# Spotlight on HOX cluster-embedded antisense lncRNAs in cardiovascular diseases (Review)

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**Abstract.** Atherosclerosis is a complex and chronic inflammatory disease driven by multiple pathophysiological processes that are responsible for diverse cardiovascular events. Atherosclerotic cardiovascular disease, despite substantial triumphs in primary and secondary prevention, remains a dominant epidemic that impairs human health. Therefore, deciphering the pathogenesis of atherosclerosis will provide a real-world translational understanding. Homeobox cluster-embedded antisense long non-coding RNAs (HOX-lncRNAs), a nascent class of lncRNA molecules with versatile roles in cancer, can also orchestrate various cell functions in cardiovascular disorders and have thus captured the attention of many researchers. Subsequently, numerous studies have demonstrated the role of HOX-lncRNAs as potential modulators of atherosclerosis. Nevertheless, given that the understanding of HOX-lncRNAs in atherosclerosis is only just emerging, ongoing research must be initiated to thoroughly pinpoint such causal roles. The present review aimed to highlight the important contributions of HOX-lncRNAs to atherosclerosis and other pivotal biological processes related to cardiovascular disease. The review concludes with a discussion of the limitations, outlook, challenges and possible solutions associated with HOX-lncRNAs in atherosclerosis. Looking forward, this may lead to extraordinary breakthroughs in revealing the molecular underpinnings of HOX-lncRNAs and may offer a promising yet challenging landscape for robust therapeutic strategies for atherosclerosis and/or associated cardiovascular disorders.

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*Abbreviations:* AF, atrial fibrillation; AMI, acute myocardial infarction; ceRNA, competing endogenous RNA; CFs, cardiac fibroblasts; EC, endothelial cell; HAVSMCs, human aortic VSMCs; HF, heart failure; HOX, homeobox; HOXC-AS1, lncRNA HOXC cluster antisense RNA 1; HOXA-AS3, lncRNA HOXA cluster antisense RNA 3; HPASMCs, human pulmonary artery smooth muscle cells; HUVECs, human umbilical vein ECs; I/R, ischemia/reperfusion; ISR, in-stent restenosis; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; MI, myocardial infarction; NF-κB, nuclear factor-κB; PAH, pulmonary arterial hypertension; PASMCs, pulmonary arterial smooth muscle cells; PPF, propofol; TAA, thoracic aortic aneurysm; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells

*Key words:* atherosclerosis, cardiovascular biology, cardiovascular disease, HOX-lncRNAs, lncRNAs, therapeutic targets

## Contents



## 1. Introduction

Atherosclerosis, a clinically important pathophysiological process characterized by lipid deposition in the vessel wall, fuels the onset and progression of diverse cardiovascular diseases responsible for the overwhelming majority of deaths worldwide (1,2) and accounting for ~17.8 million deaths annually (3). Atherosclerosis is a slow and progressive process that involves multifocal structural alterations in the vessel walls of large- and medium-sized arteries, followed by secondary atherosclerotic plaque formation (4). Several pathophysiological processes, including endothelial dysfunction, angiogenesis, inflammatory responses, lipid metabolism, aberrant cellular proliferation and apoptosis, mechanistically provide the foundation for this disease as key determinants of atherosclerosis and ultimately the development of thrombotic plaque complications, such as myocardial infarction (MI), stroke and sudden cardiac death (1,5). Despite significant advances in the clinical management of atherosclerosis and related risk factors, such as hypertension, hyperlipidemia and diabetes, atherosclerosis-associated acute ischemic events

remain the primary cause of death worldwide (6), and thus, new cellular and molecular mechanisms are urgently needed to develop novel therapeutic strategies for intervention.

Long non-coding RNAs (lncRNAs) are RNA transcripts of >200 bp in length with little or no protein-coding potential (7). Based on their genomic locations relative to adjacent protein-coding genes, lncRNAs can be classified as sense, antisense, bidirectional, intronic or intergenic (8). On the grounds of their functions, they can also be classified as signaling, decoy, guide or scaffold lncRNAs (9). In addition, lncRNAs are localized in the nucleus or cytoplasm and exhibit tissue- or cell-specific expression, thus endowing them extraordinary potential and multifarious functionality, and they can serve as biomarkers for diagnostics and treatments (10). Mechanistically, lncRNAs perform either in cis or trans mode to modulate the expression of target genes through a series of molecular mechanisms, such as acting as a scaffold for the recruitment of chromatin modifiers or transcription factors or as decoys for protein sequestration and as microRNA (miRNA) sponges to activate or repress genes (11,12). In addition, lncRNAs are also involved in the regulation of mRNA splicing, translation and turnover (13-15). Taken together, they are a unique class of functional molecules that orchestrate diverse cellular processes via multiple mechanisms involving, but not limited to, direct mRNA, DNA or protein binding (9,16). Several recent studies have shown that lncRNAs can affect the initiation and progression of cardiovascular disease. Hence, it is crucial to elucidate such functional roles for lncRNAs.

Among the several thousand lncRNAs, homeobox (HOX) cluster-embedded lncRNAs (HOX-lncRNAs) have key roles in controlling protein-coding genes under normal and pathogenic conditions (17). Burgeoning findings indicate that aberrantly expressed HOX-lncRNAs influence cancer hallmarks, such as proliferation, migration and invasion, and may also serve as potential regulators of cardiovascular disease. Thus, the underlying molecular mechanisms could provide theoretical evidence for the development of targeted therapies against cardiovascular diseases. More recently, a plethora of data has shown that HOX-lncRNAs are pivotal modulators of numerous pathophysiological processes in cardiovascular biology. As an example, the oncogenic lncRNA is HOX transcript antisense RNA (HOTAIR) alleviates cardiac injury in chronic heart failure (HF) by sponging miR-30a-5p to regulate lysine demethylase 3A (18). In addition, HOXA transcript at the distal tip (HOTTIP) knockdown blocks acute MI (AMI) progression, and further mechanistic studies have shown that HOTTIP exerts its effects through miR-92a-2 sponging (19). Moreover, its expression is significantly upregulated in sepsis-induced cardiac dysfunction and is closely associated with the development of cardiac dysfunction (20). In a streptozotocin-induced type 1 diabetes mouse model, HOTAIR overexpression ameliorated cardiac function and alleviated oxidative stress and the inflammatory response, thus providing a possible direction for targeting diabetic cardiomyopathy (21). In summary, these investigations provide a foundation for understanding the role of HOX-lncRNAs in cardiovascular disease. A follow-up delineation of how HOX-lncRNAs regulate cardiovascular biology will advance the current understanding of cardiovascular diseases, including atherosclerosis. Furthermore, molecular insight into atherosclerosis involving HOX-lncRNAs is a prerequisite for developing ground-breaking therapies for early prevention and intervention.

The main aim of the present review was to outline the contributions of HOX-lncRNAs to atherosclerosis and other crucial cardiovascular processes that directly result in the development and progression of cardiovascular events. Collectively, these investigations have provided a landscape in which HOX-lncRNAs can mediate various pathophysiological processes, including lipid metabolism, inflammatory response, angiogenesis, cellular proliferation and apoptosis, cardiac hypertrophy and fibrosis, myocardial ischemia/reperfusion (I/R) injury, cardiomyocyte apoptosis, essential hypertension and pulmonary hypertension, which are closely linked to the pathogenesis of cardiovascular disease. Disentangling the biological mechanism ascribed to HOX-lncRNAs is expected to yield compelling insight for a deeper understanding of cardiovascular dysfunction.

## 2. Brief primer on HOX-lncRNAs and their association with atherosclerosis

*HOX* genes are homeobox-containing protein-coding genes arranged into four HOX clusters at different chromosomal locations that encode numerous highly conserved lncRNAs (17,22). In humans, 18 antisense RNA genes, within the four *HOX* gene clusters, are deposited in the National Center for Biotechnology Information (NCBI) GeneBank database (https://www.ncbi.nlm.nih.gov/). The *HOXA* gene contains six *HOXA* antisense RNA genes, five *HOXB* and *HOXC* regions, and two *HOXD* regions (Fig. 1). HOX-lncRNAs have multifaceted roles in mediating the expression of *HOX* and non-HOX genes (23). Similar to diverse lncRNAs, HOX-lncRNAs govern multiple biological functions, including cell proliferation, apoptosis and the cell cycle, under normal or abnormal pathophysiological conditions (17,24). They exert unique effects owing to their tissue-specific expression in different cellular contexts. Atherosclerosis occurs mainly through stepwise and multistep biological processes involving angiogenesis, lipid metabolism, inflammatory responses, cellular proliferation and apoptosis (5). Various studies have indicated that HOX-lncRNAs participate in these processes through various mechanisms. Therefore, it is important to determine their roles in cardiovascular biology and atherosclerosis. One-third of these antisense RNAs are associated with atherosclerosis development. In the following section, the role of HOX-lncRNAs in atherosclerosis was reviewed, including lipid metabolism, inflammatory responses, angiogenesis, and cellular proliferation and apoptosis, principally focusing on their aberrant expression, cellular biological functions and mechanisms of action in atherosclerosis (Fig. 2 and Table I).

*HOX-lncRNA-mediated lipid metabolism may drive atherosclerosis*. Lipid metabolism disorders are recognized as key risk factors for atherosclerosis. Macrophages and vascular smooth muscle cells (VSMCs) engulf the accumulated lipoproteins [particularly oxidized low-density lipoprotein (ox-LDL)] in the damaged artery wall and finally transform into foam cells (25). At the same time, the accumulation of ox-LDL may result in the formation of lipid streaks and even lipid plaques, thus accelerating the development of atherosclerosis. Several

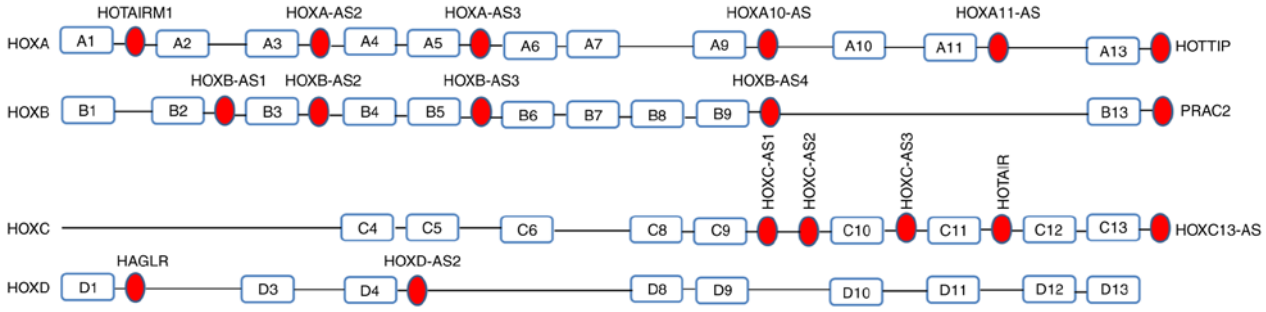


Figure 1. Diagrams of the locations of antisense long non-coding RNAs and HOX genes in the HOX clusters. HOX, homeobox; HOXC-AS1, lncRNA HOXC cluster antisense RNA 1; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip; HAGLR, HOXD antisense growth-associated lncRNA. HOTAIRM1, HOTAIR myeloid-specific 1; PRAC2, PRAC2 small nuclear protein.

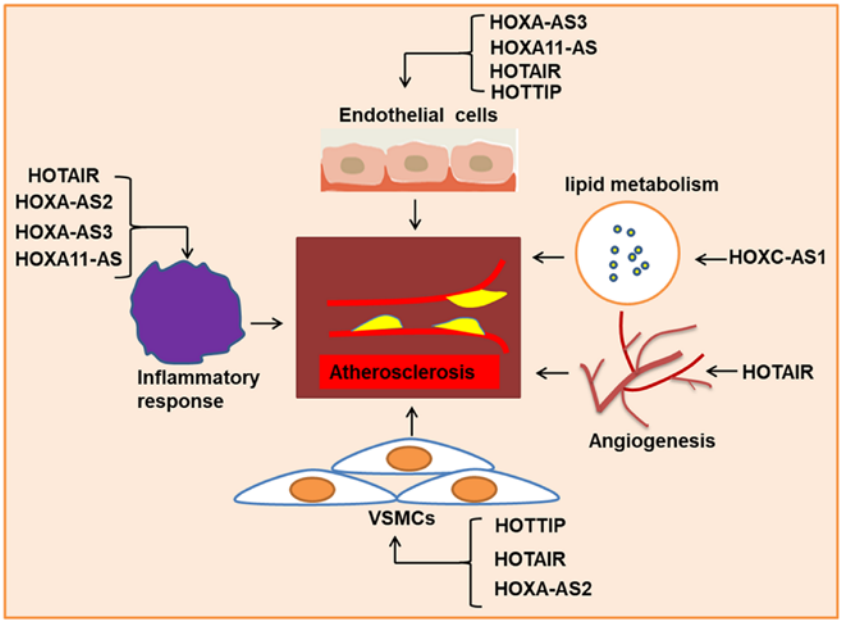


Figure 2. Central Illustration: HOX-lncRNAs involved in atherosclerosis. Emerging evidence indicates that HOX-lncRNAs serve as key regulators of atherosclerosis. Summary of HOX-lncRNAs regulating diverse biological processes involved in the pathogenesis of atherosclerosis. HOX-lncRNAs, homeobox cluster-embedded antisense long non-coding RNAs; HOXC-AS1, lncRNA HOXC cluster antisense RNA 1; VSMC, vascular smooth muscle cell; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip.

studies have indicated that HOX-lncRNAs participate in lipid metabolism. Huang *et al* (26) reported that lncRNA HOXC cluster antisense RNA 1 (HOXC-AS1) expression is downregulated in carotid atherosclerosis. Subsequent research has shown that HOXC-AS1 overexpression partly blocks the cholesterol accumulation induced by ox-LDL in THP-1 macrophages (26), which may provide insight into the regulation of cholesterol homeostasis and suggests that HOXC-AS1 is a promising therapeutic target that governs atherosclerosis. Another study indicated that HOXB-AS3 regulates lipid metabolism in endometrial cancer (27). Gariani and Jornayvaz (28) revealed that HOTAIR knockdown decreases total cholesterol and triglyceride levels. Overall, these data preliminarily show that HOX-lncRNAs have a causal role in lipid metabolism.

*HOX-lncRNAs as key players in the inflammatory response.* The inflammatory response is well-known to have a predominant role in driving the pathogenesis of atherosclerosis (1). Several mechanisms underlying the inflammatory activation of endothelial cells (ECs), foam cell formation and foam cell secretion of inflammatory cytokines contribute to the development of atherosclerosis (29). The persistent activation of the inflammatory response leads to increased EC permeability and higher rates of lipid entry, thus fueling the development of atherosclerosis. Overwhelming findings have displayed the causal effect of HOX-lncRNAs in the inflammatory response. For instance, one of the most studied HOX cluster-embedded lncRNAs is HOTAIR, which resides between *HOXC11* and *HOXC12* in the HOXC cluster on human chromosome 12q13.13 (30). HOTAIR overexpression attenuates the expression of pro-inflammatory cytokines (TNF-α and IL-1β) and potentiates the expression of anti-inflammatory cytokines (IL-4 and IL-10) in Raw264.7 cells exposed to ox-LDL (31). Likewise, another study also reported that HOTAIR facilitates oxidative stress and the inflammatory response by sponging miR-330-5p in human macrophages in the presence of ox-LDL (32). In addition, Lu *et al* (33) found that HOTAIR expression was upregulated in an AMI group compared to that

Table I. Involvement of HOX-lncRNAs in diverse pathophysiological processes in atherosclerosis.

| Functional classification | HOX-lncRNA | Model | Biological functions | Target or pathway | Mode of action | (Refs.) |
|---|---|---|---|---|---|---|
| Lipid metabolism | HOXC-AS1 | THP-1 macrophages | ↓ Ox-LDL-induced cholesterol accumulation | HOXC6 | N.D. | (28) |
| Inflammatory response | HOTAIR | Raw264.7 cells | ↓ Inflammatory response | FXR1/NF-κB pathway | N.D. | (31) |
| | | Macrophages | ↑ Inflammatory response | miR-330-5p | ceRNA | (32) |
| | | Macrophages | ↓ Inflammatory response | NF-κB pathway | N.D. | (40) |
| | | H9C2 cells | ↑ Inflammatory response | miR-138/NF-κB pathway | ceRNA | (33) |
| | | H9C2 cells | ↓ H/R-induced inflammatory | NF-κB pathway | N.D. | (36) |
| | HOXA-AS2 | HAEC/HUECs | ↓ Inflammatory response | NF-κB pathway | N.D. | (37) |
| | HOXA-AS3 | HUVECs | ↑ Endothelium inflammation | NF-κB pathway | N.D. | (38) |
| | HOXA11-AS | VSMCs/VECs | ↑ Endothelium inflammation | PI3K/AKT pathway | N.D. | (39) |
| Angiogenesis | HOTAIR | ECs | ↓ Proliferation, migration, and tube formation | VEGFA | N.D. | (43) |
| | | hBMVECs | ↓ Migratory and tube formation | EZH2 | N.D. | (45) |
| EC proliferation or apoptosis | HOXA-AS3 | HUVECs/mouse | ↑ Atherosclerosis | miR-455-5p/p27 Kip1 | ceRNA | (49) |
| | HOXA11-AS | HUVECs/mouse | ↑ Atherosclerosis | miR-515-5p/ROCK1 | ceRNA | (51) |
| | HOTAIR | ECs | ↑ Proliferation; ↓ Apoptosis | PI3K/AKT-IRF1 pathway | N.D. | (52) |
| | HOTTIP | ECs | ↑ Proliferation and migration | Wnt/β-catenin pathway | N.D. | (53) |
| VSMCs proliferation or apoptosis | HOTTIP | HAVSMCs | ↑ Proliferation and migration | miR-490-3p/HMGB1/PI3K-AKT | ceRNA | (54) |
| | HOTAIR | VSMCs | ↓ Proliferation; ↑ Apoptosis | miRNA-130b-3p/PPARα | ceRNA | (55) |
| | | VSMCs | ↑ Viability and migration | miR-148b-3p | ceRNA | (56) |
| | HOXA-AS2 | VSMCs | ↑ Proliferation; ↓ Apoptosis | miRNA-877-3p | ceRNA | (57) |
| | | VSMCs | ↑ Proliferation | miR-520d-3p/IGF2BP3 | ceRNA | (58) |

↓ indicates that the biological functions are inhibited. ↑ indicates that the biological functions are promoted. N.D., not determined; HOX-lncRNAs, homeobox cluster-embedded antisense long non-coding RNAs; HOXA-AS3, lncRNA HOXA cluster antisense RNA 3; miR, microRNA; ceRNA, competing endogenous RNA; VSMC, vascular smooth muscle cell; EC, endothelial cell; HUVECs, human umbilical vein endothelial cells; NF-κB, nuclear factor-κB; VEGF, vascular endothelial growth factor; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip; ox-LDL, oxidized low-density lipoprotein. HOXC-AS1, lncRNA HOXC cluster antisense RNA 1; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; HOXC6, homeobox C6; HAEC, human arterial endothelial cell; VEC, vascular endothelial cell; HAVSMC, human aortic vascular smooth muscle cell; hBMVEC, human brain microvascular endothelial cell; THP-1, human monocytic leukemia.

in its counterparts. Functionally, HOTAIR overexpression boosts the secretion of inflammatory cytokines, such as IL-6 and TNF-α, in H9C2 cells in the presence of a hypoxia stimulus (33). Nuclear factor-κB (NF-κB), as a major transcription factor involved in inflammatory responses, was first discovered in 1986 (34). NF-κB activators and NF-κB-mediated genes have been determined to participate directly or indirectly in the pathogenesis of atherosclerosis (35). HOTAIR modulates the inflammatory response and oxidative stress in H9C2 cells by affecting the NF-κB pathway, thus protecting cardiomyocytes (36). As a similar regulatory mechanism, it was also reported that lncRNA HOXA cluster antisense RNA 2 (HOXA-AS2)-mediated endothelium protection is partly attributed to inhibition of the NF-κB pathway (37). Another study showed that HOXA-AS3 can interact with NF-κB and positively regulate its activity by modulating the NF-κB inhibitor protein IκBα (38). HOXA11-AS knockdown markedly inhibits the expression of inflammation-related genes induced by TNF-α in VSMCs and by platelet-derived growth factor in vascular endothelial cells (VECs) (39). In addition, HOTAIR expression is upregulated in macrophages upon exposure to lipopolysaccharide (LPS). Furthermore, HOTAIR depletion diminishes NF-κB-mediated inflammatory gene and cytokine expression. Further mechanistic studies have indicated that HOTAIR knockdown leads to reduced expression of NF-κB target genes via a decrease

in the recruitment of NF-κB and associated cofactors at the target gene promoters (40). The inflammatory response normally requires high energy and, hence, is closely related to glucose metabolism. One study showed that HOTAIR has key roles in the expression of glucose transporter isoform 1, which controls glucose uptake by macrophages (41). Ultimately, in LPS-induced H9C2 cells, HOTAIR promotes the inflammatory response and apoptosis by enhancing programmed cell death 4 stability. *In vivo* experiments verified that HOTAIR knockdown alleviates cardiac injury and the secretion of inflammatory factors caused by sepsis (42). These studies suggest that HOTAIR has a significant role in mediating inflammatory responses. In conclusion, HOX-lncRNAs have important roles in inflammatory responses through several mechanisms. Ongoing research and the increasing awareness of HOX-lncRNAs will help to elucidate the important role of HOX-lncRNAs in inflammation and inflammation-mediated atherosclerosis.

*HOX-lncRNA regulation: Angiogenesis-driven atherosclerosis*. EC dysfunction is a primary contributor, driven by pathological angiogenesis within the arterial wall, to the pathogenesis of atherosclerosis (43). Angiogenesis markedly affects plaque growth and the instability of atherosclerotic lesions. Important research has shown that HOTAIR is involved in angiogenesis, and its overexpression resulted in a substantial reduction in EC proliferation, migration and tube formation. Mechanistically, HOTAIR transcriptionally inhibits vascular endothelial growth factor (*VEGF*) via direct binding to its promoter (44). VEGF is a crucial factor associated with angiogenesis (45). Furthermore, a recent study demonstrated that HOTAIR knockdown enhances the migratory and tube formation abilities of oxygen-glucose deprivation/reperfusion-induced human brain microvascular ECs (46). In summary, these data demonstrate a HOTAIR-mediated anti-angiogenic effect, thus blocking the progression of atherosclerosis. However, the role of HOX-lncRNAs in angiogenesis remains unclear and further in-depth studies on this topic will improve the current understanding of angiogenesis relevant to atherosclerosis.

*Modulation of HOX-lncRNAs in cellular proliferation and apoptosis*. VSMCs and VECs are the main cell types involved in atherosclerosis, and their abnormal proliferation and apoptosis have a key role in the development and progression of atherosclerosis (47). Given that the development of atherosclerosis comprises the orchestrated interplay between ECs and SMCs, the following chapters outline the contribution of HOX-lncRNAs to cellular proliferation and apoptosis.

*ECs*. Dysfunction of the endothelial lining of blood vessels is a critical event in atherosclerosis initiation (48). As such, abnormal EC proliferation and apoptosis contribute to this disease (49). Mounting evidence indicates that HOX-lncRNAs are closely related to the proliferation and apoptosis of VSMCs and VECs, suggesting an important role for HOX-lncRNAs in the process of atherosclerosis. HOXA-AS3 expression is upregulated in human umbilical vein ECs (HUVECs) upon ox-LDL stimulation, and its depletion significantly suppresses the progression of atherosclerosis. Mechanistically, it acts as a competing endogenous (ceRNA) for miR-455-5p to decrease the protein level of $p27^{Kip1}$ (50), a cell cycle regulator first identified as a cyclin-dependent kinase antagonist (51). Similarly, the expression of HOXA11-AS is increased in both atherosclerotic mouse aortic tissue and ox-LDL-stimulated HUVECs. HOXA11-AS knockdown markedly blunts the ox-LDL-induced inhibitory effect on cell proliferation and diminished apoptosis in HUVECs, suggesting that HOXA11-AS sponges miR-515-5p to stimulate the expression of rho-associated coiled-coil containing protein kinase 1 (ROCK1), a direct target of miR-515-5p, thus contributing to atherosclerotic injury by directly regulating the miR-515-5p/ROCK1 axis (52). In summary, these observations indicate that HOX-lncRNAs affect the proliferation and apoptosis of VECs through miRNA sponging mechanisms to modulate their target genes. Beyond functioning as ceRNA machinery, HOX-lncRNAs can also modulate the proliferation and migration of ECs by regulating related signaling pathways. An increasing number of studies have shown that HOTAIR has a significant role in cardiovascular biology and diseases. Specifically, its expression is much lower in ECs from atherosclerotic plaques. Functional assays further indicated that HOTAIR facilitates proliferation and migration and suppresses apoptosis in ECs. Mechanistically, HOTAIR, activated by thymic stromal lymphopoietin, regulates the proliferation and migration of ECs via the PI3K/AKT-interferon regulatory factor 1 pathway (53). Finally, HOTTIP expression was reported to be higher in coronary artery disease tissues than in normal tissues, and its depletion was observed to block EC proliferation and migration. Further mechanistic studies indicated that HOTTIP may govern EC proliferation and migration via Wnt/β-catenin pathway activation (54). In addition, HOTAIR facilitates pulmonary VEC apoptosis via the DNMT1-mediated hypermethylation of the Bcl-2 promoter in chronic obstructive pulmonary disease (55). Overall, the increasing evidence presented here underscores the important contribution of HOX-lncRNAs to EC functions, particularly in human EC models.

*VSMCs*. The proliferation and migration of VSMCs are key events in the progression of atherosclerotic lesions and restenosis. Several studies have investigated the potential functions of HOX-lncRNAs in VSMC proliferation and migration. HOTTIP is a well-characterized HOX-lncRNA that is induced in human aortic VSMCs (HAVSMCs) in response to ox-LDL and in the sera of patients with atherosclerosis. Functionally, HOTTIP knockdown suppresses the ox-LDL-induced proliferation and migration of HAVSMCs. Mechanistically, HOTTIP depletion blocks cell proliferation and migration through the regulation of the miR-490-3p/HMGB1 and PI3K-AKT pathways in ox-LDL-induced HAVSMCs (56). Given the recent interest in the interplay between proliferative pathways and atherosclerosis development, HOTAIR may be a prospective target for atherosclerosis interventions. Xue *et al* (57) revealed that HOTAIR overexpression facilitates viability and suppresses apoptosis in VSMCs. Mechanistically, HOTAIR serves as a ceRNA for miR-130b-3p to diminish the expression of peroxisome proliferators-activated receptors α (57). In addition, HOTAIR binds to and negatively

Table II. HOX-lncRNAs in other cardiovascular biology.

| Functional classification | HOX-lncRNA | Model | Biological functions | Target or pathway | Mode of action | (Refs.) |
|---|---|---|---|---|---|---|
| Cardiac hypertrophy | HOTAIR | Cardiomyocytes | ↓ Cardiac hypertrophy | miR-19/PTEN | ceRNA | (59) |
| Cardiac fibrosis | HOTAIR | Fibroblasts | ↑ Myocardial fibrosis | Wnt signaling pathway | N.D. | (60) |
| | | Fibroblasts/mice | ↑ Myocardial fibrosis | Wnt signaling pathway | N.D. | (61) |
| | | Fibroblasts | ↑ Myocardial fibrosis | miR-124 | ceRNA | (62) |
| Myocardial I/R injury | HOTAIR | H9c2 cells/mice | ↑ Myocardial I/R injury | miR-126 | ceRNA | (64) |
| | HAGLR | mice | ↑ Myocardial I/R injury | miR-133a-3p/MAPK1 | ceRNA | (70) |
| Cardiomyocyte apoptosis | HOTAIR | H9c2 | ↓ Apoptosis | miR130a3p/MDM4 | ceRNA | (72) |
| | | H9c2 | ↑ Cell viability; ↓ Apoptosis | miR-206/FN1 | ceRNA | (73) |
| | HOTTIP | Cardiomyocytes | ↓ Apoptosis after HOTTIP knockdown | miR-92a-2/c-Met | ceRNA | (19) |
| Pulmonary hypertension | HOXA-AS3 | HPASMCs | ↑ Growth and migration; ↓ Apoptosis | miR-675-3p | ceRNA | (83) |

↓ indicates that the biological functions are inhibited. ↑ indicates that the biological functions are promoted. N.D., not determined; HOX-lncRNAs, homeobox cluster-embedded antisense long non-coding RNAs; HOXA-AS3, lncRNA HOXA cluster antisense RNA 3; miR, microRNA; ceRNA, competing endogenous RNA; I/R, ischemia/reperfusion; HPASMCs, human pulmonary artery smooth muscle cells; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip; PTEN, phosphatase and tensin homolog; MDM4, MDM4 regulator of p53; FN1, fibronectin 1.

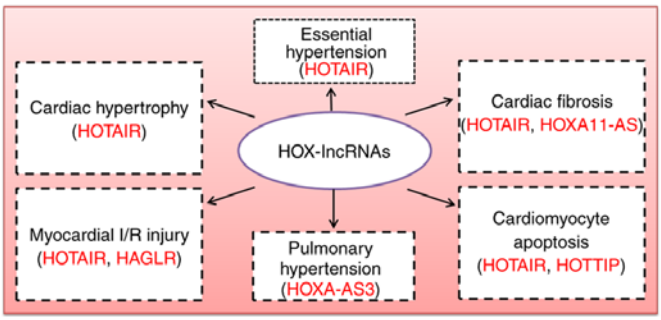


Figure 3. Interplay between HOX-lncRNAs and other aspects of cardiovascular biology. HOX-lncRNAs, homeobox cluster-embedded antisense long non-coding RNAs; HOXA-AS3, lncRNA HOXA cluster antisense RNA 3; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip; HAGLR, HOXD antisense growth-associated lncRNA.

regulates miR-148b-3p, leading to increased VSMC viability and migration (58). The lncRNA HOXA-AS2, located between and antisense to human *HOXA3* and *HOXA4*, has been reported to potentiate the proliferative and migratory abilities and decrease the apoptosis of VSMCs by absorbing miR-877-3p (59). Recently, HOXA-AS2 was found to be highly expressed in thoracic aortic aneurysm (TAA) tissues. HOXA-AS2 upregulates the expression of NHS like 3 by targeting miR-520d-3p/IGF2BP3 to drive VSMC growth in TAA (60). Therefore, HOX lncRNAs are important regulators of VSMC proliferation and migration. However, further investigations are necessary to determine the significance of HOX-lncRNAs in regulating VSMC proliferation.

## 3. HOX-lncRNAs and other aspects of cardiovascular biology

Beyond the discussion of relevant events concerning HOX-lncRNAs described previously herein, HOX-lncRNAs have been implicated in other aspects of cardiovascular biology associated with diverse cardiovascular diseases. Given that the role of HOX-lncRNAs in cardiovascular diseases has been increasingly confirmed in recent years, in addition to discussing the function of HOX-lncRNAs in atherosclerosis, the following section reviews the relevance of HOX-lncRNAs to other cardiovascular processes, such as cardiac hypertrophy, fibrosis, myocardial I/R injury, cardiomyocyte apoptosis, essential hypertension and pulmonary hypertension (Fig. 3 and Table II). These studies are expected to reveal a more profound molecular landscape of HOX-lncRNAs involved in cardiovascular dysfunction.

*HOX-lncRNA involvement in cardiac hypertrophy and fibrosis*. Cardiac hypertrophy is an initial adaptive response to various stresses, including pressure or volume overload, which lowers the increase in the wall tension and aids in maintaining cardiac output. This adaptive process is beneficial and can ameliorate cardiac functions; however, persistent exposure of the heart to increased workload leads to impaired blood flow, resulting in relative hypoxia and the subsequent loss of cardiomyocytes, ultimately causing HF. Cardiac fibrosis is closely associated with numerous heart diseases, such as chronic HF, MI, malignant arrhythmia and sudden cardiac death, and is a key pathological feature of cardiac remodeling.

Lai *et al* (61) reported that HOTAIR expression is downregulated in heart tissues from transverse aortic constriction-operated mice *in vivo* and in cultures treated with Ang-II *in vitro*. Its overexpression reduces the cell surface area and expression of the hypertrophic markers atrial natriuretic peptide, brain natriuretic peptide and β-myosin heavy chain in response to Ang-II. Regarding its molecular mechanisms in cardiac hypertrophy, HOTAIR may act as a ceRNA for miR-19, thereby modulating its target PTEN and playing an important role in inhibiting cardiac hypertrophy progression (61). Therefore, HOTAIR may have a key role in the regulation of cardiac hypertrophy. Ang-II upregulates HOTAIR expression in cardiac fibroblasts (CFs), which promotes cell proliferation and inhibits apoptosis. The mechanism by which HOTAIR regulates myocardial fibrosis may be related to activation of the Wnt signaling pathway by targeting uRI1 prefoldin like chaperone (62). Similarly, Tan *et al* (63) found that HOTAIR silencing significantly diminishes Ang-II-induced proliferation, migration and fibrosis in fibroblasts. Moreover, HOTAIR knockdown was found to markedly inhibit fibrosis in the heart tissues of atrial fibrillation (AF)-model mice via the regulation of Wnt signaling. Recently, Jiang *et al* (64) showed that HOTAIR functions as a ceRNA of miR-124 to promote myocardial fibrosis. Therefore, HOTAIR may have a role in cardiac fibrosis. In addition, another study showed that HOXA11-AS overexpression in CFs enhances the expression of transforming growth factor β1, a classic and powerful fibrogenic pathway mediator pertinent to cardiac fibrosis, thus contributing to cardiac fibrosis progression (65). Collectively, HOX-lncRNAs, such as HOTAIR and HOXA11-AS, appear to have prominent roles in regulating cardiac hypertrophy and fibrosis.

*Regulation of myocardial I/R injury by HOX-lncRNAs*. I/R injury is a major cause of the necrotic, apoptotic and autophagic death of cardiomyocytes. In recent years, studies have shown that HOX-lncRNAs have a protective effect against myocardial I/R injury. For instance, Sun and Hu (66) found that HOTAIR expression is upregulated in mice after I/R and in $H_2O_2$-induced H9c2 cells. Overexpression of HOTAIR markedly suppressed viability and increased lactate dehydrogenase release and caspase-3 activity in H9c2 cells treated with $H_2O_2$, and further mechanistic studies implied that HOTAIR aggravates myocardial I/R injury by sponging miR-126 to upregulate serine and arginine rich splicing factor 1 expression (66). Furthermore, propofol (PPF) has certain protective effects against myocardial I/R injury (67). Chen *et al* (68) showed that PPF pretreatment markedly upregulated HOTAIR expression and that HOTAIR knockdown partially reversed the protective effects of PPF on myocardial I/R injury. Likewise, HOTAIR, as a ceRNA, affects myocardial I/R injury via a HOTAIR/miRNA-1/connexin-43 axis (69). In conclusion, these data suggest that HOTAIR is of paramount importance for myocardial I/R injury. In addition to HOTAIR, expression of HOXD antisense growth-associated lncRNA (HAGLR), also known as HOXD-AS1 and Mdgt, whose gene is located in the intergenic region between *HOXD1* and *HOXD3*, has been reported to be significantly increased upon I/R *in vivo* or hypoxia-reoxygenation *in vitro*. HAGLR knockdown attenuated myocardial I/R injury, and mechanistically, HAGLR increases myocardial I/R injury by inhibiting miR-133a-3p, thereby promoting MAPK1 expression (70). Taken together, HOTAIR and HAGLR may be therapeutic targets for the treatment of myocardial I/R injury and much work is needed to fully understand how HOX-lncRNAs coordinate myocardial I/R injury.

*Involvement of HOX-lncRNAs in cardiomyocyte apoptosis*. Cardiomyocyte apoptosis, or programmed cell death, is a pivotal pathological manifestation of I/R injury and the primary cause of cardiac dysfunction (71). Therefore, an in-depth understanding of the mechanism underlying cardiomyocyte apoptosis is key to preventing myocardial injury and treating heart disease. Recently, HOX-lncRNAs were reported to be involved in cardiomyocyte apoptosis. For instance, HOTAIR, which is significantly downregulated in the ischemic myocardium of rats, inhibits H9c2 cell apoptosis induced by $H_2O_2$ *in vitro*. Mechanistically, HOTAIR binds to miR-130a-3p and acts as a sponge to block its functions in I/R injury (72). Similar results were obtained when determining the role of HOTAIR in AMI. Its expression was found to be substantially downregulated in the serum of patients with AMI and in mice. Furthermore, HOTAIR overexpression was found to promote H9c2 cell viability and inhibit apoptosis under hypoxic conditions *in vitro*. The mechanism was attributed to miR-206 binding fibronectin 1 (73). In addition, HOTTIP levels were determined to be significantly upregulated in the ischemic myocardium of mice with MI and in hypoxia-induced cardiomyocytes. Furthermore, HOTTIP functions as a ceRNA of miR-92a-2 to enhance c-Met expression and is involved in the modulation of cardiomyocyte growth and apoptosis, indicating that it is a potential therapeutic target for AMI (19). Ongoing investigations are needed to further determine their relevant roles.

*HOX-lncRNAs and essential hypertension*. Essential hypertension is a common and frequently occurring disease and a risk factor for various cardiovascular and cerebrovascular diseases. In recent years, the search for ncRNAs has attracted the attention of many researchers. According to reports, increasing studies have shown that lncRNAs have important roles in the occurrence and development of essential hypertension (74-78). As a special type of lncRNA, the roles of HOX-lncRNAs in essential hypertension have rarely been studied. However, studies have shown that HOTAIR expression is significantly downregulated in stroke patients with hypertension compared to that in stroke patients without hypertension (79), suggesting that it may be closely related to the occurrence and development of hypertension and that it could be used as a biomarker for the diagnosis and treatment of this condition.

*HOX-lncRNAs and pulmonary hypertension*. Pulmonary arterial hypertension (PAH) is a vascular remodeling disease characterized by vasoconstriction and progressive obliteration of the distal pulmonary arteries, leading to elevated pulmonary pressure and eventually right ventricular HF (80,81). Pulmonary vascular remodeling is characterized by the excessive proliferation of pulmonary arterial smooth muscle cells (PASMCs) and the dysfunction of pulmonary arterial ECs (82). Therefore, it is important to explore the cellular mechanisms underlying

the effects of HOX-lncRNAs in pulmonary VSMCs and in the pathogenesis of pulmonary hypertension. HOXA-AS3 is a novel lncRNA that is transcribed from the *HOXA* cluster. A previous study showed increased HOXA-AS3 levels in human (H)PASMCs exposed to hypoxia. Furthermore, its knockdown decreased growth and migration and induced apoptosis in HPASMCs. The mechanism associated with the effects of HOXA-AS3 was also examined; it was found to upregulate phosphodiesterase 5A expression by sponging miR-675-3p (83). Another study showed that HOXA-AS3 knockdown represses PASMC proliferation *in vitro* (84), thus providing a potential novel strategy for the treatment of PAH.

## 4. HOX-lncRNAs as potential diagnostic biomarkers for cardiovascular disease

Given the significant recent studies demonstrating the role of HOX-lncRNAs in cardiovascular diseases, outlined previously herein, there may be opportunities to treat these diseases by targeting these molecules. The cell and tissue specificity of HOX-lncRNAs makes them potential diagnostic markers for cardiovascular diseases. Mounting evidence suggests that HOX-lncRNAs are differentially expressed in various cardiovascular diseases. For instance, HOTAIRM1, HOXA-AS2 and HOXB-AS2 expression was found to be significantly downregulated in epicardial adipose tissue associated with AF using RNA sequencing (85). Likewise, HAGLR and HOTAIRM1 have robust diagnostic value for AF, which may facilitate the discovery of novel diagnostic biomarkers or therapeutic targets (86). Studies have indicated that HOTAIR can be used as a biomarker for the diagnosis of congenital heart disease (87) and AMI (88). Furthermore, another study indicated that the expression of HOTAIR is significantly downregulated with chronic HF (89). Finally, HOXA11-AS expression is downregulated in the plasma of patients with in-stent restenosis (ISR) compared to that in patients without ISR, and it was found to be an independent protective factor for ISR (90). In summary, the large amounts of data presented provide evidence for the use of HOX-lncRNAs as diagnostic markers of cardiovascular diseases, and future in-depth studies of these markers are expected to contribute to their use as potential therapeutic targets. However, more studies regarding HOX-lncRNAs are essential to affirm their feasibility as diagnostic biomarkers.

## 5. Concluding remarks

For decades, investigations into cardiovascular biology have primarily highlighted the involvement of protein-coding genes. Recently, a new class of molecules, termed lncRNAs, has been shown to have pivotal regulatory roles in coordinating multiple cellular functions, coupled with a high degree of tissue and cell specificity, making them promising target candidates for clinical practice. LncRNAs have also emerged as potential modulators of atherosclerosis and other cardiovascular events. Recently, a unique class of functional molecules, HOX-lncRNAs, has emerged. Of note, the modulation of HOX-lncRNAs has an impact on diverse aspects cardiovascular biology to a certain extent. The present review focused on the contributions of HOX-lncRNAs to atherosclerosis and the key biological processes relevant to cardiovascular problems, including cardiac hypertrophy, fibrosis, myocardial I/R injury, cardiomyocyte apoptosis, pulmonary hypertension and essential hypertension.

First, the research progress associated with HOX-lncRNAs in atherosclerosis was discussed, including abnormal lipid metabolism, inflammatory responses, angiogenesis and the proliferation and apoptosis of vascular cells. In view of this research, HOX-lncRNAs have broad prospects in atherosclerosis, indicating that they may serve as biomarkers or targets for the diagnosis and treatment of this disease. The present review then continued to explore the effects of HOX-lncRNAs on cardiomyocyte hypertrophy, cardiomyocyte apoptosis, myocardial fibrosis, myocardial I/R injury, essential hypertension and pulmonary hypertension, indicating that HOX-lncRNAs have an important role in these cardiovascular events. This report also provides a theoretical foundation for future research. In terms of the mechanism of action, it was indicated that HOX-lncRNAs can regulate the expression of downstream target genes as ceRNAs, via RNA-binding proteins and through epigenetic mechanisms. Transcription factors can bind to the promoter region of HOX-lncRNAs, thereby activating or inhibiting their transcription. In the present review, HOX-lncRNAs were mainly considered to be involved in the regulation of gene expression through ceRNA mechanisms. Other related upstream and downstream regulatory mechanisms have not yet been reported.

A preponderance of research suggests that HOX-lncRNAs are vital mediators with multifaceted roles in the pathogenesis of atherosclerosis and other cardiovascular diseases. This report provides insight into the regulation and function of HOX-lncRNAs in atherosclerosis and other cardiovascular diseases. However, given that the investigation of HOX-lncRNAs still seems to be preliminary, with deeper insight into their functions and mechanisms needed, work in this field appears to have merely scratched the surface. Consequently, a further in-depth understanding of how HOX-lncRNAs govern atherosclerosis could be very informative for the development of novel diagnostic and therapeutic strategies. The increasingly substantial data on the role of HOX-lncRNAs in the regulation of cardiovascular dysfunction will help to understand atherosclerosis or atherosclerotic cardiovascular disease.

## 6. Future outlook and challenge

To date, several HOX-lncRNAs have been identified as having a role in atherosclerosis, potentially providing a promising direction for numerous novel research areas pertaining to the cardiovascular system. However, to unequivocally understand the roles of HOX-lncRNAs in atherosclerosis, numerous important pressing questions remain.

i) Based on the detailed overview of the role of HOX-lncRNAs in atherosclerosis and cardiovascular biology, it is not difficult to see that the knowledge of the regulatory effects of HOX-lncRNAs on atherosclerosis is still not complete, with the focus of research in this area being principally concentrated on *in vitro* culture experiments and less known concerning such roles *in vivo*. Moreover, the mechanisms underlying the effects of HOX-lncRNAs are mainly limited to their role as ceRNAs, and other mechanisms, such

as RNA-RNA, RNA-DNA and RNA-protein interactions have not yet been characterized. The upstream regulatory circuits of HOX-lncRNAs also remain elusive and the reasons for their abnormal expression in atherosclerosis remain largely unexplored. In addition, in terms of HOX-lncRNAs, HOTAIR has been most extensively studied in the cardiovascular field; however, other HOX-lncRNAs have not been studied in detail. Consequently, HOTAIR is likely to be a biomarker for the diagnosis or treatment of cardiovascular diseases, but further research is needed to investigate this function. Meanwhile, abundant investigations will be launched on HOX-lncRNAs, and their functions in cardiovascular diseases have been rigorously assessed using the most robust approaches available, and these HOX-lncRNAs may have unique and critical roles in the cardiovascular field.

ii) The expression levels of multiple lncRNAs are relatively low, which leads to uncertainties regarding the reliability and reproducibility of large-scale lncRNA investigations. Therefore, a novel platform for HOX-lncRNA capture and quantification is urgently required to enhance the efficiency of the detection of HOX-lncRNA expression.

iii) The roles of more than half of the HOX-lncRNAs in atherosclerosis, i.e., HOXA10-AS, HOXB-AS1, HOXB-AS3, HOXB-AS4, PRAC2, HOXC-AS2, HOXC-AS3, HOXC13-AS and HOXD-AS2, are currently unclear. Therefore, the further investigation of HOX-lncRNAs in atherosclerosis is a prospective area for future research.

iv) Eventually, and perhaps the most key and unaddressed issue in this discussion, is how to translate these findings regarding HOX-lncRNAs from seemingly far-reaching fundamental insight into daily clinical practice. One challenge remains in terms of the conservation of HOX-lncRNAs across species; hence, the functional significance of substantially defined HOX-lncRNAs in atherosclerosis is frequently unclear. A wealth of clinical trials is also necessary to address off-target effects and determine the safety and efficacy of targeting HOX-lncRNAs. Integrated approaches based on multiomics and multilevel data are prerequisites for transforming molecular findings into clinical practice to treat cardiovascular diseases, including atherosclerosis. Addressing these pressing questions promises to yield pivotal insight into not only atherosclerosis, but also the increasingly sophisticated cardiovascular events with which it is associated. The insight on this horizon will advance our understanding of diverse HOX-lncRNAs, thereby enabling the information gained from the study of one HOX-lncRNA to be more reliably leveraged to further understand numerous other related molecules, ultimately providing a firm grasp of the number of the thousands of HOX-lncRNA genes found in the cell that are functional.

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## Authors' contributions

YZ wrote the manuscript. QW provided the research direction. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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