Deciphering the emerging landscape of HOX genes in cardiovascular biology, atherosclerosis and beyond (Review)

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Abstract. Atherosclerosis, a dominant driving force underlying multiple cardiovascular events, is an intertwined and chronic inflammatory disease characterized by lipid deposition in the arterial wall, which leads to diverse cardiovascular problems. Despite unprecedented advances in understanding the pathogenesis of atherosclerosis and the substantial decline in cardiovascular mortality, atherosclerotic cardiovascular disease remains a global public health issue. Understanding the molecular landscape of atherosclerosis is imperative in the field of molecular cardiology. Recently, compelling evidence has shown that an important family of homeobox (HOX) genes endows causality in orchestrating the interplay between various cardiovascular biological processes and atherosclerosis. Despite seemingly scratching the surface, such insight into the realization of biology promises to yield extraordinary breakthroughs in ameliorating atherosclerosis. Primarily recapitulated herein are the contributions of HOX in atherosclerosis, including diverse cardiovascular biology, knowledge gaps, remaining challenges and future directions. A snapshot of other cardiovascular biological processes was also provided, including cardiac/vascular development, cardiomyocyte pyroptosis/apoptosis, cardiac fibroblast proliferation and cardiac hypertrophy, which are responsible for cardiovascular disorders. Further in-depth investigation of HOX promises to provide a potential yet challenging landscape, albeit largely undetermined to date, for partially pinpointing the molecular mechanisms of atherosclerosis. A plethora of new targeted therapies may ultimately emerge against atherosclerosis, which is rapidly underway. However, translational undertakings are crucially important but increasingly challenging and remain an ongoing and monumental conundrum in the field.

Contents

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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HOX, homeobox; HD, homeodomain; HX, hexapeptide motif; Ox-LDL, oxidized low-density lipoprotein; LDL, low-density lipoprotein; BMP4, bone morphogenetic protein 4; ECs, endothelial cells; VSMCs, vascular smooth muscle cells; CAS, carotid atherosclerosis; HOX-lncRNAs, HOX cluster-embedded lncRNAs; EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; TNF, tumor necrosis factor; PPARγ, peroxisome proliferator-activated receptor γ; MED1, mediator subunit 1; TGF-β1, transforming growth factor β1

Key words: HOX gene, atherosclerosis, cardiovascular biology, cardiovascular disease

1. Introduction

Atherosclerosis is a chronic inflammatory disease triggered by the accumulation of cholesterol-containing low-density lipoprotein (LDL) particles in the vessel walls (1). An atherosclerosis epidemic has swept across the world, setting the stage for diverse cardiovascular diseases, such as myocardial infarction, angina and stroke (2,3), now accounting for the majority of morbidity and mortality worldwide. Atherosclerosis, which occurs principally in large- and medium-sized arteries and consists of a lipid core and an outer fibrous cap (4), is a complex but coordinated pathophysiological process that involves endothelial damage, macrophage phagocytosis of lipids into foam cells and inflammatory cell infiltration. Investigating the findings of atherosclerosis can promote a better understanding of its pathogenesis. However, the etiology of atherosclerosis remains unclear and difficult to decipher. Thus, the characterization of atherosclerosis is crucial for a thorough understanding.

Recently, the discovery of an attractive group of mediators known as the homeobox (HOX) has revealed causality in various biological processes and diseases. Overwhelming data on HOX genes have highlighted their roles in diverse cancers, such as colorectal cancer (5), breast cancer (6) and lung cancer (7). Burgeoning observations indicate that interrogation of the HOX gene is an emerging area of focus in cardiovascular biology and disease. Previous studies have underscored the role of HOX in the modulation of cardiac and vascular development (8-10). A recent study suggested that HOXA1 participates in the modulation of viability and migration of long noncoding (lnc)RNA ROR-mediated biological characteristics in ox-LDL-induced human umbilical vein endothelial cells (HUVECs) (11). Another study showed that HOXA5 protects against carotid atherosclerosis development by suppressing the phenotypic transformation of vascular smooth muscle cells (VSMCs) from a contractile to a synthetic form via activation of peroxisome proliferator-activated receptor γ (PPARγ) (12). Therefore, these data implicate HOX in cardiovascular biological processes, suggesting that it may be linked to cardiovascular disease. A strong focus has been placed not only on the exploration of their biological function, but also on unscrambling how the HOX gene comes into play at the molecular level in atherosclerosis.

In the present opinion article, the various mechanisms by which HOX gene surveillance influences atherosclerosis and other cardiovascular diseases was primarily highlighted, initially providing a detailed description of HOX gene-mediated pathophysiological processes regarding the onset and progression of atherosclerosis. This is followed by HOX gene involvement revelation in other pivotal biological processes, including cardiac/vascular development, cardiomyocyte pyroptosis/apoptosis, cardiac fibroblast proliferation and cardiac hypertrophy, which are pertinent to diverse cardiovascular problems. Finally, knowledge gaps, intriguing outlook and future directions of HOX in atherosclerosis are discussed. Such findings regarding the HOX gene will provide novel and unexpected insight with major potential to advance our understanding of normal physiology and cardiovascular diseases, including atherosclerosis. Collectively, the present study offers a compendium for understanding new potential targets of atherosclerosis with significance in the amelioration of atherosclerotic cardiovascular diseases. Despite the significant progress thus far, major challenges and conundrums remain.

2. A general characterization of HOX genes

The HOX gene family is an ancient and highly conserved group of transcription factors (TFs) that modulates master developmental processes, such as anteroposterior body axis patterning, organ morphogenesis and cell fate determination. In humans, 39 HOX genes are arranged in four clusters (HOXA, HOXB, HOXC and HOXD), located on diverse chromosomes (7p15.2, 17q21.32, 12q13.13 and 2q31.1) (13). Each cluster includes 9 to 11 paralog HOX genes, numbered 1 to 13 based on their 3' to 5' chromosomal position (Fig. 1A) (14). Initially, HOX was found to be a set of transcriptional modulators that have a crucial role in embryogenesis and body segmentation in *Drosophila* (15). Structurally, HOX contains two exons and an intron, and its functions depend on an evolutionarily conserved 60 amino acid homeodomain (HD) and a hexapeptide motif (HX) (Fig. 1B). The HD is mainly responsible for DNA binding at specifically recognized sites, leading to transcriptional inhibition or activation of target genes (16,17). HX is indispensable for binding to co-factors, such as members of the three-amino acid loop extension-TALE group (63-amino acid HD) of potential barrier chromatography proteins (18). DNA-binding is determined by helix 3 along the N-terminal arm, which identifies only four base-pair sequences (TAAT, ATTA, TTAT and ATAA), indicating low functional specificity (19). HOX genes located at the 3' end of the cluster are expressed earlier in development and in more anterior body regions, whereas those at the 5' end are expressed during later development (20). Functionally, HOX has a pivotal role in embryonic development and multiple adult tissues. HOX is initially expressed during embryogenesis, where it orchestrates a plethora of developmental processes, including limb formation, anterior-posterior axis patterning, craniofacial morphogenesis and the development of the central nervous system. It also modulates a multitude of biological processes, signaling molecules, components of various signaling pathways and other TFs (21). At the cellular level, HOX is a major regulator of various biological processes, including cell death, proliferation, differentiation, migration and apoptosis (17). Mechanistically, the mode of action is mainly via transcriptional activation or repression of target genes (Fig. 1C) (22). In addition, HOX TFs can bind enhancers, promoters and intronic and intergenic regions via interactions with histone-modifying groups and co-factors (23). However, the molecular mechanisms underlying transcriptional regulation by HOX remain unclear and only a few HOX-dependent molecular pathways have been characterized. Hence, substantial efforts are required to elucidate the underlying molecular mechanisms. In addition to its transcriptional regulatory roles, HOX also has non-transcriptional functions. They have roles in DNA damage repair (24), replication (25), translation initiation (26), protein degradation (27) and mRNA processing (26). Therefore, HOX modulates gene expression at multiple levels. The upstream regulatory mechanism of HOX is tightly regulated by a multilayered regulatory system comprising promoter DNA methylation, histone methylation, regulation by other transcription factors and post-transcriptional modulation by non-coding RNA (14).

3. A central role for HOX genes in atherosclerosis

Probing the molecular and cellular events that occur during atherosclerosis may provide new therapeutic strategies for its development. Recently, there has been increasing interest in unscrambling the HOX gene in cardiovascular diseases (28,29). Atherosclerosis is the most common underlying pathology of cardiovascular disease. Hence, extensive studies have shown that the HOX gene has a central role in atherosclerosis; for instance, HOXA1 participates in atherosclerosis via the microRNA (miR)-99a-5p-HOXA1 axis (30). The development of targeted therapies against HOX in atherosclerosis is a promising research direction. The initiation of atherosclerosis is largely a response to an imbalance in cardiovascular biology. In the following section, the prominent molecular events governed by HOX in atherosclerosis pathogenesis are emphasized, with a particular focus on lipid metabolism,

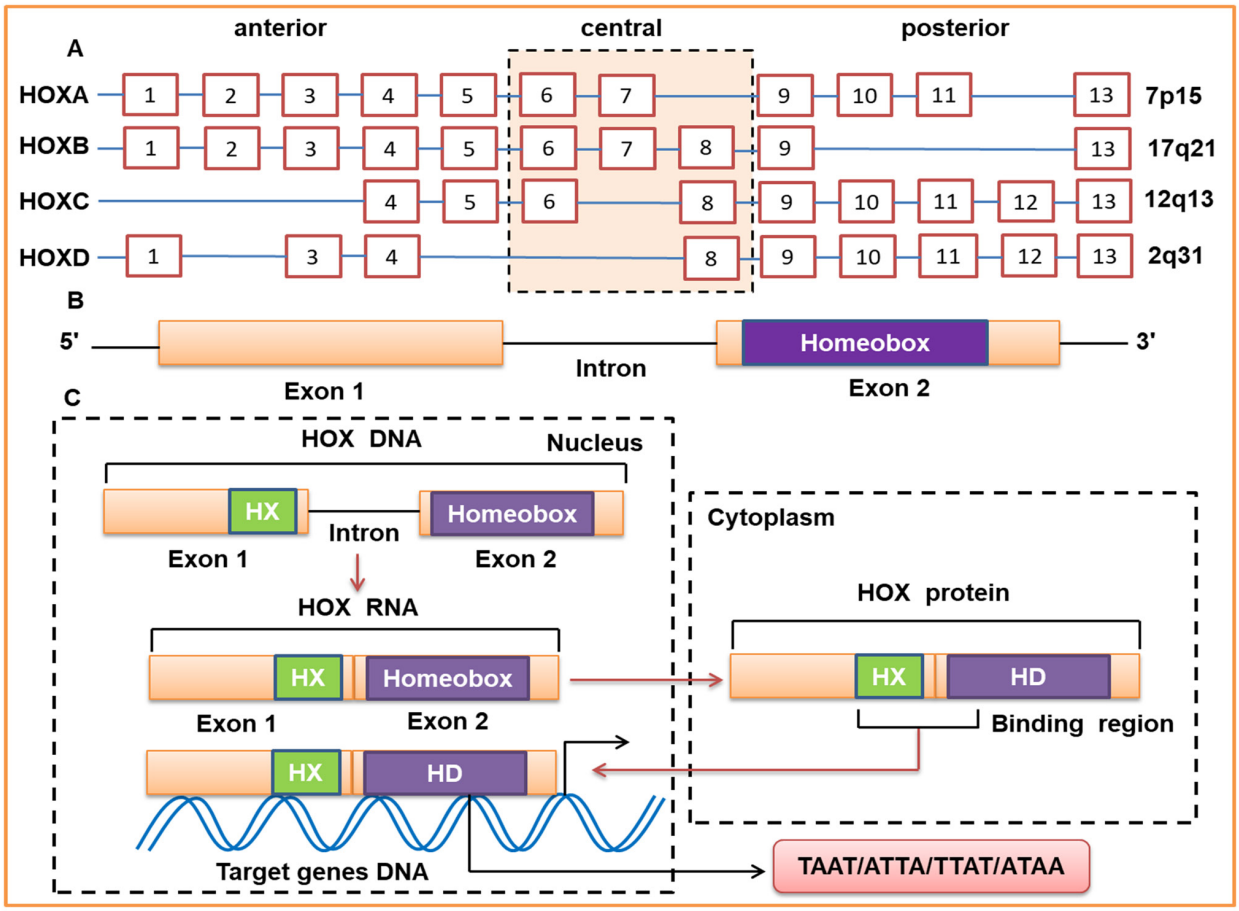

Figure 1. HOX gene genome organization and structure as well as main transcriptional role. (A) In humans, the 39 human HOX genes are clustered into the four HOX families HOXA, HOXB, HOXC and HOXD, with each family consisting of 9 to 11 paralogous genes. (B) HOX genes contain two exons and a single intron. Exon 2 contains a 120-nucleotide sequence, known as HOX. This HOX encodes a 60 amino acid DNA-binding domain known as the HOX (homeodomain). (C) For the transcriptional roles, HOX proteins bind to promoter regions of the target genes to activate or repress target gene transcription. HD, homeodomain; HX, hexapeptide; HOX, homeobox.

inflammatory response, angiogenesis, cellular proliferation and apoptosis, vascular remodeling and macrophage polarization (Fig. 2 and Table I).

HOX gene-mediated lipid metabolism may drive atherosclerosis. Oxidized LDL (ox-LDL) particles are associated with atherosclerosis (31,32). LDL accumulation during atherosclerosis initiates distinct pathological processes, including endothelial damage, foam cell formation and inflammation (33). However, the mechanism by which ox-LDL contributes to atherosclerosis remains largely unknown. Previously published observations showed that HOXC6 may be an orchestrator involved in ox-LDL regulation, indicating that HOXC6 may exert a critical effect on lipid metabolism (34). The mechanism of relevant events is currently unclear and there is still a long journey ahead to understand the function and mechanism of the HOX gene. Furthermore, studies focusing on the mechanism of HOX in lipid metabolism are lacking; therefore, further investigations are warranted to decipher their interplay.

HOX genes as a key player in inflammatory response. Atherosclerosis is a chronic inflammatory disease of the vessel walls that occurs in response to inflammatory response (35). Besides affecting lipid metabolism, multiple lines of evidence have documented that HOX participates in the pathophysiology of atherosclerosis by tuning inflammatory processes. For instance, HOXA5 overexpression dampens inflammation by inhibiting tumor necrosis factor (TNF)-α-inducible monocyte binding to HUVECs (36,37). Consistent with this, HOXA5 knockdown leads to endothelial inflammation in lipopolysaccharide-induced cells (38). Another study has reported that HOXA5 is an atheroprotective gene that suppresses blood flow-dependent endothelial inflammation (39). The activation of NF-κB is in response to inflammatory stimuli and has emerged as a gene essential for a plethora of inflammatory response processes. HOXA9 depletion leads to both a decrease in the inflammatory status and amelioration of the microcirculation of coronary arteries in atherosclerotic rats via downregulation of platelet factor 4, E-selectin and vascular cell adhesion molecule-1 protein (40). As such, HOXA9 was found to be involved in regulating the cellular processes of ECs, and HOXA9 knockdown suppressed E-selectin expression in response to inflammatory cytokines, which is an endothelial mediator of the initial adhesion of leukocytes to the endothelium during inflammation (41). Trivedi *et al* (42) demonstrated that HOXA9 participates in maintaining the inactivated state of ECs and inhibits the expression of adhesive

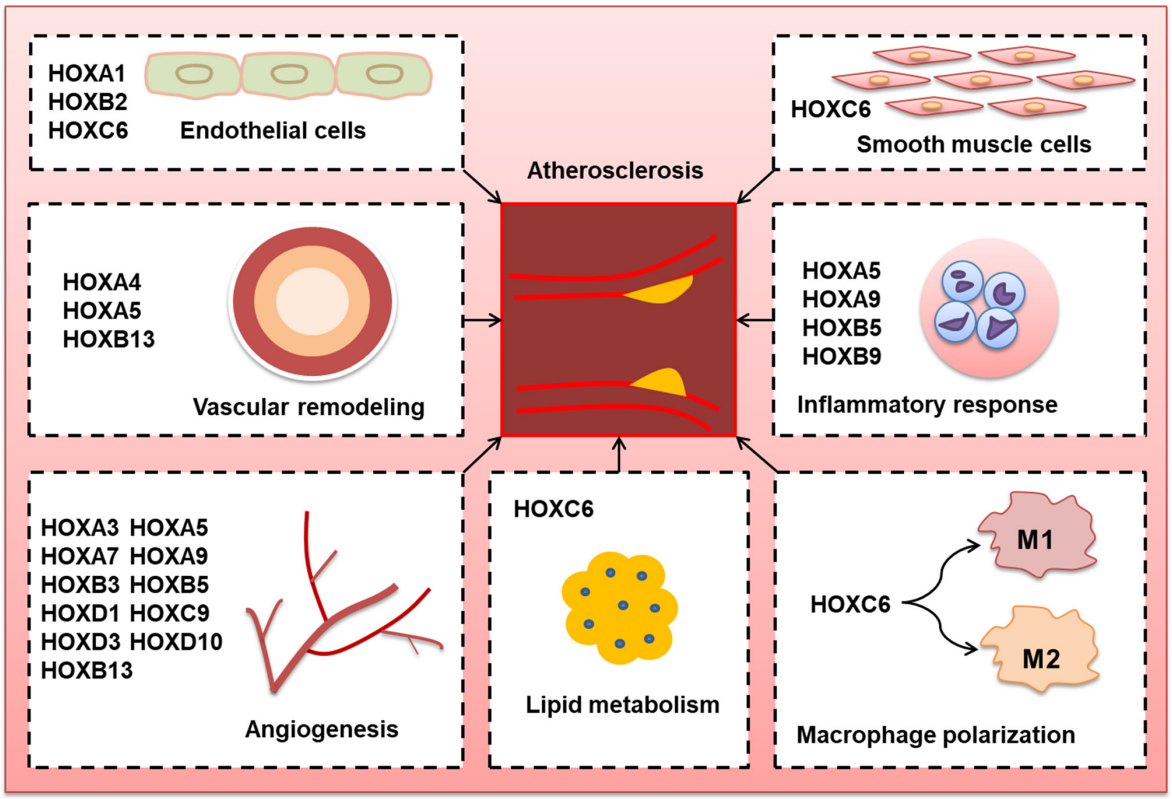

Figure 2. Schematic of the involvement of HOX genes in atherosclerosis. Abundant evidence indicates that the HOX gene, as a key regulator, has a crucial role in atherosclerosis. The framework of HOX genes regulating diverse biology responsible for the pathophysiological processes of atherosclerosis is provided. HOX, homeobox.

factors induced by TNF-α through inhibiting NF-κB. In addition, HOXA9 downregulation is considered an essential event for endothelial cell activation in response to TNF-α (43). The expression of HOX paralogs is often governed by the same regulatory mechanisms as the concerted expression of HOX genes that occurs during development. As a paralog of HOXA9, HOXB9 interacts with bone morphogenetic protein 4 to initiate endothelial cell inflammation in atherosclerosis (44). Another study suggested that HOXB5 overexpression was able to enhance blood vessel perfusion *in vivo* by increasing major capsid protein-1 and IL-6 expression and enhancing leukocyte infiltration and blood vessel remodeling in ischemic diseases (45). Despite their overwhelming roles in the inflammatory response, there appears to be a large lacuna in characterizing the concrete mechanisms that orchestrate these causalities; thus, a rigorous and thorough investigation of HOX genes in the inflammatory response needs to be conducted in the future.

HOX gene regulation: Angiogenesis-driven atherosclerosis. Inflammation is closely associated with atherosclerosis occurrence and development. Inflammation and angiogenesis are intertwined in atherosclerosis. The initiation of atherosclerosis is partly due to the modulation of angiogenesis. It markedly affects plaque growth and causes instability in atherosclerotic lesions. Recently, substantial efforts have been devoted to elucidating the role of HOX in angiogenesis. HOXA3 contributes to angiogenesis in endothelial and epithelial cells (46). Similarly, HOXD3 has a key role in promoting angiogenesis *in vivo* by modulating integrins (47). Conversely, HOXD10 and HOXA5 are anti-angiogenic genes that have a fundamental role in suppressing angiogenesis (48,49), and it was indicated that HOXA5 functions by downregulating pro-angiogenic genes, including VEGFR2, ephrin A1, hypoxia-inducible factor 1 alpha and cyclooxygenase-2, as well as upregulating the expression of the anti-angiogenic gene thrombospondin-2 (49). A follow-up study also showed that HOXA5 stabilizes adherens junctions through β-catenin retention in ECs (50), thus blocking the initial process of angiogenesis. HOXB5 is an important angiogenesis modulator during embryonic development (51). Park *et al* (52) demonstrated that HOXD1 depletion in ECs results in significant inhibition of migration and adhesion, as well as tube-like structure formation, by regulating integrin b1. Consistent with this finding, HOXA9 exerts a proangiogenic effect on ECs (53). Conversely, *in vitro* experiments have shown that HOXC9 overexpression blocks endothelial cell proliferation, migration and tube formation by regulating its target gene interleukin 8 (54,55). Ultimately, analysis of the HOX gene expression profile implied that the expression of four HOX genes, HOXA7 and HOXB3 was markedly increased, whereas that of HOXA3 and HOXB13 decreased during angiogenesis (56). Taken together, the emerging evidence presented here strongly suggests that HOX has an important stimulatory role in angiogenesis. Despite these investigations, the role of HOX in angiogenesis has not been fully addressed. Most of the evidence stems mainly from the cellular level, and further experiments, such as analyzing patient samples or angiogenesis model rats with HOX gene

Table I. Involvement of HOX genes in the multiple pathophysiological processes of atherosclerosis.

Functional classification	HOX gene	Biological function	Target or pathway	(Refs.)
Lipid metabolism	HOXC6	Involved in the regulation of ox-LDL in THP-1 macrophages	HOXC-AS1/ HOXC6	(34)
Inflammatory response	HOXA5	Inhibiting inflammation	ND	(36,37)
Inflammatory response	HOXA5	Promoting endothelial inflammation upon knockdown HOXA5	NF-κB	(38,39)
Inflammatory response	HOXA9	Inhibiting inflammation upon knockdown HOXA9	PF4/E-selectin/ VCAM-1	(40,41)
Inflammatory response	HOXB9	Promoting endothelial cell inflammation	BMP4	(44)
Inflammatory response	HOXB5	Promoting inflammation	MCP-1 and IL-6	(45)
Angiogenesis	HOXA3	Promoting angiogenesis	ND	(46)
Angiogenesis	HOXD3	Promoting angiogenesis	Integrin	(47)
Angiogenesis	HOXA5	Inhibiting angiogenesis	β-catenin retention	(49,50)
Angiogenesis	HOXD10	Inhibiting angiogenesis	ND	(48)
Angiogenesis	HOXD1	Inhibiting angiogenesis upon knockdown HOXD1	Integrin b1	(52)
Angiogenesis	HOXC9	Inhibiting angiogenesis	Interleukin 8	(54,55)
Angiogenesis	HOXA9	Promoting angiogenesis	EphB4 receptor	(53)
EC proliferation or apoptosis	HOXC6	Inhibiting apoptotic of VECs upon knockdown of HOXC6	PLCβ/PKCζ/ NF-κB/IL-18	(59)
EC proliferation or apoptosis	HOXA1	Inhibiting proliferation of HUVECs upon knockdown of HOXA1	ND	(11)
VSMC proliferation or apoptosis	HOXC6	Inhibiting proliferation of VSMCs	p53 and PCNA	(64)
Vascular remodeling	HOXA4	Inhibiting vascular remodeling	YAP/TEAD	(66)
Vascular remodeling	HOXA5	Inhibiting vascular remodeling	PPARγ	(75)
Vascular remodeling	HOXB13	Involved in the phenotypic modulation of VSMCs in miR-17-5p/HOXB133 axis	MicroRNA-17-5p/ HOXB13	(67)
Macrophage polarization	HOXA5	Promoting polarization of M2 macrophage	PPARγ pathway	(75)
Macrophage polarization	HOXA5	Promoting macrophage polarization toward M2	MED1	(76)

HOX, homeobox; NF-κB, nuclear factor κB; BMP4, bone morphogenetic protein 4; PF4, platelet factor 4; VCAM-1, vascular cell adhesion molecule 1; MCP-1, major capsid protein-1; EphB4, EPH receptor B4; PCNA, proliferating cell nuclear antigen; YAP, Yes-associated protein; TEAD, transcriptional enhancer activator domain; PPARγ, peroxisome proliferator-activated receptor γ; MED1, mediator subunit 1; ND, not determined.

knockout are required to expound functional roles employed by the HOX gene in angiogenesis.

HOX gene regulation of cellular proliferation and apoptosis. ECs and VSMCs are the key cell types involved in the onset and progression of atherosclerosis. Given that atherosclerosis is an orchestrated process between endothelial and smooth muscle cells, the contributions of HOX to each of these cells were outlined, as discussed below.

ECs. From a normal pathophysiological perspective, ECs, as a single-cell layer connected by tight junctions, have a dominant role in maintaining vascular homeostasis owing to their anatomic location close to the circulating blood and vascular wall. Upon the occurrence of blood flow disturbance, ECs and their tight junctions become 'leaky', thus fueling the uptake of plasma LDL and TG-rich lipoproteins, as well as further driving the activation of the ECs accompanied by the release of various inflammatory factors (57,58). Therefore, ECs have crucial roles in atherosclerosis initiation and progression. A previous study by our group suggested that HOXC6 knockdown leads to blunted apoptosis of VECs (59), and further mechanistic study showed that HOXC6 exerts its function through the phospholipase Cβ/protein kinase Cζ/NF-κB/IL-18 signaling pathway (59). HOXA1 expression is upregulated in patients with atherosclerosis. Functionally, its knockdown impairs the viability and migration of HUVECs in the absence of ox-LDL (11). Antisense oligonucleotide-mediated HOXB2 knockdown attenuates HUVEC proliferation (60). Overall, the data presented here underscore the major contribution of HOX to EC biology. However, robust observations are required to systematically substantiate the specific mode of action of HOX in ECs.

VSMCs. VSMCs, a dominant component of the arterial wall, exhibit marked phenotypic plasticity and may de-differentiate from a contractile to a synthetic state, following accelerated proliferation and migration (61). Functionally, VSMCs are involved in multiple stages of atherosclerosis. From a pathological perspective, they undergo phenotypic switching from a contractile to a proliferative synthetic state upon stimulation by various factors and migrate into the intima, where they proliferate, generate extracellular matrix, participate in protective fibrous cap formation and promote plaque stability (62,63). Previous results by our group showed that HOXC6 expression is increased in the atherosclerotic aortic walls of rats (64). HOXC6 knockdown blocks the proliferation and migration of VSMCs *in vitro* (64). Hence, our preliminary results suggested that HOXC6 modulates the proliferation and migration of VSMCs. However, the biological role of HOX in VSMCs is poorly understood and more studies are needed to confirm its relevant regulatory role. Future perspectives based on animal model investigations coupled with advanced experimental methods will undoubtedly reveal the crucial role of HOX in regulating VSMC functions.

Partaking of HOX genes in vascular remodeling. Despite substantial efforts to improve therapeutic strategies, vascular remodeling remains the master event essential for atherosclerosis. Vascular remodeling, characterized by morphological and structural changes, refers to changes in the cell, including VSMCs, ECs and fibroblasts in multiple cell proliferation, migration and apoptosis (65). HOXA4 induces vascular remodeling by inhibiting Yes-associated protein/transcriptional enhancer activator domain transcriptional activity (66). Another study has shown that HOXA5 blocks carotid atherosclerosis progression. Mechanistically, it maintains a contractile form of VSMCs by activation of PPARγ (12). In addition, Yu *et al* (67) demonstrated that HOXB13 is involved in the phenotypic modulation of VSMCs induced by platelet-derived growth factor-BB in the miR-17-5p-HOXB13 axis. Although the aforementioned findings have shown that the HOX gene is linked to vascular remodeling, key mechanistic insight into governing vascular remodeling remains poor and a gamut of HOX gene investigation, particularly *in vivo* exploration, is currently lacking, limiting our understanding of its causal role in vascular remodeling; thus, abundant work remains to be done in the future.

Modulation of macrophage polarization by HOX genes. Macrophages are the most well-studied inflammatory cell type in atherosclerotic lesions (68,69). Macrophage polarization is responsible for the inflammatory responses and plaque formation in atherosclerosis (70,71). It is reported that M1 cells preferably secrete pro-inflammatory cytokines (such as IL-1β, IL-6 and IL-12) to activate inflammatory cascades, while M2-like macrophages often yield anti-inflammatory cytokines (such as IL-4 and IL-10) (72,73). Therefore, increased M1 macrophages in human atherosclerotic plaques aggravate atherosclerosis progression (74). In recent years, it has been shown that HOXA5 binds to the PPARγ promoter and transcriptionally activates the PPARγ pathway to facilitate the polarization of M2 macrophages, which attenuates chronic inflammation (75). Consistently, HOXA5 alleviates atherosclerotic plaque formation and intimal hyperplasia in carotid atherosclerosis mice by contributing to macrophage polarization toward the M2 status by binding to mediator subunit 1 (76). Because the HOX gene described here has been shown to mediate macrophage polarization, it would be interesting to further examine its contribution to this field. Given the mounting interest in developing novel strategies that target lesions, HOX exploration is perhaps a promising avenue for macrophage polarization pertinent to atherosclerosis.

4. HOX genes in other cardiovascular biology

Besides the HOX gene surveillance mechanisms summarized above, other HOX gene surveillance machinery types exist. In the following sections, the functional roles and molecular mechanisms of HOX in cardiac/vascular development, cardiomyocyte pyroptosis/apoptosis, cardiac fibroblast proliferation and cardiac hypertrophy related to cardiovascular problems were discussed (Fig. 3 and Table II).

Involvement of the HOX genes in cardiac/vascular development. Over the past few decades, the HOX gene as a transcription factor has played a critical role in embryonic development and organ morphology. HOX also has a key role in the development of the heart and blood vessels. The emerging role of anteriorly expressed HOX genes (HOXA1, HOXB1 and HOXA3) is in cardiac development, particularly in their contribution to the patterning of progenitor cells and the formation of great arteries (77). In addition, HOXB13 contributes to the maturation and proliferation of infant cardiomyocytes (78). HOXA5 knockdown in VSMCs promotes the formation of additional aortic arch arteries, suggesting its potential role in vascular development (79,80). Similarly, Klein *et al* (81) demonstrated that transcription factors (HOXB7, HOXC6 and HOXC8) participate in vascular wall-resident multipotent stem cell differentiation into smooth muscle cells. HOXB5, a paralog of HOXA5, is an upstream transcriptional switch for the differentiation of vascular endothelium from precursor cells (82). Collectively, the aforementioned data on several HOX genes indicate their relevance in cardiac or vascular development. Nevertheless, further interpretation of the role of HOX in this field requires further clarification.

HOX genes and cardiomyocyte proliferation/pyroptosis/apoptosis. As a transcription factor, HOXA3 has a predominant role in the modulation of embryonic development, inflammatory responses and cell death (83-85). Recently, experimental evidence has indicated that HOX participates in regulating pyroptosis and apoptosis in cardiomyocytes. For instance, HOXA3 upregulation is involved in growth differentiation factor 11-mediated inhibition of cardiomyocyte pyroptosis in mice with acute myocardial infarction (86). Lung cancer associated transcript 1 results in increased proliferation and decreased apoptosis of cardiomyocytes via the miR-612/HOXA13 axis in chronic heart failure (87). Cardiomyocyte-specific deletion of HOXB13 can lengthen the postnatal window of cardiomyocyte proliferation and reactivate the cardiomyocyte cell cycle in the adult heart, thereby regulating cardiomyocyte maturation and proliferation (78). Despite the occurrence of a preliminary correlation, abundant and in-depth investigations will be

Table II. Relevance of HOX genes in other cardiovascular biology.

Functional classification	HOX gene	Biological function	(Refs.)
Cardiac/vascular development	HOXB13	Promoting the maturation and proliferation of infant cardiomyocytes	(78)
Cardiac/vascular development	HOXA5	Promoting the formation of additional aortic arch arteries	(79,80)
Cardiac/vascular development	HOXB7 HOXC6 HOXC8	Participating in vascular wall-resident multipotent stem cell differentiation into smooth muscle cells	(81)
Cardiac/vascular development	HOXB5	Regulating differentiation of the vascular endothelium from precursor cells	(82)
Cardiomyocyte proliferation/ pyroptosis/apoptosis	HOXA3	Involved in GDF11-mediated cardiomyocyte pyroptosis inhibition	(86)
Cardiomyocyte proliferation/ pyroptosis/apoptosis	HOXA13	Involved in LUCAT1-mediated cardiomyocyte proliferation promotion and apoptosis inhibition	(87)
Cardiomyocyte proliferation/ pyroptosis/apoptosis	HOXB13	Deletion of HOXB13 can lengthen the postnatal window of cardiomyocyte proliferation	(78)
Cardiac fibroblast proliferation	HOXA4	Inhibiting proliferation upon knockdown of HOXA4	(88)
Cardiac hypertrophy	HOXA9	Involved in UCA1-mediated cardiac hypertrophy progression	(89)
Cardiac hypertrophy	HOXA9	Involved in PEG10-mediated cardiac hypertrophy progression	(90)
Cardiac hypertrophy	HOXA10	HOXA10 overexpression rescues Ang II-induced myocardial hypertrophy	(91)
Cardiac hypertrophy	HOXA5	Promoting the development of cardiac hypertrophy	(92)

HOX, homeobox; GDF11, growth differentiation factor 11; LUCAT1, lung cancer associated transcript 1; UCA1, urothelial cancer associated 1; PEG10, paternally expressed 10.

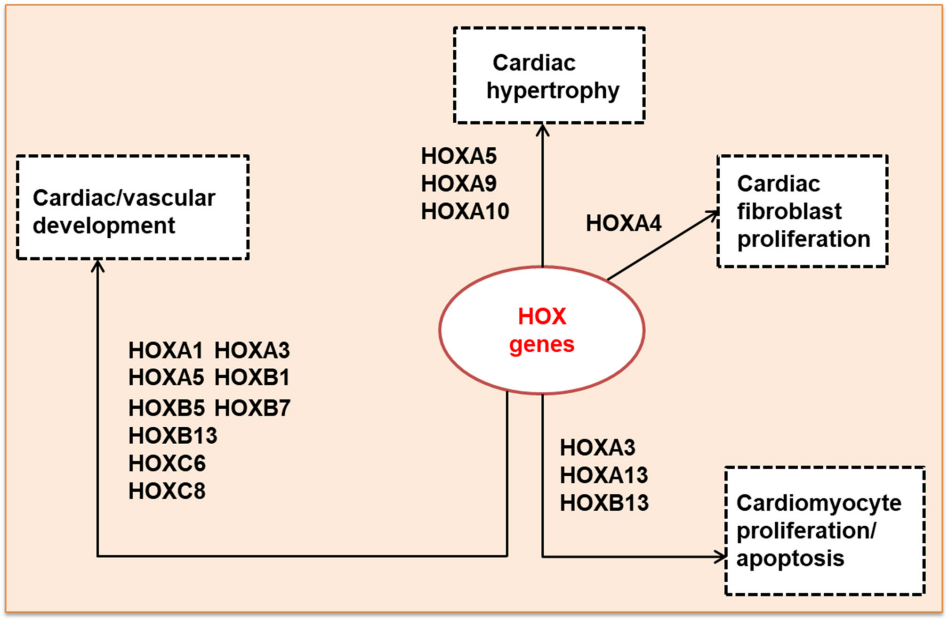

Figure 3. Modulation of HOX genes has been indicated to exert pivotal roles in other cardiovascular biology processes pertinent to various cardiovascular problems. HOX, homeobox.

conducted to further elaborate on the causal role of HOX in cardiomyocyte pyroptosis or apoptosis.

HOX genes and cardiac fibroblast proliferation. Few studies have delineated the role of HOX in the proliferation of cardiac

fibroblasts. HOXA4 is upregulated in patients with heart failure and cardiac fibroblasts isolated from ischemic myocardium exposed to hypoxia/reoxygenation. Functionally, HOXA4 knockdown blunted cardiac fibroblast proliferation and migration. Mechanistically, HOXA4 is a direct and functional target of myocardial infarction associated transcript/miR-150 in the hearts and cardiac fibroblasts (88). Except for this report, investigations into the contributions of HOX genes to cardiac fibroblast proliferation are scarce. Hence, further investigations need to be conducted. We are only beginning to understand its numerous roles in cardiac fibroblast proliferation.

HOX genes and cardiac hypertrophy. Cardiac hypertrophy, as an initial adaptive response to diverse stresses comprising pressure or volume overload, blunts increased wall tension and aids in sustaining cardiac output. Initially, the adaptive process is favorable and can ameliorate cardiac function. However, long-term exposure of the heart to an aggravated workload results in impaired blood flow, leading to relative hypoxia and the subsequent loss of cardiomyocytes, eventually inducing heart failure. Recently, several studies have verified the role of HOX in cardiac hypertrophy. For instance, a report showed that urothelial cancer associated 1 facilitates cardiac hypertrophy progression by competitively binding to miR-184 to increase HOXA9 expression (89). Consistently, lncRNA paternally expressed 10 accelerates cardiac hypertrophy by positively modulating HOXA9 (90). In addition, Cao *et al* (91) indicated that HOXA10 overexpression rescued Ang II-induced myocardial hypertrophy and electrical remodeling in cardiomyocytes. Recent evidence reveals that HOXA5 promotes the development of cardiac hypertrophy principally by transcriptional activation of transforming growth factor β1 via direct binding to its promoter (92). Collectively, these data suggest that HOX participates in regulating cardiac hypertrophy. However, the exact molecular mechanisms are yet to be elucidated. Further investigation is required to dissect the implications of HOX in cardiac hypertrophy.

5. New emerging themes in HOX gene regulatory circuits

The identification of non-coding RNAs as functional players has revolutionized the field of RNA biology. In addition to encoding transcription factors, transcription of HOX genes yields non-protein-coding genes, including lncRNAs (93). A broad array of studies has indicated that HOX cluster-embedded lncRNAs (HOX-lncRNAs) are crucial for diverse cancer biology (94,95). In humans, there are 18 antisense RNA genes within the four HOX gene clusters in the National Center for Biotechnology GenBank database (https://www.ncbi.nlm.nih.gov/). HOX-lncRNAs play a major role in modulating the expression of HOX and non-HOX genes (96). Investigations have indicated that HOX-lncRNAs could regulate HOX expression in a cis- or trans-regulatory manner. For instance, HOTAIR, a HOX-lncRNA resulting from the HOXC cluster, acts in a trans-regulatory manner and modulates HOXD cluster expression by recruiting polycomb repressive complex 2 in adult human primary fibroblasts (97). HOTAIRM1 can regulate the expression of both 3' HOXA genes in cis and other genes involved in the alteration of β2-integrin signaling in a trans-regulatory manner (98,99). Additional HOX-lncRNAs require further investigation and the pivotal effects of HOX-lncRNAs on HOX expression remain unclear. Further, little is known about the mechanisms by which HOX genes govern HOX-lncRNA expression. Hence, further studies are needed to explore these regulatory circuits. HOX-lncRNAs are the most widely studied within the HOX network. HOTAIR is involved in various pathological conditions. Several recent studies have suggested that HOX-lncRNAs have an important role in cardiovascular diseases. For instance, HOTAIR can affect atherogenesis by regulating diverse biological processes, including the inflammatory response (100,101), angiogenesis (102), and cellular proliferation and apoptosis (103,104). These studies have filled a substantial gap in the mechanisms orchestrating cardiovascular disease in HOX-mediated regulatory circuits. An in-depth investigation of HOX-lncRNAs will likely yield novel insight into biological mechanisms and is a promising area for future research on cardiovascular disease. Understanding the roles of HOX genes and how they coordinate their relationship with HOX-lncRNAs will provide a more comprehensive understanding of the relevant cells and biology. However, HOX genes associated with diverse HOX-lncRNAs are yet to be fully functionally and mechanistically characterized. Capitalizing on the signaling pathways previously identified in cancer disorders and deciphering their mechanisms of action are likely to be useful strategies in the cardiovascular field. In addition, miRNAs can regulate the expression of HOX and thus participate in the occurrence and development of atherosclerosis. For example, mi-99a-5p alleviates atherosclerosis via regulating HOXA1 (30). In addition, the miR-17-5p/HOXB13 axis participates in the phenotypic modulation of VSMCs (67). In short, ncRNAs may regulate the expression of HOX genes and have a potential role in atherosclerosis.

6. HOX genes as potential diagnostic biomarkers for cardiovascular disease

Given that numerous studies have implicated HOX genes in regulating diverse cardiovascular biology, there may be opportunities to treat relevant diseases by modulating HOX genes. Several HOX genes, including HOXA5, HOXB5, HOXC6, HOXC8 and HOXB7, are differentially expressed in epicardial adipose tissue and subcutaneous adipose tissue of patients with coronary artery disease (105). Another study showed that HOXB4 serves as a potential diagnostic marker of acute myocardial infarction (106). HOXC5, a hub gene, is differentially expressed in abnormal coronary endothelial function samples compared to their counterparts, suggesting that it may be involved in the development of early coronary atherosclerosis (107). HOXA5 is upregulated in the lungs of patients with pheophytinase compared to normal lung tissue (108). Hence, HOX genes are expected to be useful biomarkers for diagnosing cardiovascular disease. HOX genes structurally occupy rich CPG islands in their promoters. Therefore, methylated HOX genes and HOX-associated histones have been recognized as potential biomarkers in numerous cancers. Epigenetic therapy using histone demethylases and deacetylases inhibitors may represent a promising treatment strategy. However, ample technical and theoretical details must be considered when designing biomarkers to

determine their specificity and sensitivity. Precise quantification and determination of value normalization are critical for decreasing variability and are therefore essential for rigorous biomarker interrogation. Further investigations are warranted to identify HOX as a novel class of molecules for therapeutic intervention against cardiovascular disorders. As mentioned above, HOX influences numerous cardiovascular biological processes, particularly atherosclerosis development and progression, by coordinating various pathophysiological processes. Consequently, an in-depth investigation of HOX genes is expected to enable their use as potential diagnostic biomarkers for specific diseases.

7. Concluding remarks

Over the past decade, interest in elucidating cardiovascular disease has increased owing to its high morbidity and mortality. In recent years, dysregulation of HOX gene regulatory circuits has been linked to atherosclerosis. Therefore, understanding how various intricate molecular landscapes contribute to atherosclerosis is pivotal. To this end, atherosclerosis-associated investigations have been conducted to elucidate the underlying molecular mechanisms. To a certain extent, the advancement of gene function has led to remarkable alterations in the appreciation of HOX beyond its existing function in bodily development. The present review outlined the state-of-the-art HOX gene for atherosclerosis. Other critical biological processes dominated by the HOX gene, which is essential for cardiovascular diseases, including cardiac/vascular development, cardiomyocyte pyroptosis/apoptosis, cardiac fibroblast proliferation and cardiac hypertrophy, were also discussed. Overall, a preponderance of data supports the notion that HOX dysregulation may be causally linked to several cardiovascular diseases, including atherosclerosis. Thus, we are optimistic that the ongoing investigation of HOX holds outstanding promise to provide new directions with great potential to ameliorate the current bottleneck in treating atherosclerosis. Most findings have yet to be pinpointed in detail. Of the 39 HOX genes in humans, only a few have been exhaustively substantiated, and perhaps even a limited number have a biologically significant impingement on atherosclerosis, let alone translate into the clinic. Taken together, HOX, a previously underappreciated central modulator, is being considered for atherosclerosis, thus showcasing a fascinating yet challenging landscape for developing new therapeutic strategies for atherosclerosis. However, much remains to be done in future journeys.

8. Outlook and future challenges

Mounting evidence has shown HOX involvement in atherosclerosis; however, several core issues concerning HOX go beyond the scope of the aspects presented above. Besides celebrating existing advances, delving into the molecular basis of HOX in atherosclerosis, such as overwhelming molecular insight *in vitro* and rigorous functional roles *in vivo*, requires further investigation. Monumental challenges exist in moving forward and substantial knowledge gaps must be addressed in detail.

In the laboratory, a large collection of studies is warranted to elucidate the fundamental far-reaching roles of HOX in atherosclerosis. However, several outstanding questions remain to be resolved: i) The epigenetic mechanisms by which HOX gene expression is crucial for the understanding of diverse cardiovascular diseases are still poorly characterized. An in-depth understanding of the HOX gene epigenetic landscape that dissects pathogenesis during the atherosclerosis process will be needed to provide causality at the transcriptional level. ii) How the HOX gene orchestrates its downstream target genes and how they are targeted to specific genetic loci remain less well documented. iii) The molecular crosstalk between different HOX genes may delineate a subtle network to regulate sequential expression during development (109,110). However, details of the interplay and molecular crosstalk between HOX gene members, as well as key insights in atherosclerosis-harnessing animal models particularly, are still not widely imprinted. iv) As previously mentioned, a large fraction of HOX cluster-embedded lncRNAs have not yet been functionally characterized, particularly in the cardiovascular field. More specifically, the interaction between HOX-lncRNAs and HOX genes remains largely vague; thus, plentiful work underscoring their regulatory layers is necessary to open a new chapter for dissecting the interplay between HOX-lncRNAs and HOX genes in atherosclerosis.

In translational undertakings, perhaps the most challenging aspect is how the scientific discoveries of the HOX gene described herein yield benefits for cardiovascular diseases. Therefore, detailed studies in animal models and rigorous pre-clinical research trials are likely to be paramount in filling this gap. Follow-up work is needed to address whether the changes in HOX gene expression are i) a cause or contributor to atherosclerosis or ii) the effect of atherosclerosis. If HOX gene expression is a cause of atherosclerosis, it may be favorable to develop anti-atherosclerosis therapies that target HOX gene expression. Furthermore, if this is the case, such expression may be helpful as a robust biomarker of atherosclerosis or for evaluating the effect of anti-atherosclerosis therapy. Certainly, to target particular HOX genes in atherosclerosis, ongoing work is imperative to determine causal links between diverse signaling pathways concerning the HOX gene at both the transcriptomic and proteomic levels before clinical application.

In general, the governance of major regulatory mechanisms involving multiple stepwise factors related to atherosclerosis is complex and often requires the integration of multiple layers of control. Consequently, it is impossible to shed light on atherosclerosis onset and progression using a single mechanism, and future efforts to disentangle its pathogenesis and exploit new effective therapeutics will need comprehensive approaches as a prerequisite, taking into consideration all kinds of regulatory mechanisms. A focus addressing these questions is needed to integrate multi-dimensional data derived from cellular, organoid-based, *in vivo*, molecular, genetic, epigenetic, transcriptomic and proteomic mechanisms, coupled with state-of-the-art technologies that allow detection of more HOX gene characteristics at the level of single cells, leveraging atherosclerosis-relevant tissues and ultimately translate unparalleled molecular findings into clinical practice to benefit patients with atherosclerosis, from the lab to the clinic.

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Authors' contributions

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

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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