Sun *et al*, 2023	Myocardial fibrosis	Myocardial fibrosis mouse model	ETS-1	Lnc TUG1 weakens the inhibitory effect on ETS-1 through sponge adsorption of miR-495-3p, thereby promoting the process of myocardial fibrosis.	(128)
Li *et al*, 2025	Myocardial fibrosis	Myocardial infarction rat model	ETS-1	miR-1180-3p can be delivered to CFs via Exo to attenuate TGF-β1-induced fibrosis by inhibiting ETS-1 signaling.	(129)

Table I. Continued.

Authors, year	Cardiovascular disease	Models	Target	Effects	(Refs.)
Mattina *et al*, 2009	Jacobsen syndrome	ETS-1-deficient mouse model	ETS-1	ETS-1 is a gene in the critical region of Jacobsen syndrome and its deletion results in ventricular septal defects and abnormal ventricular morphology in mice.	(133)
Ye *et al*, 2010	Jacobsen syndrome	ETS-1-deficient mouse model	ETS-1	Deletion of ETS-1 leads to a decrease in migrating cells expressing Sox10 in E10.5 C57/B6 mouse embryos, which results in impaired cardiac neural crest cell function and causes congenital heart defects.	(135)
Tan *et al*, 2023	HF	HF model	ETS-2	ETS-2 can promote cardiomyocyte apoptosis and autophagy in heart failure by regulating the lncRNA TUG1/miR-129-5p/ATG7 axis.	(140)
Deng *et al*, 2022	HF	DOX-induced heart failure in a rat model	ETS-1	DNMT1 may inhibit miR-152-3p expression by promoting methylation of miR-152-3p and enhancing ETS-1 expression, which induces RHOH transcriptional activation and inhibits mitochondrial autophagy, ultimately contributing to the development of heart failure.	(143)

AS, atherosclerosis; ETS-2, E26 transformation-specific 2; PTP1B, protein tyrosine phosphatase 1B; PAI-1, plasminogen activator inhibitor 1; MCP-1, monocyte chemoattractant protein 1; p21CIP, cyclin-dependent kinase inhibitor 1A; $ApoE^{-/-}$, apolipoprotein E knockout; miR-126-3p, microRNA-126-3p; Spred1, sprouty-related EVH1 domain-containing protein 1; VCAM-1, vascular cell adhesion molecule 1; HUVEC, human umbilical vein endothelial cells; AngII, angiotensin II; TrkB, tropomyosin receptor kinase B; AT1R, angiotensin II type 1 receptor; ECs, endothelial cells; MIRI, myocardial ischemia-reperfusion injury; ADSC-CM, adipose-derived stem cell-conditioned medium; PUMA, p53 upregulated modulator of apoptosis; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ADSC-Exo, adipose-derived stem cell exosomes; KDM3A, lysine demethylase 3A; ROS, reactive oxygen species; HMGB1, high mobility group box 1; ERK, extracellular signal-regulated kinase; EMT, endothelial-mesenchymal transition; CTGF, connective tissue growth factor; TGF-β1, transforming growth factor β1; Smad2/3, mothers against decapentaplegic homolog 2/3; MMP-2, matrix metalloproteinase 2; Lnc TUG1, long non-coding RNA taurine upregulated gene 1; Exo, exosomes; CFs, cardiac fibroblasts; Sox10, sex-determining region Y-box 10; HF, heart failure; ATG7, autophagy related 7; DOX, doxorubicin; DNMT1, DNA methyltransferase 1; RHOH, ras homolog family member H.

ETS-1/ETS-2 are members of the ETS family characterized by broad tissue distribution and potent transcriptional regulatory capacity. Their biological functions span the development and differentiation of lymphocytes and they can markedly regulate the proliferation, migration and invasion phenotypes of multiple cell types. In the tumor pathological process, the dysregulated expression of ETS-1/ETS-2 is closely associated with the progression of various malignant tumors. By participating in key steps of cancer invasion, including angiogenesis, extracellular matrix degradation and tumor metastasis, ETS-1/ETS-2 serve as important molecules mediating tumor malignant phenotypes (145). Therefore, ETS-1/ETS-2 are regarded as promising targets for cancer therapy and their comprehensive investigation holds substantial scientific and clinical value.

For ETS-1, targeted intervention strategies have exhibited considerable potential across multiple tumor types: in breast cancer, ETS-1 overexpression is found to enhance the angiogenic capacity of tumor cells by modulating the interaction between paracrine cells and endothelial cells and *in vivo* experiments have demonstrated that ETS-1 inhibition can suppress the angiogenic patterns of experimental breast tumors (146); in hepatocellular carcinoma (HCC), ETS-1 has been identified as a mediator of sorafenib resistance through regulating the mitochondrial ROS pathway via the ETS-1-GPX-2 signaling axis and it effectively restores the sensitivity of sorafenib-resistant HCC cells to sorafenib (147). As for ETS-2, targeted silencing has shown remarkable anti-tumor efficacy in esophageal squamous cell carcinoma: RNA interference-mediated ETS-2 depletion promotes apoptosis, inhibits proliferation and invasion, induces G_0/G_1 cell cycle arrest *in vitro* and markedly suppresses tumor formation and metastasis in xenograft mouse models by inactivating the mTOR/p70S6K signaling pathway (148). Furthermore, ETS-2 in tumor-associated macrophages (TAMs) drives breast cancer lung metastasis by suppressing angiogenesis-inhibitory genes and conditional depletion of ETS-2 in TAMs has been shown to reduce tumor angiogenesis and metastatic burden in multiple murine breast tumor models (149).

Overall, these preclinical studies have underscored the feasibility of targeting ETS-1/ETS-2 for cancer therapy.

Table II. Proteins and NCBI gene ID.

Protein	NCBI gene ID
ETS-1	2113
ETS-2	2114
VE- cadherin	100488458
PUMA	27113
DLK1	8788
VCAM-1	25361
DKK1	22943
PTP1B	5770
TrkB	25054
KDM3A	55818
HMGB1	3146
Cadherin	100144934
NFAT	6551030
CHI3L1	1116

ETS, E26 transformation-specific; PUMA, P53 upregulated modulator of apoptosis; VCAM-1, vascular cell adhesion molecule-1; DKK1, Dickkopf1; PTP1B, protein tyrosine phosphatase 1B; TrkB, tyrosine kinase receptor B; KDM3A, lysine (K)-specific demethylase 3A; HMGB1, high mobility group box 1; NCBI, National Center for Biotechnology Information; NFAT, nuclear factor of activated T-cells; CH3L1, chitinase-3-like protein 1; DLK1, delta-like non-canonical Notch ligand 1.

Moreover, with the in-depth understanding of the mechanisms underlying the roles of ETS-1/ETS-2 in tumors and the development of their inhibitors has emerged as a research priority. Currently, the strategies for ETS-1 inhibition include small-molecule compounds (150), antisense oligonucleotides (151) and CRISPR/Cas9-based gene editing tools (152) Although preliminary data have demonstrated the potential therapeutic value of ETS-1 inhibitors, they are still in the preclinical development stage. In animal models, ETS-1 inhibitors have been shown to markedly suppress tumor growth and metastasis while enhancing anti-tumor immune responses (153). Nevertheless, the clinical translation process still faces multiple challenges, including key issues such as target specificity, therapeutic efficacy, drug safety and optimal administration regimens. Future clinical trials should focus on evaluating the human safety, tolerability and efficacy of ETS-1 inhibitors, so as to clarify whether they can be developed into clinically valuable anti-cancer agents.

6. Conclusions and perspectives

In recent years, with the in-depth progression of research into the pathogenesis of cardiovascular diseases, the transcription factors ETS-1/ETS-2 have gradually emerged as a research hotspot in this field. A growing body of evidence has confirmed that ETS-1/ETS-2 are closely associated with cardiovascular diseases and can regulate the occurrence and development of such diseases through multiple mechanisms, thereby providing an important theoretical basis and potential targets for the early warning, targeted therapy and prognostic evaluation of cardiovascular diseases (Table I). However, as ubiquitously acting transcription factors, ETS-1/ETS-2 are associated with intricate signaling pathways and mechanisms of action. At present, research on their roles in the cardiovascular system is still in its infancy and such studies are confined to the scope of preclinical basic research. Large-sample, long-term follow-up longitudinal cohort studies have not been conducted, resulting in a lack of sufficient evidence-based medical support for their application value in clinical settings. Meanwhile, their downstream targets and extensive regulatory networks have not been fully elucidated and further investigations are therefore warranted. As previously proposed, no experimental data have been reported regarding whether ETS-2 can prevent ischemia-reperfusion (I/R) injury through specific mechanisms or by regulating its downstream signaling pathways. Notably, the translational application of ETS-1/ETS-2 for cardiovascular disease therapy is confronted with multiple challenges: First, it is difficult to achieve target-specific regulation. Since ETS-1/ETS-2 are widely expressed in various tissues and organs, they participate in multiple physiological and pathological processes such as cell proliferation, differentiation and apoptosis. Second, regulatory networks are complex. ETS-1/ETS-2 exert their regulatory functions through crosstalk with multiple signaling pathways and the synergistic and antagonistic relationships among these pathways have not been fully elucidated, making it difficult to accurately identify key intervention nodes. Third, translational bridging studies are lacking for clinical translation. Current research mostly remains at the cellular and animal experimental levels, which are quite different from human clinical pathological conditions and there is a lack of intermediate translational research data linking basic research to clinical application. Fourth, the absence of longitudinal studies results in unclear prognostic evaluation value.

Nevertheless, it is considered that with the innovation in research techniques and the deepening of interdisciplinary collaboration, systematically conducting longitudinal cohort studies to clarify their clinical correlations, leveraging precision regulation technologies to overcome the challenge of target specificity and gradually improving the mechanisms underlying their regulatory networks will effectively address the current predicaments in research and application. This will enable ETS-1/ETS-2 (the accession numbers of all identified proteins are listed in Table II) to emerge as a promising and reliable therapeutic target for cardiovascular diseases, thereby providing more effective novel strategies for clinical diagnosis and treatment.

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Author's contributions

SY and JZ were involved in the conceptualization of the article and the writing of the manuscript. YY and YL provided writing guidance and reviewed the manuscript. JY and HW made substantial contributions to the selection of the topic, writing guidance and financial support for the article. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools DeepL (version 2025; https://www.deepl.com/translator) and Doubao (version 2026; https://www.doubao.com) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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