



# The role of noncoding RNA in aortic dissection

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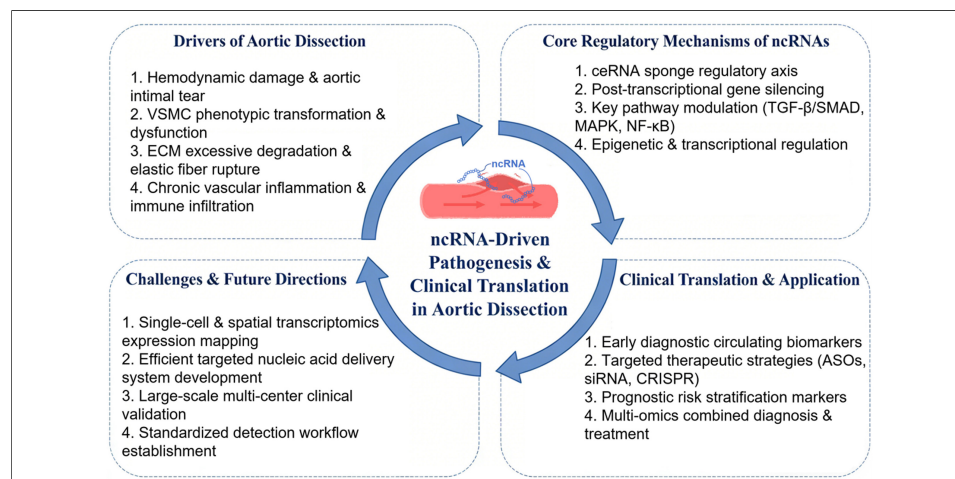
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## Abstract

Aortic dissection (AD) is a rapidly progressive cardiovascular disease associated with high mortality. The core pathogenic mechanisms of AD include apoptosis and phenotypic switching of vascular smooth muscle cells (VSMCs), remodeling and degradation of the extracellular matrix (ECM), and vascular inflammation. However, the detailed molecular mechanisms remain incompletely understood. Noncoding RNAs (ncRNAs) are RNA molecules that do not encode proteins. Recent studies have confirmed that ncRNAs with aberrant expression exert critical regulatory functions in the pathogenesis and progression of AD, and several ncRNAs have shown significant application potential in the early diagnosis, conservative treatment, and prognostic assessment of AD. This review summarizes the latest research progress on the regulatory mechanisms of various ncRNAs in AD, and critically evaluates their potential clinical utility as clinical biomarkers and therapeutic targets for AD.



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## INTRODUCTION

Aortic dissection (AD) is a cardiovascular disease characterized by sudden onset, rapid progression, and extremely high mortality. According to the 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease, AD is defined as a pathological condition in which blood penetrates into the aortic media through a tear in the aortic intima, leading to the separation of the elastic lamellae and smooth muscle cell layer of the media. This tear spreads along the longitudinal axis of the aorta, forming an abnormal cavity (false lumen) parallel to the original vascular lumen (true lumen)<sup>[1]</sup>. This process can lead to the destruction of the aortic wall structure and impaired blood supply to branch vessels, which can induce fatal complications such as myocardial infarction, stroke, visceral ischemia, and aortic rupture<sup>[2]</sup>. The pathological essence of AD lies in the destruction of the structural integrity of the aortic wall, involving the abnormal phenotypic switching of vascular smooth muscle cells (VSMCs), excessive degradation of the extracellular matrix (ECM), and the involvement of sustained inflammatory and immune responses. These changes ultimately result in a significant decrease in the mechanical strength and elasticity of the aortic wall, rendering it susceptible to tearing and dilatation under hemodynamic stress<sup>[3-5]</sup>.

According to the 2023 Report on Cardiovascular Health and Diseases in China, AD accounts for 48% of aortic diseases among Chinese residents<sup>[6]</sup>. Based on the extent of involvement, AD is classified into Stanford type A (including type I and II) and type B<sup>[7]</sup>. Data show that the mortality rate of patients with untreated type A AD increases by 1%-2% per hour after onset, reaching 33% at 48 h, over 50% at 1 week, and over 80% at 1 month<sup>[8]</sup>. Even for type B AD, which has a relatively better prognosis, it still poses a serious threat to the patients' lives if not treated in a timely manner<sup>[9]</sup>. The high mortality rate of AD not only brings devastating blows to patients' families but also imposes a heavy burden on social medical resources<sup>[10]</sup>.

Noncoding RNAs (ncRNAs) are a class of RNA molecules that do not encode proteins or only encode short peptides after transcription, constituting the vast majority of the genome transcriptome<sup>[11]</sup>. According to molecular size and structural characteristics, ncRNAs are mainly divided into the following categories:

MicroRNAs (miRNAs): ~20-25 nucleotides in length. They are key molecules for rapid and precise gene regulation, which act by forming incomplete complementary binding with the 3' untranslated region (3'UTR) of target messenger RNAs (mRNAs), thereby inducing mRNA degradation or translational repression<sup>[12]</sup>.

Long noncoding RNAs (lncRNAs): over 200 nucleotides in length, with diverse structures and complex functions. They exert regulatory effects at the epigenetic, transcriptional, and post-transcriptional levels through multiple mechanisms, including chromatin modification, transcriptional interference, acting as competing endogenous RNA (ceRNA) "sponges" to sequester miRNAs, and interacting with proteins<sup>[13]</sup>.

Circular RNAs (circRNAs): a class of closed-loop ncRNAs with high stability and conservation. One of their main functions is to act as highly efficient miRNA "sponges", which relieve the inhibitory effect of miRNAs on target genes, thereby participating in various pathophysiological processes<sup>[14]</sup>.

In recent years, a growing body of evidence has demonstrated that ncRNAs affect the pathogenesis and progression of AD by regulating the proliferation/phenotypic switching of VSMCs, inflammatory activation, and ECM remodeling through mechanisms such as post-transcriptional repression, sponge activity, and signaling pathway regulation<sup>[15]</sup>. Early research in this field focused predominantly on the regulatory roles of miRNAs in AD pathogenesis and progression. lncRNAs have more recently emerged as a major research hotspot, while circRNA research remains in its early exploratory phase. This review systematically delineates

the functional mechanisms of distinct ncRNA subtypes in AD, outlines their translational progress as diagnostic biomarkers and therapeutic targets, discusses existing challenges in clinical translation, and highlights future research directions in this field.

## **PATHOPHYSIOLOGICAL MECHANISMS OF NCRNAS IN AD**

### **Dysregulation of vascular smooth muscle cell function and its regulation by ncRNAs**

As the principal cellular component of the aortic media, VSMCs and their functional dysregulation constitute the central driver of AD pathogenesis. During disease progression, ncRNAs exert their effects mainly by regulating key biological processes of VSMCs, including phenotypic switching, proliferation, apoptosis, and migration<sup>[16]</sup>. Among these, abnormal phenotypic switching is the core regulatory link, which is mainly achieved through key signaling pathways such as Transforming Growth Factor  $\beta$  (TGF- $\beta$ ), Mitogen-Activated Protein Kinase (MAPK), and Nuclear Factor-kappa B (NF- $\kappa$ B)<sup>[17,18]</sup>.

ncRNAs (miRNAs, lncRNAs, and circRNAs) regulate signal transduction by targeting key molecules within these pathways - including receptors, kinases, inhibitory proteins, transcription factors - thus determining whether VSMCs maintain a normal contractile phenotype or switch to a pathogenic synthetic phenotype. Specifically, the TGF- $\beta$ /SMAD (Sma/Mothers against decapentaplegic) axis is the core pathway for phenotypic regulation: ncRNAs regulate pathway activation and phenotypic switching by targeting TGF- $\beta$  ligands, receptors, or SMAD family molecules (e.g. miR-145 targets and inhibits SMAD3<sup>[19]</sup>). The MAPK pathway (ERK1/2, JNK, p38) mediates the synthetic phenotype, as well as proliferation and migration: ncRNAs exert regulatory effects by targeting key kinases of the pathway (e.g. miR-22 targets and inhibits p38<sup>[20]</sup>). The NF- $\kappa$ B pathway links inflammation and phenotypic switching: ncRNAs target its key molecules to activate the pathway and upregulate pro-inflammatory factors, synergistically promoting the synthetic phenotype. Some ncRNAs can coordinately regulate multiple pathways, ultimately leading to the degradation of elastic fibers in the aortic media, impairment of vascular wall structure and function, and driving the progression of AD. The roles of ncRNAs in VSMCs are summarized in [Table 1](#).

### *miRNAs regulating VSMC function*

Multiple miRNAs participate in the development of AD by regulating VSMC function through targeting different genes. miR-21 inhibits VSMC apoptosis and promotes proliferation by targeting Phosphatase and Tensin homolog deleted on chromosome ten (PTEN), and simultaneously suppresses VSMC proliferation and promotes vascular remodeling by regulating its target gene SV2C<sup>[21]</sup>. miR-22 inhibits VSMC apoptosis by targeting p38 during vascular remodeling in AD; its knockdown significantly accelerates disease progression in a mouse model of AD, suggesting the potential therapeutic target value of the MAPK signaling pathway<sup>[20]</sup>. Wang *et al.* found that miR-107-5p is highly expressed in acute AD tissues. Overexpression of this miRNA promotes the proliferation and inhibits the apoptosis of rat aortic smooth muscle cells (RASMCs) by targeting ITM2C<sup>[22]</sup>.

In addition, miR-124 is significantly downregulated in the aortic adventitia of clinical AD specimens, and regulates VSMC phenotypic switching by targeting Sp1<sup>[23]</sup>. miR-134-5p is downregulated in thoracic aortic dissection (TAD) tissues, and inhibits PDGF-BB-induced phenotypic switching and migration of VSMCs, while promoting the expression of differentiation and contractile markers<sup>[24]</sup>. miR-145 induces the proliferation, migration, and apoptosis of VSMCs by targeting SMAD3, a core mediator of the TGF- $\beta$  signaling pathway<sup>[19]</sup>. Furthermore, miR-200c-3p promotes the synthetic phenotypic switching of human aortic smooth muscle cells (HASMCs) by downregulating CASZ1 and inhibiting the RhoA/Egfl7 pathway<sup>[25]</sup>.

### *lncRNAs regulating VSMC function*

lncRNAs affect VSMC function mainly through the ceRNA mechanism or by regulating specific signaling pathways. The lncRNA H19 is aberrantly upregulated in the aorta of AD patients, and exerts its effects by competitively binding to and inhibiting miR-193b-3p. Knockout of H19 effectively inhibits PDGF-BB-induced phenotypic dedifferentiation and migration of HASMCs<sup>[26]</sup>. SENCER, a myocardin-related pro-differentiation factor for VSMCs, is downregulated in aortic tissues of AD patients. It is inhibited by miR-206 via sponge activity, and its overexpression suppresses the proliferation and migration of HASMCs to maintain the contractile phenotype<sup>[27]</sup>.

Zhang *et al.* found that HIF1A-AS2 acts as a ceRNA for miR-33b to inhibit the proliferation and migration of VSMCs, and simultaneously promotes phenotypic switching by regulating HMGA2<sup>[28]</sup>. PVT1 is also involved in disease progression and is upregulated in AD tissues. It reduces the expression of  $\alpha$ -SMA and SM22 $\alpha$  by targeting miR-27b-3p, thereby promoting the phenotypic switching of VSMCs<sup>[29]</sup>. Animal studies have shown that overexpression of CDKN2B-AS1 promotes VSMC apoptosis and inhibits their proliferation by acting as a molecular sponge for miR-320d to positively regulate STAT3 expression<sup>[30]</sup>.

The lncRNA PTENP1 is a pseudogene of phosphatase and tensin homolog. Lai *et al.* found that PTENP1 promotes PTEN expression by acting as a molecular sponge for miR-21, thereby inhibiting downstream Akt signaling and affecting VSMC proliferation and apoptosis<sup>[31]</sup>. X-Inactive Specific Transcript (XIST) regulates the proliferation and apoptosis of smooth muscle cells by inhibiting miR-17 and its downstream *PTEN* gene<sup>[32]</sup>. LINC01278 downregulates ACTG2 by acting as a molecular sponge for miR-500b-5p, promoting smooth muscle phenotypic switching<sup>[33]</sup>. lncRNA-RP11-465L10.10 is highly expressed in AD tissues, and promotes VSMC phenotypic switching, MMP9 expression, and proliferation/migration via the NF- $\kappa$ B signaling pathway<sup>[34]</sup>.

### *circRNAs regulating VSMC function*

circRNAs, as a class of ncRNAs with stable structure and no free ends, mainly achieve precise regulation of VSMC function by forming a specific regulatory axis or binding functional proteins. The main functional mode of circRNAs is to sponge miRNAs through the ceRNA mechanism, thus forming a complete regulatory axis.

Liu *et al.* found that in the diseased tissues of AD patients, the expression levels of circ\_0000006 and circ\_0000160 were significantly upregulated, while the expression of miRNA hsa-let-7e-5p was downregulated. The three together formed a circRNA-miRNA-mRNA regulation axis targeting *UBQLN4* gene, which affected the abnormal phenotypic switching, migration and proliferation of VSMC by regulating the expression of *UBQLN4*, and promoted the pathological progression of aorta from aortic aneurysm (AA) to AD<sup>[35]</sup>. Other studies have revealed that circ\_0022920 is significantly downregulated in AD lesion tissues, and it exerts a protective effect by targeting miR-650. miR-650 negatively regulates TGF $\beta$ R1 expression via targeting IRF1, and the circ\_0022920/miR-650/IRF1/TGF $\beta$ R1 axis ultimately inhibits the abnormal proliferation and migration of HASMCs, thus delaying AD pathological progression<sup>[36]</sup>. Cao *et al.* further clarified its mechanism of action through RNA immunoprecipitation (RIP) experiments, and confirmed that circNRIP1 can enhance the stability of CXCL5 mRNA by competitively binding with insulin-like growth factor 2 binding protein 1 (IGF2BP1), thereby promoting the disease progression of TAD<sup>[37]</sup>. Xu *et al.* found that circ-TGFBR2 can act as a molecular sponge of miR-29a, and its inhibitory effect on KLF4 gene can be relieved by adsorbing miR-29a, while the overexpression of circ-TGFBR2 can significantly upregulate the expression of VSMC contractile phenotype markers, downregulate the expression of synthetic phenotype markers, effectively inhibit the abnormal activation of VSMC, thus delaying the pathological progression of AD<sup>[38]</sup>.

**Table 1. ncRNAs influencing AD development by regulating VSMC functions**

ncRNA type	Expression status	Target/pathway	Primary regulatory process	Role in AD	Potential application directions	References
miR-145	Downregulation	SMAD3	Promotes VSMC proliferation, migration, and apoptosis	Inhibits AD formation	Therapeutic target	[19]
miR-22	Downregulation	p38, MAPK	Inhibits VSMC apoptosis	Inhibits AD formation	Therapeutic target	[20]
miR-21	Upregulation	PTEN, SV2C	Promotes VSMC proliferation	Promotes AD development	Therapeutic target	[21]
miR-107-5p	Upregulation	ITM2C	Promotes VSMC proliferation	Promotes AD development	Therapeutic target	[22]
miR-124	Downregulation	Sp1	Promotes VSMC phenotypic switching	Inhibits AD formation	Therapeutic target	[23]
miR-134-5p	Downregulation	-	Inhibits VSMC phenotypic switching and migration	Inhibits AD formation	Therapeutic target	[24]
miR-200c-3p	Upregulation	CASZ1, Rho A/Egfl7	Promotes VSMC phenotypic switching	Promotes AD development	Therapeutic target	[25]
lncRNA H19	Upregulation	miR-193b-3p	Promotes VSMC phenotypic switching	Promotes AD development	Diagnostic/therapeutic target	[26]
lncRNA SENCR	Downregulation	miR-206	Maintains VSMC contractile phenotype	Inhibits AD formation	Therapeutic target	[27]
lncRNA-HIF1A-AS2	Upregulation	miR-33b	Promotes VSMC phenotypic switching	Promotes AD development	Therapeutic target	[28]
lncRNA-PVT1	Upregulation	miR-27b-3p	Promotes VSMC phenotypic switching	Promotes AD development	Therapeutic target	[29]
lncRNA-CDKN2B-AS1	Upregulation	miR-320d, STAT3	Promotes VSMC apoptosis	Promotes AD development	Therapeutic target	[30]
lncRNA-PTENP1	Upregulation	miR-21, Akt	Promotes VSMC apoptosis	Promotes AD development	Diagnostic/therapeutic target	[31]
lncRNA-XIST	Upregulation	miR-17	Promotes VSMC apoptosis	Promotes AD development	Therapeutic target	[32]
lncRNA-LINC01278	Downregulation	miR-500b-5p	Maintains VSMC contractile phenotype	Inhibits AD formation	Therapeutic target	[33]
lncRNA-RP11-465L10.10	Upregulation	NF-κB	Promotes VSMC phenotypic switching Promotes ECM degradation	Promotes AD development	Diagnostic/therapeutic target	[34]

circ_0000006	circ_0000160	Upregulation	hsa-let-7e-5p, UBQLN4	Promotes VSMC phenotypic switching	Promotes AD development	Diagnostic/therapeutic target	[35]
circ_0022920		Downregulation	miR-650	Inhibits VSMC proliferation and migration	Inhibits AD formation	Therapeutic target	[36]
circ-NRIP1		Upregulation	IGF2BP1, CXCL5	Promotes VSMC proliferation and migration	Promotes AD development	Diagnostic/therapeutic target	[37]
circ-TGFBR2		Upregulation	miR-29a	Inhibits VSMC proliferation, migration, and phenotypic switching	Inhibits AD development	Therapeutic target	[38]
piRNA-823		Upregulation	HDAC1	Promotes VSMC proliferation, migration and phenotypic switching	Promotes AD development	Therapeutic target	[39]

VSMCs: Vascular smooth muscle cells; ECM: extracellular matrix; AD: aortic dissection; ncRNAs: noncoding RNAs.

Other ncRNAs regulating VSMC function

In addition, researchers have identified a novel small ncRNA, piRNA-823, which is highly expressed in patients with AD. This piRNA directly binds to and inhibits the expression of histone deacetylase 1 (HDAC1), and regulates the acetylation of histone H3 through H3K9ac and H3K27ac modifications, thereby promoting the proliferation, migration, and phenotypic switching of VSMCs<sup>[39]</sup>.

Extracellular matrix dysregulation and associated ncRNA regulation

The ECM is a key component of the aortic wall, mainly composed of collagens type I and III, elastin, proteoglycans, glycosaminoglycans, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs). These components collectively maintain the elasticity and mechanical stability of the vascular wall<sup>[40,41]</sup>. ncRNAs mainly disrupt the balance of ECM degradation/synthesis by promoting the overexpression of MMPs (such as MMP-2 and MMP-9) and inhibiting the activity of TIMPs (such as TIMP-1 and TIMP-2). This leads to extensive degradation of collagen and elastin, destroying the structural integrity of the vascular wall, and ultimately promoting the occurrence and development of AD. The roles of ncRNAs in ECM regulation are summarized in Table 2.

ECM-related miRNAs

Sun *et al.* confirmed that Nanog homeobox (NANOG) promotes the transcription of miR-20a by binding to the promoter region within the miR-17-92 gene cluster. Upregulated miR-20a expression inhibits TIMP-2 expression, thereby activating MMP-2 and inducing ECM degradation to promote the development of thoracic aortic aneurysm and dissection (AAD)<sup>[42]</sup>. Wei *et al.* verified via quantitative real-time polymerase chain reaction (qRT-PCR) and Western blot that miR-183 may participate in ECM remodeling and promote AAD progression by regulating MMP-9 expression in smooth muscle cells<sup>[43]</sup>.

ECM-related lncRNAs

MAP2K6 is a member of the MAPK signaling pathway. Using high-throughput sequencing (HTS), Sun *et al.* identified the upregulated lncRNA ENSG00000269936, which may target the cis-acting protein-coding gene MAP2K6 to promote ECM degradation<sup>[44]</sup>. Through HTS analysis and bioinformatics prediction, Zhang *et al.* identified STAT3 as a downstream target of Lnc-C2orf63-4-1. Downregulation of Lnc-C2orf63-4-1 increases



**Table 2. ncRNAs influencing AD development by regulating ECM functions**

ncRNA type	Expression status	Target/pathway	Primary regulatory process	Role in AD	Potential application directions	References
miR-20a	Upregulation	TIMP-2, MMP-2	Promotes ECM degradation	Promotes AD development	Therapeutic target	[42]
miR-183	Upregulation	-	Promotes ECM remodeling	Promotes AD development	Therapeutic target	[43]
LncRNA-ENSG00000269936	Upregulation	MAP2K6	Promotes collagen degradation	Promotes AD development	Therapeutic target	[44]
Lnc-C2orf63-4-1	Downregulation	STAT3	Inhibits ECM degradation and VSMC apoptosis	Inhibits AD formation	Therapeutic target	[45]
hsa_circRNA_101238	Upregulation	hsa-miR-320a	Promotes ECM degradation	Promotes AD development	Diagnostic/therapeutic target	[46]
hsa_circRNA_082317	Upregulation	ITGA5	Disrupts ECM-cell adhesion stability	Promotes AD development	Therapeutic target	[47]

VSMCs: Vascular smooth muscle cells; ECM: extracellular matrix; AD: aortic dissection; ncRNAs: noncoding RNAs.

STAT3 expression, promotes Ang II-induced VSMC apoptosis via the STAT3 pathway, and simultaneously significantly reduces Ang II-induced upregulation of MMP-2 and MMP-9. The increased STAT3 expression induced by low Lnc-C2orf63-4-1 expression enhances Ang II-induced VSMC apoptosis, thereby promoting the development of AD<sup>[45]</sup>.

### *ECM-associated circRNAs*

By comparing arterial segments from human patients with type A TAD and healthy donors, researchers found that hsa-miR-320a was downregulated and MMP9 was upregulated in the TAD group, suggesting that hsa\_circRNA\_101238 may increase MMP9 expression by inhibiting hsa-miR-320a<sup>[46]</sup>. Liu *et al.* verified that hsa\_circRNA\_082317 and ITGA5 were significantly upregulated in AD, while hsa-miR-149-3p was downregulated. hsa\_circRNA-082317 may regulate the pathogenesis and progression of AD by competing with hsa-miR-149-3p to mediate ITGA5, a target related to the ECM-receptor interaction pathway and focal adhesion pathway<sup>[47]</sup>.

### **Inflammatory response and associated ncRNA regulation**

AD pathogenesis is closely related to chronic vascular wall inflammation and acute inflammatory storms. Inflammatory cells such as neutrophils and macrophages infiltrate the aortic media, and the expression levels of most *MMP* genes are significantly elevated in macrophages<sup>[48]</sup>. These inflammatory cells release a large number of pro-inflammatory cytokines; for example, Interleukin-1 $\beta$  (IL-1 $\beta$ ) significantly upregulates the expression of MMP-2 and MMP-9, leading to elastic fiber rupture and ECM degradation<sup>[49]</sup>. Meanwhile, they induce VSMC dysfunction, ultimately destroying the structural stability of the vascular wall and promoting the formation and progression of dissection. The roles of ncRNAs in inflammatory regulation are summarized in Table 3.

### *Inflammation-associated miRNAs*

Using a rat model of AD, Wu *et al.* found that miR-30a expression was increased in the model group. Inhibition of miR-30a ameliorated the inflammatory response, suggesting that it may participate in

**Table 3. ncRNAs influencing AD onset by regulating inflammatory functions**

ncRNA type	Expression status	Target/pathway	Primary regulatory process	Role in AD	Potential application directions	References
miR-181b	Downregulation	Serotonin receptor 6, NF-κB	Inhibits vascular inflammation	Inhibits AD formation	Therapeutic target	[21]
miR-30a	Upregulation	MAPK	Promotes vascular inflammation	Promotes AD development	Therapeutic target	[50]
miR-127-3p	Upregulation	NF-κB	Promotes vascular inflammation	Promotes AD development	Therapeutic target	[51]
Lnc-OIP5-AS1	Upregulation	miR-143-3p	Promotes vascular inflammation and VSMC apoptosis	Promotes AD development	Diagnostic/therapeutic target	[52]
hsa_circ_0079929	Upregulation	hsa_mir_944, NF-κB	Promotes vascular inflammation	Promotes AD onset	Diagnostic/therapeutic target	[53]
circNOX4, circAMN1, circUSP3, circPTGR1	Upregulation	-	Promotes inflammatory infiltration and ECM degradation	Promotes AD development	Diagnostic/therapeutic target	[54]

VSMCs: Vascular smooth muscle cells; ECM: extracellular matrix; AD: aortic dissection; ncRNAs: noncoding RNAs; NF-κB: nuclear factor-kappa B; MAPK: mitogen-activated protein kinase.

inflammation-related AD formation by regulating the MAPK signaling pathway<sup>[50]</sup>. Using Agilent human miRNA microarray technology, researchers detected that the downstream target gene of miR-181b, 5-hydroxytryptamine receptor 6, can directly inhibit the cyclic adenosine monophosphate (cAMP) signaling pathway. By regulating the expression of protein kinase A (PKA), this mechanism modulates the NF-κB signaling pathway and promotes the release of inflammatory mediators such as IL-8 and IL-1β, thereby participating in the pathogenesis of AD<sup>[21]</sup>. The expression of miR-127-3p is significantly upregulated under vascular injury conditions. Daniel *et al.* found that miR-127-3p may exert its effects by regulating inflammatory signaling pathways such as NF-κB. Overexpression of miR-127-3p may exacerbate inflammatory infiltration at the site of vascular injury, thereby promoting vascular remodeling<sup>[51]</sup>.

### Inflammation-related lncRNAs

Wang found that Lnc-OIP5-AS1 was highly expressed, while miR-143-3p was lowly expressed in aortic tissues of AD patients. Subsequent studies showed that Lnc-OIP5-AS1 indirectly upregulates Tubby bipartite transcription factor (TUB) expression by competitively binding to miR-143-3p, thereby inhibiting the proliferation and promoting the apoptosis of human aortic endothelial cells (HAECs) and HASMCs, suppressing HASMC migration, disrupting the balance of the MMP-2/9 and TIMP-1/2 system, and enhancing the secretion of inflammatory cytokines in human aortic adventitial fibroblasts (HAAFs), ultimately promoting the occurrence and development of AD<sup>[52]</sup>.

### Inflammation-related circRNAs

Researchers found that hsa\_circ\_0079929 is highly expressed and localized in the cytoplasm of human umbilical vein endothelial cells (HUVECs). Knockdown of hsa\_circ\_0079929 inhibited cell proliferation, invasion, and inflammatory responses. It forms a regulatory pathway together with hsa\_miR\_944 and PDE4D. Inhibition of hsa\_miR\_944 activates the NF-κB pathway, indicating that the hsa\_circ\_0079929/hsa\_miR\_944/PDE4D pathway may participate in early endothelial injury in AD via NF-κB activation<sup>[53]</sup>.



Liang *et al.* identified four circRNAs - circNOX4, circAMN1, circUSP3, and circPTGR1 - that are highly expressed in Thoracic Aortic Aneurysm and Dissection (TAAD) tissues and serum. Among them, circNOX4, circAMN1, and circUSP3 are closely related to inflammatory cell infiltration and matrix component loss, while circPTGR1 shows a negative correlation with stromal cell components. These circRNAs promote inflammatory cell infiltration and ECM degradation by interacting with miRNAs, accelerating the progression of TAAD<sup>[54]</sup>.

## CLINICAL DIAGNOSIS AND APPLICATIONS

### ncRNAs as Biomarkers for early diagnosis of AD

The early diagnosis of acute AD remains challenging. Conventional imaging examinations are costly and often fail to detect early or atypical cases<sup>[55]</sup>. Accumulating evidence indicates that circulating ncRNAs in the blood exhibit remarkable stability, tissue specificity, and accessibility, making them potential biomarkers for the diagnosis of early and atypical AD<sup>[56]</sup>.

Among these, miRNAs have been the most extensively investigated. Multiple miRNAs that regulate VSMC transformation and inflammatory signaling show significant differential expression in the blood of AD patients. Numerous studies have confirmed that the levels of miRNAs related to VSMC contraction (such as miR-143, miR-145, and members of the miR-29 family) are decreased in the blood of AD patients<sup>[57,58]</sup>, while the levels of inflammation-related miRNAs (including miR-155, miR-221, and miR-222) are elevated<sup>[59,60]</sup>.

For example, the plasma levels of miR-143/145 in patients with acute Stanford type A AD are significantly lower than those in the control group, with reported area under the receiver operating characteristic curve (AUC) values of 0.78-0.89, indicating moderate-to-high diagnostic efficiency. Similarly, elevated circulating levels of miR-155 and miR-221/222 are correlated with inflammatory activity and disease severity, suggesting their combined diagnostic and pathophysiological significance<sup>[59,61,62]</sup>.

In addition to miRNAs, lncRNAs and circRNAs also show differential expression. For instance, lncRNAs related to ECM remodeling (such as MALAT1) and circRNAs associated with vascular integrity (including circRNA\_0001806 and circRNA\_002178) are aberrantly expressed in AD patients<sup>[54,63]</sup>. Taken together, these findings indicate that ncRNAs have important potential as biomarkers for the early diagnosis of AD.

### Clinical therapeutic targets

ncRNAs affect the development of AD by regulating the phenotypic switching of VSMCs, ECM degradation and inflammatory activation. Therefore, targeting regulatory related ncRNAs can delay, inhibit or even repair the pathological state of aortic fragility, thereby maintaining vascular stability. For example, supplementing miR-143/145 gene cluster can stabilize the contractile phenotype of VSMCs and reduce aortic wall degeneration<sup>[54,57]</sup>, while inhibiting miR-323a-3p and miR-449b-5p can alleviate inflammatory injury and abnormal VSMC proliferation<sup>[64]</sup>. The expression and function of lncRNAs and circRNAs can be modulated using nucleic acid-based strategies including antisense oligonucleotides (ASOs), small interfering RNA (siRNA), and CRISPR-Cas9 gene editing technology. For instance, targeting the lncRNA MALAT1 reduces ECM degradation, while restoration of lncRNA GAS5 expression alleviates vascular inflammatory stress and VSMC apoptosis<sup>[65,66]</sup>.

Research based on multi-omics integration and RNA association networks has revealed that the ceRNA regulatory network formed by ncRNAs can maintain vascular microenvironment homeostasis through multi-dimensional regulation, which has become the core basis for molecular typing and target screening of AD. Meanwhile, CRISPR-Cas9 gene editing technology enables precise knockout or overexpression of ncRNA targets, providing an efficient genetic manipulation tool for the modulation of the above core

regulatory network<sup>[67]</sup>. In addition, the restoration of protective circRNA expression can enhance aortic intimal stability<sup>[68]</sup>.

Notably, deep learning algorithms can construct highly accurate models for AD molecular subtyping and therapeutic efficacy prediction, based on the sequence characteristics, target correlation, and expression profile data of ncRNAs. These models can provide intelligent analytical tools for the screening of CRISPR-Cas9 editing targets, as well as the personalized optimization of ncRNA-targeted therapies<sup>[69]</sup>.

These studies are still in the preclinical stage, but the cross-integration of multi-omics analysis, RNA association research, gene editing technology and deep learning is expected to markedly improve the precision and efficacy of ncRNA-targeted therapies. This integrated approach will also provide novel research directions and technical support for slowing disease progression in patients with early-stage AD, and for the development of new targeted treatments for Stanford type B AD.

### **ncRNAs as prognostic biomarkers for AD**

Alterations in circulating ncRNAs not only reflect disease onset but also correlate with postoperative complications and long-term survival rates. Elevated levels of MALAT1 and miR-155 are closely associated with an increased risk of re-dissection, adverse events, and reduced survival rates<sup>[63,70]</sup>, indicating that these molecules reflect persistent molecular instability of the aortic wall. Conversely, elevated levels of protective ncRNAs such as miR-143/145 and GAS5 predict favorable vascular remodeling and a reduced recurrence rate<sup>[54,65]</sup>.

Taken together, these findings suggest that ncRNAs constitute a multidimensional biomarker system that can provide a basis for the diagnosis, treatment decision-making, and prognostic assessment of AD. The integration of ncRNAs into clinical workflows is expected to enable earlier disease detection, more accurate risk stratification, and more effective personalized treatment regimens.

### **Current detection technologies for ncRNA biomarkers**

The translation of ncRNA biomarkers into clinical diagnostic tools is highly dependent on reliable detection platforms. The current main technologies include:

**qRT-PCR:** The most widely used clinical validation tool due to its high sensitivity and specificity. However, standardization strategies remain inconsistent, and pre-analytical variability (sample processing, hemolysis) significantly affects reproducibility<sup>[59]</sup>.

**Digital PCR (dPCR):** Provides high-precision absolute quantitative analysis and is being widely applied to the detection of low-abundance circulating ncRNAs. It has broad prospects for clinical scalability, but is limited by cost and equipment availability<sup>[71,72]</sup>.

**Next-generation sequencing (NGS):** Enables comprehensive profiling of biomarkers. Despite its powerful capabilities, high costs, complex bioinformatics processing, and the lack of standardized workflows currently limit its routine clinical application<sup>[16]</sup>.

**Microarray platforms:** Suitable for large-scale screening, but have low sensitivity for lowly expressed ncRNAs and are gradually being replaced by sequencing technologies<sup>[59]</sup>.

### Challenges in clinical translation

Although these biomarkers show considerable translational potential, their clinical application still faces multiple key barriers, including the lack of large-scale multi-center validation cohorts, insufficient control of pre-analytical variability and standardized workflows, significant biological heterogeneity between disease subtypes, and regulatory and compliance limitations of nucleic acid diagnostics. Meanwhile, their cost-effectiveness relative to existing imaging diagnostic pathways remains uncertain.

Effective advancement of clinical translation urgently requires expanding the evidence base through multi-center collaborative clinical studies, establishing a unified and reproducible standardized operating system, and integrating molecular biomarkers into a multimodal diagnostic framework to improve the reliability and clinical feasibility of overall diagnosis.

## SUMMARY AND OUTLOOK

### Current research and emerging directions

Current research on ncRNAs in AD has made phased progress. Research hotspots focus on three major molecular categories: miRNAs, lncRNAs, and circRNAs. These molecules have been confirmed to participate in the pathogenesis of AD by regulating VSMC phenotypic switching, ECM homeostasis, and vascular inflammatory responses. For example, miR-20a accelerates ECM degradation by inhibiting TIMP-2 and promoting MMP-2 activation<sup>[42]</sup>, the lncRNA SENCRC regulates VSMC proliferation and apoptosis by targeting miR-206<sup>[27]</sup>.

Meanwhile, ncRNAs with tissue-specific differential expression have shown potential as diagnostic biomarkers for AD, such as hsa-miRNA-4787-5p<sup>[73]</sup> and miR-15a<sup>[74]</sup>, opening up new avenues for the early detection of AD. In addition, exploring the role of ncRNAs in the regulation of metabolic and signaling pathways has become a key breakthrough point for deciphering the pathophysiological mechanisms of AD.

### Technical limitations and gaps in clinical validation

Current research on ncRNAs in AD is still limited by key technical bottlenecks, including insufficient cellular resolution, missing spatial expression information, and low in vivo delivery efficiency. Traditional bulk transcriptome analysis fails to effectively reveal the cellular heterogeneity of the aortic wall and the cell-specific regulatory networks of ncRNAs.

Future research should establish a closed-loop research framework of “single-cell resolution-spatial localization-functional validation”: (1) identifying key ncRNA regulatory modules via single-cell multi-omics; (2) clarifying their hierarchical distribution in the aortic wall microenvironment in combination with spatial transcriptomics; (3) verifying their causal roles in VSMC phenotypic switching and inflammatory remodeling using targeted intervention technologies. Meanwhile, cross-modal computational models should be introduced to integrate high-dimensional data and screen regulatory nodes with translational potential<sup>[75]</sup>.

At the therapeutic level, two core breakthrough directions should be prioritized. First, we need to break through the delivery limitations of nucleic acid drugs in the high-shear force vascular environment, and develop cell-targeted, biomimetic, and microenvironment-responsive carrier systems. Second, the stability of biomarkers and the standardization of detection methods should be verified through multi-center clinical cohorts, so as to promote the translation of ncRNA research from mechanistic correlation to precise clinical intervention.

## Future research priorities and directions

### *Constructing Precise Expression Maps*

Future efforts should integrate single-cell sequencing, spatial transcriptomics, and artificial intelligence (AI) to systematically map the dynamic expression profiles of ncRNAs across different AD subtypes and disease stages. This will clarify the cellular localization and expression characteristics of key ncRNAs, enabling the selection of highly specific and sensitive biomarkers to support early diagnosis and risk stratification in AD.

### *In-depth exploration of regulatory mechanisms*

Research should focus on the interaction networks between ncRNAs and DNA, RNA, and proteins to decipher their molecular mechanisms in core pathological processes such as VSMC phenotypic switching and metabolic reprogramming. This includes elucidating the regulatory pathways of lncRNA-encoded functional peptides.

### *Developing efficient targeted therapeutics*

Based on mechanistically validated targets, researchers should advance ncRNA-targeted drug development by designing nucleic acid therapeutics or small-molecule modulators. Prioritize addressing drug delivery efficiency, tissue specificity, and safety concerns. Achieve precise ncRNA enrichment at diseased aortic sites through optimized delivery systems. Concurrently conduct large-scale clinical studies to validate therapeutic efficacy, ultimately bridging the gap from mechanistic research to clinical translation.

## Ethical and safety considerations in the clinical application of ncRNAs

With the extension of ncRNAs into the field of clinical diagnosis and treatment, their ethical and safety challenges have become increasingly prominent. ncRNAs have multi-pathway regulatory properties, and their intervention may cause off-target effects or long-term transcriptional remodeling. Therefore, it is necessary to systematically evaluate multi-organ toxicity and long-term safety in preclinical studies.

Nucleic acid delivery materials may also induce immune responses, especially in vascular diseases with an inflammatory background, and the risk should be reduced through carrier optimization and dose control. At the same time, ncRNA diagnosis and treatment rely on the collection of high-dimensional molecular data, involving ethical issues such as privacy protection, data sharing, and informed consent, which urgently require the establishment of a standardized governance framework.

At the clinical implementation level, the principles of evidence-based and phased validation should be followed, and multidisciplinary ethical review and risk monitoring should be strengthened. Synchronous integration of safety assessment, ethical norms, and technology development into the research design is a fundamental prerequisite for ensuring the sustainable advancement of the translational application of ncRNAs.

## DECLARATIONS

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Conceptualization, manuscript drafting, and manuscript polishing: Yang J

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Not applicable.

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### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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