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Targeting epigenetics and non-coding RNAs in atherosclerosis: from mechanisms to therapeutics

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ABSTRACT

Atherosclerosis, the principal cause of cardiovascular death worldwide, is a pathological disease characterized by fibro-proliferation, chronic inflammation, lipid accumulation, and immune disorder in the vessel wall. As the atheromatous plaques develop into advanced stage, the vulnerable plaques are prone to rupture, which causes acute cardiovascular events, including ischemic stroke and myocardial infarction. Emerging evidence has suggested that atherosclerosis is also an epigenetic disease with the interplay of multiple epigenetic mechanisms. The epigenetic basis of atherosclerosis has transformed our knowledge of epigenetics from an important biological phenomenon to a burgeoning field in cardiovascular research. Here, we provide a systematic and up-to-date overview of the current knowledge of three distinct but interrelated epigenetic processes (including DNA methylation, histone methylation/acetylation, and non-coding RNAs), in atherosclerotic plaque development and instability. Mechanistic and conceptual advances in understanding the biological roles of various epigenetic modifiers in regulating gene expression and functions of endothelial cells (vascular homeostasis, leukocyte adhesion, endothelial-mesenchymal transition, angiogenesis, and mechanotransduction), smooth muscle cells (proliferation, migration, inflammation, hypertrophy, and phenotypic switch), and macrophages (differentiation, inflammation, foam cell formation, and polarization) are discussed. The inherently dynamic nature and reversibility of epigenetic regulation, enables the possibility of epigenetic therapy by targeting epigenetic "writers", "readers", and "erasers". Several Food Drug Administration-approved small-molecule epigenetic drugs show promise in pre-clinical studies for the treatment of atherosclerosis. Finally, we discuss potential therapeutic implications and challenges for future research involving cardiovascular epigenetics, with an aim to provide a translational perspective for identifying novel biomarkers of atherosclerosis, and transforming precision cardiovascular research and disease therapy in modern era of epigenetics.

Contents

Abbreviations: ABCA1, ATP binding cassette subfamily A member 1; Ang-II, Angiotensin-II; ANRIL, CDKN2B antisense RNA 1; ApoE, Apolipoprotein E; BET, Bromodomain and extra-terminal motif; CAD, Coronary artery disease; CD36, Cluster of differentiation 36; CSE, Cystathionine gamma-lyase; CVD, Cardiovascular diseases; eNOS, Endothelial nitric oxide synthase; DNMT, DNA methyltransferase; ET-1, Endothelin-1; EZH2, Enhancer of zeste homolog 2; HFD, High fat-diet; HDAC, Histone deacetylase; ICAM1, Intercellular adhesion molecule 1; IL1β, Interleukin-1 beta; IL6, Interleukin-6; KLF2, Kruppel like factor 2; LDL, Low-density lipoproteins; LDLr, Low density lipoprotein receptor; LXR, Liver X receptor; MCP1, Monocyte chemoattractant protein-1; MMPs, Matrix metalloproteinases; NF-kB, Nuclear factor-kappa B; NO, Nitric oxide; PCSK9, Proprotein convertase subtilisin/kexin type 9; PPAR, Peroxisome proliferator-activated receptor; ROS, Reactive oxygen species; SIRT, Sirtuin; TET2, Tet methylcytosine dioxygenase 2; TGFβ, Transforming growth factor-β; TGFBR, Transforming growth factor-β receptor; TNFα, Tumor necrosis factor-alpha; VCAM1, Vascular cell adhesion molecule 1; VSMCs, Vascular smooth muscle cells.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide (Atlas Writing et al., 2018; Benjamin et al., 2018; Fang, Little, & Xu, 2018; Xu et al., 2018; Xu, Bai, Little, & Liu, 2014; Xu, Pelisek, & Jin, 2018). According to the 2018 Statistic Report of Heart Disease and Stroke released by the American Heart Association (Benjamin et al., 2018), CVD causes 17.9 million deaths per year, and this number is expected to increase to >23.8 million by 2030. It is reported that 45.1% adults in the United States population have some form of CVD. CVD also inflicts major socioeconomic burdens in society. The direct and indirect costs of CVD and stroke exceed US$1.1 trillion annually (Benjamin et al., 2018). The pathologies of CVD include atherosclerosis, cardiac hypertrophy, heart failure, hypertension, stroke, valvular heart disease, peripheral artery disease, and other circulatory disease conditions (Benjamin et al., 2018). Atherosclerosis represents a major component of CVD that preferentially develops at branched or curved regions in medium and large sized arteries (Lusis, 2000). It is a multifactorial disease, which involves chronic inflammation (Libby, Ridker, & Maseri, 2002; Ross, 1999), lipid metabolism and accumulation (Gould, 1951), oxidative stress (Harrison, Griendling, Landmesser, Hornig, & Drexler, 2003), genetic predisposition (Lusis, 2012), immune disorders (Hansson & Hermansson, 2011), epigenetics (Xu, Pelisek, & Jin, 2018), and multiple non-genetic risk factors (environmental pollution, smoking, mental health, diet, and lifestyle) (Zhong, Agha, & Baccarelli, 2016) (Fig. 1). The "multiple hit" hypothesis considers all these insults acting together to initiate atherosclerosis. After initial endothelial injury, endothelial dysfunction occurs, resulting in monocyte adhesion/transmigration/differentiation, lipid uptake, and the formation of "foam cell" (fatty streak). Subsequently, vascular smooth muscle cells (VSMCs) residing in media layer migrate to sub-endothelial space, leading to fibroatheroma formation and atherosclerosis. In conditions of large necrotic core covered by thin fibrous caps, the plaques are prone to rupture (Bentzon, Otsuka, Virmani, & Falk, 2014; Davies, 1996; Finn, Nakano, Narula, Kolodgie, & Virmani, 2010; Little, Osman, & O'Brien, 2008), which lead to several life-threatening conditions, such as ischemic stroke and myocardial infarction (Hansson, Robertson, & Soderberg-Naucler, 2006). Although reducing low-density lipoprotein (LDL) level and cardiovascular events by statins and emerging inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), residual cardiovascular burden remains very high even in the subgroup of patients receiving statin therapy (Reith & Armitage, 2016). This reality underscores the importance to identify novel disease mechanisms and complementary therapeutic approaches; such approaches would need to work along with lipid-lowering therapies to delay the initiation and progression of atherosclerosis.

Epigenetics is a rapidly advancing and evolving field of biomedical research. More recently, C. David Allis (Rockefeller University) and Michael Grunstein (University of California, Los Angeles) have been awarded **2018 Albert Lasker Basic Medical Research Award** for discoveries elucidating how histone modification influence gene expression (http://www.laskerfoundation.org). Histone and DNA modifications represent the two most common forms of epigenetic regulation, which have far-reaching implications in understanding molecular mechanisms of disease pathogenesis and designing new therapies for various diseases. Emerging evidence in the past two decades has suggested the importance of epigenetic mechanisms as a new layer of biological regulation in CVD. Epigenetics are critically involved in

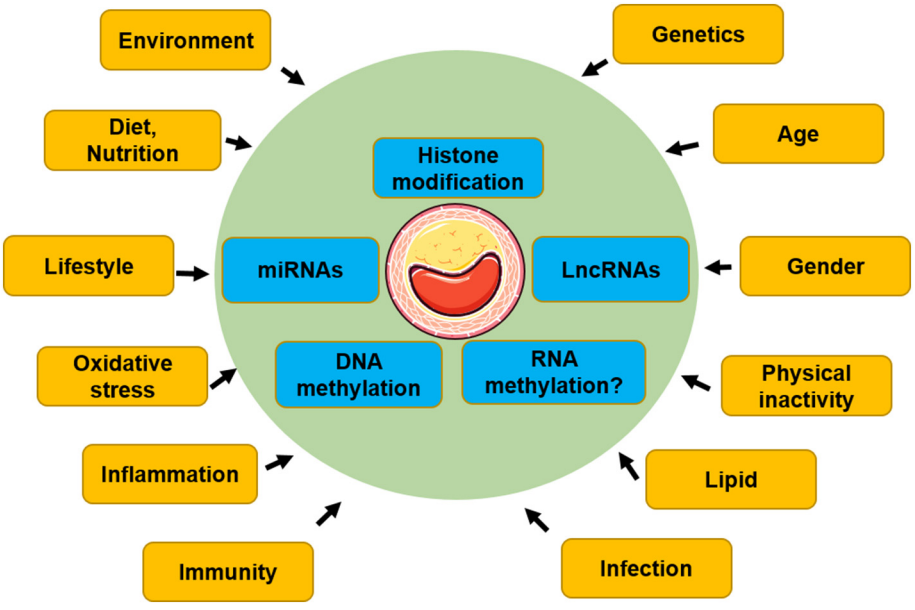

Fig. 1. A conceptual "multiple hit" hypothesis for the development of atherosclerosis. The "multiple hit" hypothesis consider all these insults acting together on genetically predisposed subjects to induce atherosclerosis.

atherosclerosis plaque development and vulnerability (Costantino et al., 2017). The term of "epigenetics", was originally coined by Conrad Waddington in 1940s as 'the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being' (Waddington, 1942). Since then, epigenetics has been considered being involved in embryonic development, imprinting, X chromosome inactivation, and other biological processes (Delcuve, Rastegar, & Davie, 2009). Currently, epigenetics is defined as "studies of heritable changes to the genome that occur independent of alternations in the primary DNA sequence" (Sharma, Kelly, & Jones, 2010). In atherosclerosis, several vascular cells (mainly including endothelial cells, VSMCs, and monocytes/macrophages) harbor global epigenetic alternations, which complement genetic abnormalities. Although much of our knowledge on the importance of epigenetics stem from the cancer research (Sharma et al., 2010), research interest in cardiovascular epigenetics has significantly increased recently (Baccarelli, Rienstra, & Benjamin, 2010). The pathogenesis of cardiovascular diseases and cancers share many similar mechanisms, such as oxidative stress, inflammation, and susceptibility to common risk factors (Koene, Prizment, Blaes, & Konety, 2016). Starting from the mid-1990s', there has been a steady growth in the number of publications in epigenetic research. Cardiovascular epigenetic research has been growing exponentially in recent years, albeit the increase in the number of cardiovascular publications has lagged behind cancer epigenetic research (Fig. 2). For example, only 3 cardiovascular epigenetic-related articles were published in 1997 and that number was just 49 in 2007. The projected number for 2017 is 401, amounting to near 10-fold increase since 2007 (Fig. 2).

Epigenetic modifications can be broadly categorized into: (1) DNA methylation and emerging RNA methylation; (2) Histone modifications (including methylation, acetylation, phosphorylation, sumoylation, ubiquitination, and ADP ribosylation); and (3) Non-coding RNAs mechanisms, such as microRNAs, and long non-coding RNAs (lncRNAs) (Khyzha, Alizada, Wilson, & Fish, 2017) (Fig. 2D). Distinct from genetic mutations, epigenetic alternations are reversible, and susceptible to nutritional and environmental factors, and thus more accessible for modification and/or drug targeting (Xu, Pelisek, & Jin, 2018). Epigenetic disorder can be normalized by epigenetic cardiovascular therapies, making targeting epigenetic processes clinically and therapeutically relevant (Baccarelli et al., 2010). Deepened understanding of the epigenetic basis of atherosclerosis could provide novel insights into mechanisms of atherosclerosis and support the potential of epigenetic mechanisms as druggable targets (Pons et al., 2009). In this article, we provide a comprehensive review of diverse epigenetic mechanisms and epigenetic-targeted therapies in atherosclerotic plaque development and instability, and we also propose the rationale for developing novel therapeutic strategies by targetting epigenetic processes.

2. Epigenetic mechanisms in atherosclerosis

In the realm of epigenetic modifications (Gillette & Hill, 2015; Yang, Hsu, Chen, & Yang, 2018), DNA/RNA methylation, and histone modifications have specific epigenetic "readers", "writers", and "erasers". Epigenetic "readers," have specialized domains, such as the plant homeodomain finger (which detects methylated histones), and bromo- and extra-terminal domain (BET) (which binds acetyl–lysine), that bind to various covalent histone modifications. Epigenetic "writers" include DNA methyltransferases (DNMTs, mediating DNA methylation), histone acetyltransferases (HATs, mediating histone acetylation),

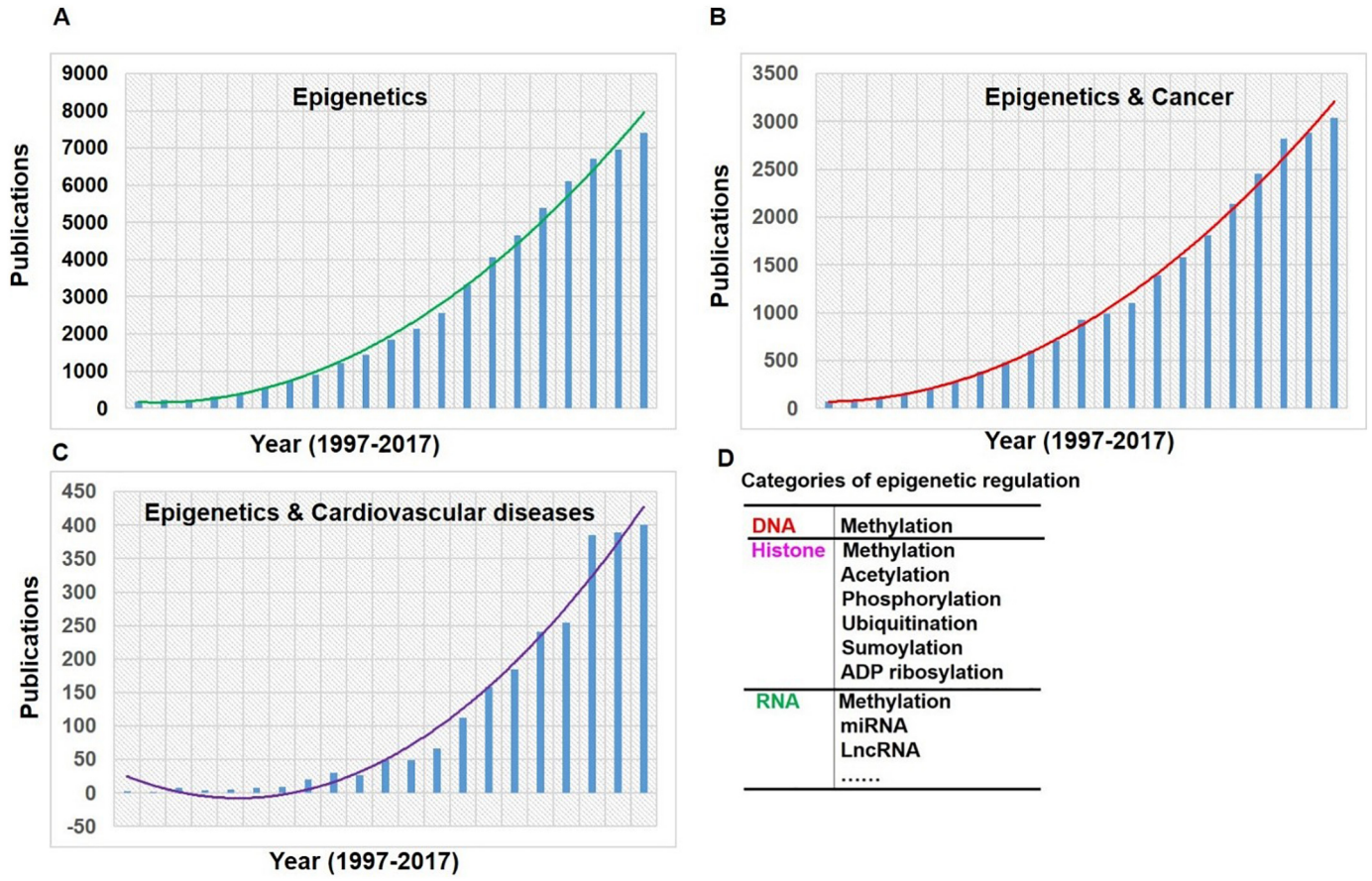

Fig. 2. Trends of cardiovascular epigenetics. Yearly publication of epigenetic (**A**), cancer & epigenetic (**B**), cardiovascular disease & epigenetic (**C**). PubMed Search was performed on May 18, 2018 using the subject terms (epigenetic) for "epigenetic"; and (cancer AND epigenetic) for cancer epigenetics, and (cardiovascular disease AND epigenetic) for "cardiovascular disease"; Epigenetics (**D**) covers DNA and RNA methylation, histone modifications (acetylation, methylation, phosphorylation, etc.) and non-coding RNAs (micro-RNA and lncRNA-based mechanisms). These three broad categories of epigenetic modulation are distinct but are interrelated and coordinate to regulate gene expression.

histone methyltransferases (HMTs, and histone methylation), and protein arginine methyltransferases (PRMTs, mediating arginine methylation). Epigenetic "erasers" include methylcytosine dioxygenase ten-eleven translocation (TET), histone deacetylases (HDACs), and sirtuins. The coexistence and coordinated actions of epigenetic readers, writers, and erasers fine-tune gene expression by recruiting either active epigenetic marks (H3K4me3, H3K36me3, and H3K79me3), or repressive epigenetic marks (such as H3K9me3, H3K27me3, and H4K20me3) to target gene promoters (Fig. 3) (Zhang, Cooper, & Brockdorff, 2015). The specific role of DNA and histone-modifying enzymes in atherosclerosis and related vascular diseases is summarized in Table 1.

2.1. DNA methylation/demethylation

Several studies reported increased TET1 expression, reduced DNMT1 expression (Greissel et al., 2015), and decreased global DNA methylation (Aavik et al., 2015; Wierda et al., 2015) in atherosclerotic plaques compared to healthy control arteries. However, studies examining global methylation patterns in blood components yield contradictory results. A recent study in Chinese Han population has shown that 5-methylcytosine (5-mC) and DNMT1 expression are decreased in THP-1 macrophage-derived foam cells as well as in circulating leukocytes from patients with coronary artery disease (CAD) (Deng et al., 2018). While, another study has shown elevated DNMT1 and decreased peroxisome proliferator-activated receptor gamma (PPAR-γ) levels in the monocytes of patients with atherosclerosis (Yu et al., 2016). Potential reasons of these discrepancies include different ethnic groups of patients, different stages of disease, and the type of comparison (diseased artery compared to healthy control artery or disease-free adjacent regions). In the following sections, we will provide a synthesis on the context- and cell type-dependent gene regulation by DNA methylation *in vitro* and *in vivo*.

2.1.1. DNA methylation mediated by DNMTs

To date, there are three different DNMTs (i.e., DNMT1, DNMT3a and DNMT3b) in mammals. DNMT1 is the maintenance DNMT during mitosis, which preferentially methylates already hemi-methylated DNA, thereby maintaining methylation status in cell replication. DNMT3a and DNMT3b are *de novo* methylating enzymes which act by directly adding methyl groups to unmethylated DNA (Jeltsch & Jurkowska, 2014). DNA methylation primarily occurs at specific dinucleotide sites (CpG islands). Generally, DNA methylation is a repressive modification that mediates gene silencing by inhibiting the binding of transcription complexes to target gene promoters. DNA methylation in the CpG

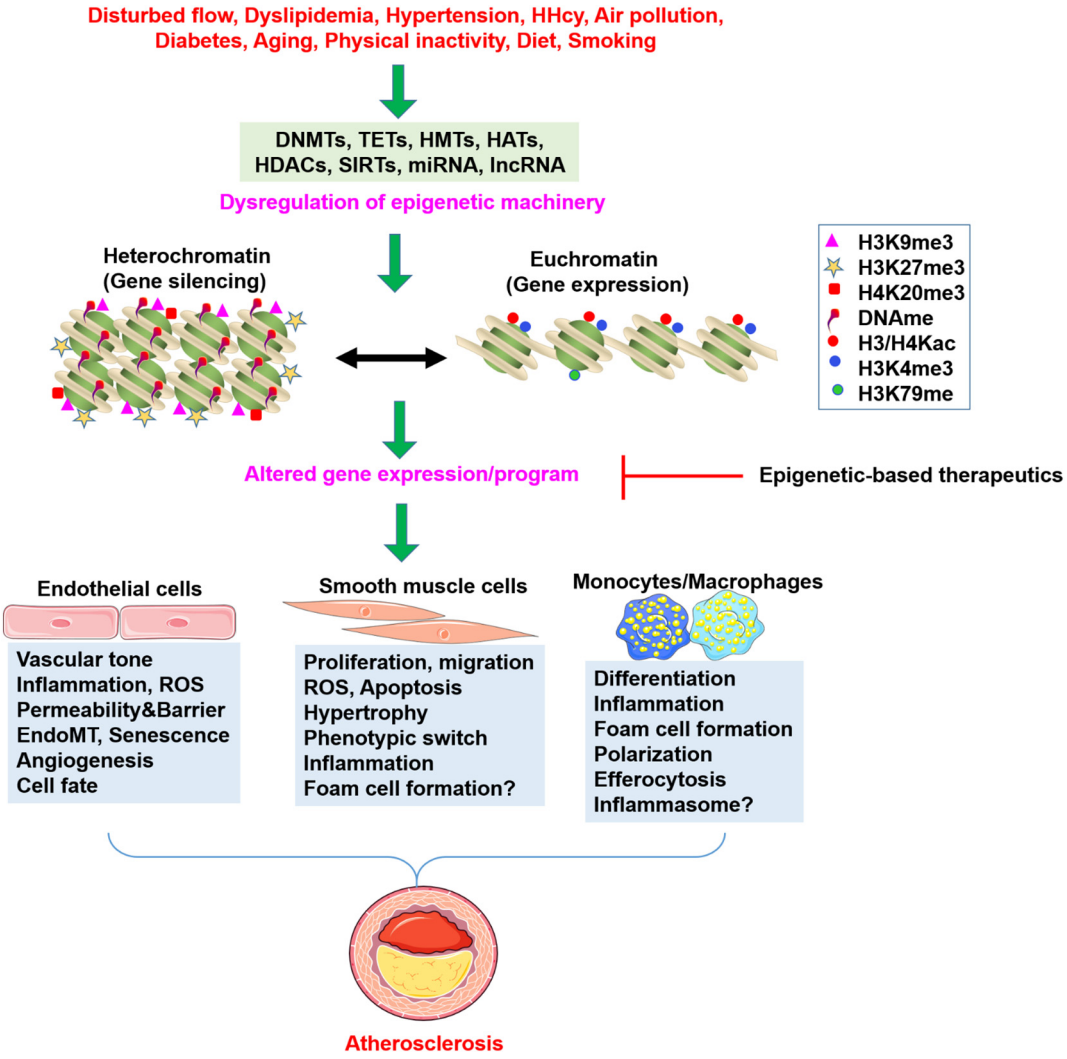

Fig. 3. Epigenetic modifications in the development of atherosclerosis. Multiple disease-associated risk factors lead to dysregulated epigenetic machinery and altered the binding of multiple epigentic marks to target gene promoters. This leads to altered gene expression and cellular phenotypes, which directly drives atherosclerosis. Lysine methylation at H3K4, H3K79, and lysine acetylation of histone 3 and 4 (H3/H4Kac) is associated with euchromatin status and transcriptional activation, whereas methylation at H3K9, H3K27, and H4K20 is related to heterochromatin formation and transcriptional repression (Martin & Zhang, 2005). Altered gene expression/program can be modulated by several categories of epigenetic drugs discussed in this review.

Table 1
Role of DNA and histone modification enzymes in experimental atherosclerosis and associated vascular diseases *in vivo*.

Animal models	Target	Phenotype	Reference
DNMT1^{Tg}; ApoE$^{-/-}$	DNMT1	↑ Plaques sizes ↑Macrophage inflammation ↑Increase PPAR-γ methylation ↓PPAR-γ	(Yu et al., 2016)
TET2^{KD}; TET2^{OE}	TET2	OE↓Neointima hyperplasia KD↑ Neointima hyperplasia	(Liu et al., 2013)
Tet2^{OE}; ApoE$^{-/-}$ Tet2^{KD}; ApoE$^{-/-}$	TET2	OE↓ Plaque sizes, inflammation, ↑autophagy KD↑ Plaque sizes, inflammation, ↓autophagy	(Peng et al., 2016)
TET2$^{\Delta Mye}$; LDLr$^{-/-}$ 10% TET2^{KO} BMT	TET2	↑ Plaque sizes, IL-1β-dependent inflammasome	(Fuster et al., 2017)
TET2$^{\Delta Hem}$ BMT	TET2	↑ Plaque sizes, inflammatory cytokines/chemokines	(Jaiswal et al., 2017)
EZH2^{OE}; ApoE$^{-/-}$	EZH2	↑ Plaque sizes, foam cell formation ↓ ABCA1-dependent cholesterol efflux	(Lv et al., 2016)
HDAC3^{KD}; ApoE$^{-/-}$	HDAC3	↑ Plaque sizes and vessel rupture in isografted vessels ↓EC survival	(Zampetaki et al., 2010)
HDAC3$^{-/-}$; ApoE$^{-/-}$	HDAC3	↓Plaques sizes ↑ Plaque stability	(Hoeksema et al., 2014)
HDAC9$^{-/-}$; LDLr$^{-/-}$	HDAC9	↑Atherosclerotic plaques ↓Cholesterol efflux	(Cao, Rong, et al., 2014)
HDAC9$^{-/-}$; ApoE$^{-/-}$	HDAC9	↑Plaque sizes and severity	(Azghandi et al., 2015)
SIRT1^{TgEC}; ApoE$^{-/-}$	SIRT1	↓ Plaques sizes ↑Improved EC-dependent vasorelaxation ↑ eNOS	(Zhang et al., 2008)
SIRT1$^{+/-}$; ApoE$^{-/-}$	SIRT1	↑ Plaques sizes ↑NF-kB/LOX-1 pathway ↑Foam cell formation ↑Macrophage/T cell infiltration	(Stein, Lohmann, et al., 2010)
SIRT1$^{+/-}$; ApoE$^{-/-}$	SIRT1	↑Endothelial activation, ↑ Vascular inflammation, - endothelium-dependent vasorelaxation p-eNOS (S1177), eNOS	(Stein, Schafer, et al., 2010)
SIRT 1^{Tg}; LDLr$^{-/-}$	SIRT1	Increased atherosclerotic lesions; Worse lipid profile; Increased Creb deacetylation	(Qiang et al., 2011)
SIRT1 $^{\Delta VSMC}$; ApoE$^{-/-}$	SIRT1	↑ Atherosclerotic lesions; ↓ Fibrous cap thickness; ↑ VSMC DNA damage and senescence, media degeneration	(Gorenne et al., 2013)
SIRT1 $^{\Delta VSMC}$; ApoE$^{-/-}$ + Ang-II	SIRT1	KO↑AAA formation and rupture, inflammaging KO↓ CR induced protection against AAA	(Chen et al., 2016; Liu et al., 2016)
SIRT1 ^{TgVSMC}; ApoE$^{-/-}$ + Ang-II		TG↓ AAA formation and rupture, inflammaging	
SIRT1 $^{\Delta VSMC}$ + Ang-II	SIRT1	↑Disorganized elastic lamellae ↑Elastin fragmentation ↑ROS production, MMP2/9 activity ↑Aortic stiffness	(Fry et al., 2015)
SIRT1 ^{TgVSMC} + HFHS		↓ Arterial stiffness, inflammation, ROS	(Fry et al., 2016)
SIRT1$^{\Delta EC}$; ApoE$^{-/-}$	SIRT1	↑Atherosclerotic lesions	(Wen et al., 2013)
SIRT1$^{\Delta Mye}$	SIRT1	↑Insulin resistance ↑Metabolic derangement ↑Hyperacetylation and activation of NF-kB	(Schug et al., 2010)
SIRT1$^{\Delta Mye}$ + Ang-II	SIRT1	↑ Incidence and severity of AAA ↑ M1 macrophages ↓M2 macrophages	(Zhang, Xu, Liu, et al., 2018)
SIRT2^{KD}, SIRT2^{OE} LDLr$^{-/-}$	SIRT2	OE↓Atherosclerotic lesion KD↑ Atherosclerotic lesion	(Zhang, Ma, & Xiang, 2018)
SIRT3$^{-/-}$; LDLr$^{-/-}$	SIRT3	-Plaque size -Plaque vulnerability ↑ Weight gain	(Winnik et al., 2014)
SIRT6$^{+/-}$; ApoE$^{-/-}$	SIRT6	↑Atherosclerotic lesion ↑ Necrotic core and unstable plaques	(Zhang, Ren, et al., 2016)
SIRT6$^{+/-}$; ApoE$^{-/-}$	SIRT6	↑ Atherosclerotic lesion ↓ EC-dependent vasorelaxation	(Xu, Yin, et al., 2016)
SIRT ^{6KD}; ApoE$^{-/-}$	SIRT6	↑Atherosclerotic lesion ↓EC-dependent vasorelaxation ↑ Unstable plaques ↑ EC inflammation and monocyte adhesion	(Liu, Wang, Huang, et al., 2016)
JMJD1^{OE}, JMJD1^{KD}, balloon injury +HFD + STZ	JMJD1	OE↑ neointimal hyperplasia KD↓ neointimal hyperplasia	(Chen et al., 2017)
JMJD3$^{\Delta mye}$ + BMT (into LDLr$^{-/-}$)	JMJD3	↑Advanced atherosclerotic lesions ↑ Plaque necrosis -Plaque size	(Neele et al., 2018)
JMJD1^{KD}+ balloon injury JMJD1^{KD}+ left carotid artery partial ligation	JMJD3	↓Neointimal hyperplasia ↓VSMC proliferation, migration, inflammation	(Luo et al., 2018)

Abbreviations: AAA, abdominal aortic aneurysm; ABCA1, ATP binding cassette subfamily A member 1; Ang-II, angiotensin II; ApoE, apolipoprotein E; BMT, bone marrow transplantation; DNMT, DNA methyltransferase; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; Hem, hematopoietic cells; HFHS, high fat high sucrose; JMJD3, JmjC domain-containing *protein* 3; JMJD1, JmjC domain-containing protein 1; KD, knockdown; KO, knockout; LOX-1, lectin-like oxidized LDL receptor 1; MMP, matrix metalloproteinase; NF-kB, nuclear factor-kappa B; OE, overexpression; PPAR, peroxisome proliferator-activated receptor SIRT, sirtuin; TET2, TET methylcytosine dioxygenase 2; Tg, transgene; VSMC, vascular smooth muscle cells; ΔHem, hematopoietic cell-knockout; ΔMye, myeloid cell-specific knockout; ΔVSMC, vascular smooth muscle cell- specific knockout.

regions can also promote the binding of methylated DNA binding proteins, such as methyl CpG binding protein 2 (MECP2), thereby repressing gene transcription by reducing the accessibility of promoter sequences to various transcription factors DNA (Jeltsch & Jurkowska, 2014). Generally, DNA methylation is fundamentally implicated in development and disease, including embryonic development, cell identity establishment, genomic imprinting, X chromosome inactivation, and lineage specification (Hanna, Demond, & Kelsey, 2018).

Aberrant DNA methylation is characteristic of many human diseases, such as cancer (Kulis & Esteller, 2010). A recent study (Wei et al., 2018) has shown increased methylation of the promoter regions of SMAD7 (mothers against decapentaplegic homolog 7) and decreased expression of SMAD7 in atherosclerotic plaques, compared with healthy arteries. The methylation level of SMAD7 gene promoter were positively associated with the level of homocysteine and the risk score of carotid plaques, raising the notion that methylated SMAD7 represents a possible biomarker and therapeutic target for treating atherosclerosis (Wei et al., 2018). Lectin-like oxidized LDL receptor-1 (LOX-1) is the principal scavenger receptor responsible for oxidized LDL (oxLDL) uptake in endothelial cells, and LOX-1 upregulation is associated with endothelial dysfunction (Xu et al., 2013; Tian, Ogura, Little, Xu, & Sawamura, 2018). DNA hypomethylation of LOX-1 was involved in hyperhomocysteinemia (HHcy)-induced endothelial cell injury. The mechanism is related to toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB)/DNMT1 pathway (Ma et al., 2017). HHcy, also causes hypermethylation of estrogen receptor-alpha (ERα) promoter region, thus allowing VSMCs to proliferate excessively, and thus contribute to the development of atherosclerotic lesions (Huang et al., 2007). Endothelial nitric oxide (NO) synthase (eNOS, also known as NOS3) is another example that is regulated by DNA methylation. eNOS is an important regulator of vascular homeostasis by regulating NO production via multi-sites phosphorylation in endothelial cells (Heiss & Dirsch, 2014). The expression of eNOS can be regulated at transcriptional, post-transcriptional, translational, and post-translational levels (Forstermann & Sessa, 2012; Xu et al., 2016). Kruppel-like factor 2 (KLF2), the transcriptional factor of eNOS, is a critical anti-inflammatory and athero-protective transcriptional factor in vascular endothelium (Atkins et al., 2008; SenBanerjee et al., 2004). Multiple pro-inflammatory factors, such as lipopolysaccharides (LPS), can induce inflammatory response and KLF2 downregulation. Recent evidence (Yan, Deng, Jiao, Guo, & Ou, 2017) has suggested that epigenetic mechanisms are involved in LPS-induced KLF2 downregulation. Upon LPS stimulation, DNMT1-dependent methylation at 12 CpG sites of KLF2 is increased in HUVECs. Moreover, LPS induced KLF2 downregulation as well as the KLF2 downstream genes (E-selectin, vascular cellular adhesion molecule 1 (VCAM1), eNOS, and thrombomodulin) can be reversed by DNMT1 inhibition (Yan et al., 2017). This study suggests that pro-inflammatory LPS stimulation leads to hypermethylation of the KLF2 gene promoter, thereby reducing its gene expression (Yan et al., 2017). The above- described studies indicate that complex epigenetic mechanisms coexist to regulate expression and activity of eNOS.

In 2014, three simultaneous studies (Dunn et al., 2014; Jiang et al., 2014; Zhou, Li, Wang, & Chien, 2014) reported that disturbed blood flow induced atherosclerosis in several murine models via DNMT1 and DNMT3a-dependent DNA methylation alterations of mechanosensitive factors Homeobox protein A5, KLF3, and KLF4. Disturbed flow increases DNA methylation of promoters of three endothelial cell marker genes CD31 (cluster of differentiation 31), vWF (von Willebrand factor) and CDH5 (also known as VE-cadherin), but reduces the DNA methylation of distinct promoter regions of mesenchymal genes (CDH2, FSP1, and vimentin) (Lai et al., 2018). The direct role of DNMTs in atherosclerosis has been demonstrated by the evidence that DNMT1 transgene increases atherosclerosis plaque area in ApoE$^{-/-}$ mice fed an atherogenic diet (Yu et al., 2016). While, pharmacological inhibition of DNMTs by 5-Aza and its analogs inhibits experimental atherosclerosis induced either by atherogenic diets or partial ligation surgery (Cao et al., 2014; Dunn et al., 2014; Zhuang et al., 2017). A reciprocal regulation between miR-143 and DNMT3a has been reported to mediate VSMC proliferation induced by homocysteine. One the one hand, miR-143 directly targets DNMT3a. One the other hand, increased DNMT3a expression causes the hypermethylation of miR-143 in homocysteine-induced VSMC proliferation (Zhang et al., 2016). In addition, a recent study has found that higher methylation levels of cyclin-dependent kinase inhibitor 2A/2B (CDKN2A/2B) increases the risk for aortic arch and coronary artery calcification in patients with ischemic stroke (Zhou et al., 2016; Zhou et al., 2017).

In summary, methylation patterns of promoter regions of a plethora of genes contributing to atherosclerosis undergo significant changes during the disease development. The state of DNA methylation depends upon the expression of DNMTs, whose expression changes in atherosclerosis and is also regulated by various miRNAs. The current findings provide clear evidence of a concordant role and relevance of DNA methylation in atherosclerotic plaque development and progression toward vulnerable lesions.

2.1.2. TET-mediated DNA demethylation

A. TET1 and TET3

DNA demethylation is a counter mechanism for reactivating silenced genes induced by DNMTs. DNA demethylation can be catalyzed by TET methylcytosine dioxygenases family members, including TET1, TET2, and TET3, which convert 5-methylcytosine (5-mC) into 5-hydroxymethylcytosine (5-hmC). TET proteins also oxidize 5-hmC to 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC) (Wu & Zhang, 2017). Increased expression of TET1 in line with global DNA hypomethylation was observed in advanced carotid atherosclerotic lesions compared with healthy arteries (Greissel et al., 2015). The exact role of TET1 in atherosclerosis is not known. TET3 has been described being crucial for efficient DNA repair and maintaining genome stability (Jiang, Wei, Chen, Zhang, & Li, 2017), however, its role in atherosclerosis has yet to be elucidated.

B. TET2

Increasing evidence in the past several years have suggested an anti-atherosclerotic and vasoprotective role of TET2 (Liu et al., 2018). For example, Liu et al. (Liu et al., 2013) have elegantly shown that TET2 functions as a master regulator of VSMC plasticity. Specifically, gain- and loss-of-function studies have shown that TET2 overexpression drives a contractile program (myocardin, serum response factor, alpha-smooth muscle actin) in VSMCs, while TET2 depletion activates a dedifferentiation program and induces kruppel like factor 4. Most importantly, TET2 negatively regulates intimal hyperplasia in response to arterial injury *in vivo*. Interestingly, the TET2 promoter itself can be methylated by DNMT1 in VSMCs, and this abnormal methylation status can be attenuated by 5-aza-2′-deoxycytidine treatment, which in turn increases 5-hmC enrichment in the myocardin gene promoter (Zhuang et al., 2017).

The role of TET2 in endothelial cell function has also been recognized very recently. Specifically, TET2 expression is downregulated by disturbed blood flow *in vitro* and during the progression of atherosclerotic lesions *in vivo*. Compared with laminar blood flow, disturbed flow down-regulated autophagic markers-Beclin-1 and LCII/LCI, which can be reversed by TET2 overexpression. Moreover, TET2 positively regulates eNOS expression, while negatively regulating production of endothelin-1 (ET-1) in endothelial cells, suggesting a potential role of TET2 in maintaining endothelial homeostasis (Yang et al., 2016). Furthermore, TET2 overexpression decreases, while TET2 short hairpin RNA increases diet-induced atherosclerosis in ApoE$^{-/-}$ mice. The mechanism is related to TET2-mediated demethylation of Beclin-1 gene promoter, which contributed to the downregulation of oxLDL-induced impairment of endothelial cell autophagy and vascular inflammation (intracellular adhesion molecule 1 (ICAM1), VCAM1, interleukin 1 beta (IL-1β), and monocyte chemoattractant protein-1 (MCP1))

(Peng et al., 2016). Another mechanism of TET2-mediated protection against oxLDL-induced endothelial dysfunction is exerted through activating the cystathionine gamma-lyase (CSE)/hydrogen sulphide (H_2S) signaling pathway (which is atheroprotective (Xu, Liu, & Liu, 2014)) by promoting demethylation of CSE gene promoter (Peng et al., 2017).

In monocytes/macrophages, TET2 regulates monocyte to macrophage differentiation and multiple facets of macrophage function. A DNA methylation dynamics study revealed that during differentiation from human monocytes to macrophages, substantial gene sets related to macrophage identity was dependent on TET2 mediated DNA demethylation (Vento-Tormo et al., 2016). Li et al. (2015) have shown that TET2 gene and protein expression in macrophages is downregulated by oxLDL treatment, concurrent with decreased expression of autophagic markers. TET2 expression was upregulated by LPS treatment, potentially in a NF-κB-dependent manner. By this mechanism, TET2 inhibits LPS-induced macrophage activation via attenuating the expression of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin 12 (IL-12), and promoting the macrophage phenotypic switch from M1 to M2 subtype (Li, Huo, Lin, & Wang, 2017). TET2 also restrains inflammation in murine macrophages and mice (Cull, Snetsinger, Buckstein, Wells, & Rauh, 2017). Recently, TET2 has been shown to selectively regulate macrophage inflammatory gene expression via DNA methylation-independent mechanisms. For example, TET2 recruits histone deacetylase 2 (HDAC2) to repress the transcription of pro-inflammatory gene IL6 via histone deacetylation (Zhang et al., 2015). In line with the important role of TET2 in regulating vascular cell functions, three seminal studies have recently shown that clonal hematopoietic TET2 deficiency drives atherosclerosis and heart failure in mice by increasing NACHT, LRR and PYD domains-containing protein 3 (NLRP3)/IL-1β-dependent inflammasome activation as well as pro-inflammatory pathways (Fuster et al., 2017) (Jaiswal et al., 2017) (Sano et al., 2018). These evidence suggests the increase of TET2 expression and its demethylase activity by genetic manipulation or pharmacological activation could be exploited as a novel therapeutic strategy to combat atherosclerosis.

In summary, TETs, TET2 in particular, seem to be an important factor regulating the fate of VSMCs, endothelial hemostasis, and proper macrophage functions, which play crucial roles in atherosclerosis. Again, DNA demethylation works in concert with other epigenetic mechanisms, such as histone methylation/acetylation, thus accentuating a rather complex role of epigenetics in vascular diseases.

2.2. Histone modification

Core histone proteins, histone 3 (H3) and histone 4 (H4) in particular, are globular proteins that can be modified by multiple post-translational modifications, for example, acetylation, methylation, ubiquitination, phosphorylation, sumoylation, citrullination, and ADP-ribosylation (Zhang, Wu, Stenoien, & Pasa-Tolic, 2014). In addition, lysine residues on H3 an H4 can be mono-, di-, or trimethylated by diverse histone methyltransferases (HMTs). The biological consequence of histone modification is gene transcription or repression, depending on the site of the modified residues, the type of chromatin remodeling factors, as well as specific type of modification. These modifications regulate the switch of chromatin status from a condensed heterochromatin to an open euchromatin (Bennett & Licht, 2018).

Histone acetyltransferases (HATs) and HDACs regulate the acetylation status of chromatin, while, histone HMTs and demethylases (HDMs) regulate methylation status of chromatin. The intricate interplay between epigenetic writers HATs, epigenetic erasers HDACs, and bromodomain-containing epigenetic readers provides a finely-tuned and reversible gene regulation pathway (Bennett & Licht, 2018). Histone acetylation by HATs (such as p300/CBP) generally promotes gene expression, whereas HDACs exert opposite effects. Sirtuins are class III NAD^+-dependent HDACs that impact multiple cellular functions by orchestrating various key biological processes through the deacetylation of a number of histones (i.e., H3K9, H3K18, and H3K56) and non-histone protein substrates which are critically involved in regulating cell senescence, inflammation and metabolism, such as p53, liver X receptor (LXR), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), NF-kB and forkhead box protein O (FOXO) (D'Onofrio, Servillo, & Balestrieri, 2018; Sosnowska et al., 2017; Vitiello et al., 2017; Winnik, Auwerx, Sinclair, & Matter, 2015; Xu, Bai, & Jin, 2016). In contrast to histone acetylation, the role of histone methylation on gene transcription or repression is more complex and is site-specific. For example, H3K4me3 is an epigenetic mark that leads to gene expression, while H3K9me3, and H3K27me3 lead to gene repression. The histone-writing and -erasing enzymes also interact with DNMTs/TETs to drive context-dependent gene transcription or repression (Bennett & Licht, 2018).

2.2.1. Histone methylation/demethylation

To assess the role of histone methylation and demethylation in atherosclerosis, Greißel et al. (Greissel et al., 2015; Greissel et al., 2016) have recently systematically analyzed the expression pattern of histone methylation enzymes (by real-time PCR) and corresponding epigenetic marks (by immunohistochemistry) in human patients with different stages of atherosclerosis. Decreased expression of H3K9me3 and H3K27me3 was observed in plaque-derived VSMCs and inflammatory cells as well as whole atherosclerotic plaques (Greissel et al., 2015). Moreover, the expression of H3K4me3 and its corresponding methyltransferase MLL2/4 was strongly associated with the severity of atherosclerosis (Greissel et al., 2016). In the next section, we will discuss the specific role of histone methyltransferase in atherosclerosis.

2.2.1.1. Histone methyltransferases (HMTs). So far, >50 humane lysine histone methyltransferases (HMTs, also named lysine [K] histone methyltransferases, KMTs) have been described. These transferases have high selectivity for specific targeted lysine residues (H3K4, H3K9, H3K27, H3K36, H3K79, and H4K20), as well as the degree of methylation, which is nicely summarized in various review articles (Morera, Lubbert, & Jung, 2016; Peter & Akbarian, 2011; Zhang, Wen, & Shi, 2012). In this review, we focused on selected HMTs that were intensively studied in the last three years.

A. Enhancer of zeste 2 (EZH2)

EZH2, the catalytic subunit of PRC2 (polycomb repressive complex 2), is one of the well-studied HMTs in cardiovascular development and diseases. PRC2 is an evolutionarily conserved complex with gene suppressing activities. Other components of PRC2 include Suz12, embryonic ectoderm development (EED), and RbAp48 (Kim & Roberts, 2016). PRC2 has histone methyltransferase activity and mainly trimethylates histone H3 lysine 27 (i.e. H3K27me3) on target gene promoters, leading to transcriptional silencing. PRC2 is critical for embryonic development, cell differentiation, and multiple human diseases (Kim & Roberts, 2016). Elevated LDL level is a major risk factor for atherosclerosis. One pro-atherogenic mechanism of LDL is to promote endothelial dysfunction. Kumar et al. (2013) observed that LDL and its oxidized form (oxLDL) decrease the expression and activity of endothelial KLF2 via epigenetic mechanisms. LDL induces DNMT1 expression/activity and promotes the binding of MeCP2 and EZH2, whereas decreases the binding of the MEF-2 (myocyte enhancing factor-2), to gene promoters of KLF2 in endothelial cells. Pharmacological inhibition of DNMT1 or knockdown of DNMT1 or EZH2 prevents the downregulation of KLF2 by LDL. This finding suggests that LDL reduces KLF2 expression via enhancing DNA and histone methylation (Kumar et al., 2013). More importantly, EZH2 overexpression exaggerates atherosclerosis lesion development in $ApoE^{-/-}$ mice fed a western-type diet, suggesting EZH2 upregulation drives atherosclerosis development *in vivo* (Lv et al., 2016). Mechanistically, EZH2 promotes oxLDL induced foam cell formation in mouse and human macrophages by reducing ABCA1 mRNA and protein expression via DNMT1-mediated

DNA methylation. While, pharmacological inhibition of DNMT1 or application of DNMT1 siRNA reversed EZH2 induced ABCA1 downregulation and foam cell formation, suggesting that EZH2 and DNMT1 act in concert to repress ABCA1-dependent cholesterol efflux and promote foam cell formation (Lv et al., 2016). Similar to LDL, hyperhomocysteinemia (HHcy) is a risk factor for atherosclerosis. After challenging with high-methionine diet, EZH2 and corresponding H3K27me3 levels were increased in ApoE$^{-/-}$ mice. EZH2 overexpression increase, while EZH2 siRNA decrease, global H3K27me3 level and the accumulation of lipids (total cholesterol and triglycerides) in foam cells, suggesting that EZH2 is associated with HHcy-mediated atherosclerosis (Xiaoling et al., 2016).

In endothelial cells, Tie2-Cre mediated targeted deletion of EZH2 in endothelial cells and hematopoietic cells causes embryonic lethality (Delgado-Olguin et al., 2014; Neo et al., 2018). EZH2 silencing in endothelial cells lead to the overrepresentation of genes in the Wnt signaling pathway (Dreger et al., 2012) as well as the reactivation of vasohibin1, thereby regulating angiogenesis (*Lu* et al., 2010). Recently, we (Xu, Xu, et al., 2018) and others (Maleszewska, Vanchin, Harmsen, & Krenning, 2016) have identified that EZH2 gene and protein expression is downregulated by fluid shear stress (FSS) (which is generated by laminar flow). This EZH2 downregulation is responsible for laminar flow-mediated anti-inflammatory effects (Xu, Xu, et al., 2018) and cell quiescence (Maleszewska et al., 2016). FSS downregulates EZH2 via miR-101. By using next generation RNA-sequencing, insulin like growth factor binding protein 5 was identified as an EZH2 downstream target that mediates anti-inflammatory effects (Xu, Xu, et al., 2018). In addition, EZH2 is also upregulated in sepsis rat hearts and LPS-induced cardiac microvascular endothelial cells, and EZH2 downregulation is involved in ulinastatin-induced protection against LPS-induced endothelial cell hyperpermeability and apoptosis (Yu, Rayile, Zhang, Li, & Zhao, 2017).

In VSMCs, EZH2 promotes cell migration and proliferation, while suppressing apoptosis of pulmonary artery VSMC, and regulates the development of pulmonary arterial hypertension (PAH) (Aljubran et al., 2012). EZH2 also suppresses a differentiation program of VSMCs. EZH2 deficiency reactivates the expression of myocardin and T-box 18, two important regulators of VSMC differentiation (Snitow, Lu, Cheng, Zhou, & Morrisey, 2016). Pharmacological inhibition of EZH2 by EPZ005687 reverses experimental PAH induced by transverse aortic constriction via targeting antioxidant gene superoxide dismutase 1 (SOD1) (Shi et al., 2018). This evidence suggests a potential role of EZH2 in regulating diseases-associated cardiovascular remodeling.

EZH2 also controls LPS-induced macrophage activation and inflammatory responses (X. Zhang, Y. Wang, et al., 2018). In particular, EZH2 mediates LPS-induced myeloid differentiation primary response 88 (MyD88)-dependent pro-inflammatory gene expression in macrophages by epigenetically silencing suppressor of cytokine signaling 3 (SOCS3, an anti-inflammatory gene) and dependent TNF receptor associated factor (TRAF6) ubiquitination. Genetic ablation (EZH2 deficiency) or pharmacological inhibition (by GSK126, a potent and specific inhibitor of EZH2 methyltransferase activity (McCabe et al., 2012)) of EZH2 reduces the expression of multiple pro-inflammatory genes (IL-6, TNFα, and MCP1) in bone marrow-derived macrophages. Consistent with this evidence, EZH2 depletion also decreases TNFα expression by reducing nuclear expression of NF-κB p65 subunit (Zhang et al., 2018). Both studies highlight the therapeutic potential of EZH2 inhibitors to epigenetically control macrophage activation and treat inflammation-associated diseases (Neele & de Winther, 2018), including atherosclerosis. However, it must be noted that, in addition to functioning as a transcriptional repressor, EZH2 can also act as a transcriptional activator in cancer cells, an effect independent of PRC2-mediated H3K27 trimethylation (Kim & Roberts, 2016). EZH2 can also directly methylate non-histone substrate proteins, such as androgen receptor and signal transducer and activator of transcription 3 (STAT3), and control gene transcriptional activity or facilitate protein degradation via ubiquitination (Kim & Roberts, 2016). Tissue specific knockout (or inducible knockout) of EZH2 in endothelial cells, VSMCs, or macrophages are needed to address the tissue specific roles of EZH2 in atherosclerosis. Future studies are also warranted to elucidate direct and indirect effects of EZH2 in various vascular cells.

Taken together, emerging studies have suggested a pivotal role of EZH2 in mature vascular cells, in addition to its crucial functions in the development stage. Thus, EZH2 represents a promising therapeutic target for treatment inflammatory disorders, such as atherosclerosis. In the light of the important role of plaque angiogenesis driving plaque vulnerability (de Vries & Quax, 2016), further studies are warranted to evaluate the potential role of EZH2 in regulating plaque angiogenesis.

B. SET7/9 (SETD7)

Emerging evidence has also shown the involvement of other HMTs in regulating vascular functions. For example, SET7/9, a HMT that specifically monomethylates H3K4 (H3K4me1), and positively regulates inflammatory gene expression in endothelial cells (Keating et al., 2014) and THP1 cells (Li et al., 2008), by functioning as a new coactivator of NF-κB. Depletion of SET7/9 by siRNA blocks TNFα induced inflammatory gene expression by inhibiting H3K4me3 and NF-κB p65 recruitment to promoters of MCP1 and TNFα (Li et al., 2008). Notably, in TNFα-treated monocytes, 25% of NF-κB downstream target genes, including H3K27me3 demethylase JmjC domain-containing protein 3 (JMJD3), is reduced by SET7/9 depletion. The final outcome is reduced monocyte adhesion to endothelial cells as well as VSMCs (Li et al., 2008). SET7/9 knockdown also reduces inflammatory gene upregulation in monocytes stimulated with S100B, an established ligand of receptor of advanced glycation end-products (AGEs) (Li et al., 2008). In agreement with this evidence, genetic depletion or pharmacological inhibition of SETD7/9 reduces oxidative stress (hydrogen peroxide and cigarette smoking extract) induced expression and production of IL-6 and IL8 by recruiting the binding of H3K4me1 to NF-κB p65 (He, Owen, Jelinsky, & Lin, 2015).

In summary, these results indicate that SETD7/9 is both important for delicate regulation of redox and inflammatory status of macrophages. Therefore, SET7/9 seems to play a relevant role in regulating atherosclerosis. However, it remains elusive whether genetic or pharmacological inhibition of SET7/9 (*i.e.*, by Sinefungin (Sasaki et al., 2016)) ameliorate atherosclerosis in pre-clinical animal models.

C. G9a (Ehmt2)

G9a (also known as Ehmt2) is a HMT responsible for mono-and dimethylation of H3K9 (H3K9me1 and H3K9me2). Depletion (by shRNA) or pharmacological inhibition of G9a (by BIX-01294) inhibits proliferation, and causes cell cycle arrest in human microvascular endothelial cells. This evidence suggests that G9a inhibition could suppress angiogenesis and tumor neovascularization (Wojtala, Macierzynska-Piotrowska, Rybaczek, Pirola, & Balcerczyk, 2018). As a potential therapeutic drug, BIX-01294 has already been shown to inhibit angiogenesis in human hepatocellular carcinoma cells (Oh et al., 2015). BIX-01294 treatment also inhibits the proliferation and migration of VSMCs (Yang, Lu, Singh, & Raj, 2012). Thus, these results are suggesting the therapeutic potential of G9a inhibitors in treating neointimal hyperplasia, pulmonary hypertension and atherosclerosis.

D. SUV39H1

SUV39H1 is responsible for H3K9 trimethylation (H3K9me3), which is a repressive epigenetic mark that leads to transcriptional silencing. Studies in cultured VSMCs and macrophages demonstrate a protective role of SUV39H1 in regulating vascular functions. For example, SUV39H1 depletion by shRNA increased inflammatory gene expression in normal human VSMCs, while, SUV39H1 overexpression inhibited TNFα induced upregulation of IL6 and MCP1 in VSMCs (Villeneuve et al., 2008). In macrophages, high glucose treatment decreases protein level of SUV39H1 and global level of H3K9me3, as well as H3K9me3 recruitment to gene promoters of IL6, macrophage inflammatory protein (MIP) 1α, and MIP1β (Li et al., 2016). Inhibition of SUV39H1 with chaetocin in the presence or absence of high glucose increases the

expression of inflammatory cytokines (IL6, MIP1α, and MIP1β). However, SUV39H1 overexpression decreases the expression of these inflammatory cytokines at basal level and in the presence of high glucose (Li, Zhang, et al., 2016). The role of SUV39H1 homolog-SUV39H2 in regulating vascular functions remains unknown. Taken together, this evidence suggests that increased expression of SUV39H1 could possibly confer protective effects against inflammation associated vascular dysfunction. It remains to be investigated whether SUV39H1 can protect against atherosclerosis in pre-clinical models of atherosclerosis.

2.2.1.2. Histone demethylases. Dysregulation of histone methylation by methyltransferases or demethylases are associated with various diseases. Albeit histone methylation has been discovered >50 years ago (Murray, 1964), the methylation of lysine residues was considered as irreversible for a long time, until in 2004 Shi *et al.* reported that a lysine-specific demethylase 1A (KDM1A) demethylates H3K4 (Shi et al., 2004). Ever since, a plethora of other HDMs has been found in humans (Hyun, Jeon, Park, & Kim, 2017). In this article, we update HDMs described in the last three years in the context of vascular function and atherosclerotic plaque development.

A. UTX (Kdm6a)

Ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX) is H3K27me3 demethylase that regulates inflammation in macrophages. UTX gene expression was downregulated in macrophages after treatment with LPS (a TLR4 ligand), polyinosinic:polycytidylic acid (Poly (I:C), a TLR3 ligand) or CpG (a TLR9 ligand) (Li et al., 2017). Further studies revealed that UTX depletion inhibits LPS induced IL6 production by increasing the enrichment of H3K27me3 epigenetic mark at IL6 promoter (Li, Zhang, et al., 2017). Consistent with this evidence, UTX was also downregulated after long-term exposure (after 48 h) to particulate matter 2.5 (PM 2.5). PM2.5 increases pro-inflammatory cytokine expression by increasing the binding of H3K4me3 and H3K9me3 to IL6 and interferon beta (IFNβ) promoters, while UTX depletion reduces PM2.5 induced IL6 and IFNβ production (Ma et al., 2017). To date, the precise role of UTX in macrophage-derived foam cell formation and atherosclerosis remains unknown.

B. JMJD3 (Kdm6b)

JMJD3 is a specific H3K27me3 demethylase that is increased upon LPS stimulation via an NF-κB-dependent pathway (De Santa et al., 2007). Interestingly, 70% of LPS-responsive genes were reported to be regulated by JMJD3 (De Santa et al., 2009). Genetic deficiency (De Santa et al., 2009) or pharmacological inhibition of JMJD3 activity by GSK-J1 inhibits LPS-induced TNFα expression (Kruidenier et al., 2012). JMJD3 is also highly inducible by serum amyloid A (SAA, acute-phase protein that potently triggers inflammatory response) in macrophages and regulates SAA-induced inflammatory gene expression (Yan et al., 2014). JMJD3 depletion attenuated SAA-induced expression of pro-inflammatory genes (such as TREM-1) *in vitro* (cultured macrophages) and *in vivo* (peritonitis model), along with enrichment of H3K27me3 onto target gene promoters. More importantly, JMJD3 depletion reduces oxLDL-induced foam cell formation in SAA-treated macrophages (Yan et al., 2014). In addition, TNFα also upregulates JMJD3 expression in monocytes, and silencing of SET7/9 with siRNA reduces TNFα-induced JMJD3 expression (Li et al., 2008), indicating that SET7/9 dependent H3K4me3 methylation and JMJD3 dependent H3K27me3 demethylation could act in concert in driving pro-inflammatory gene expression. GSK-J4 also reduces cytokine (IFNγ, TNFα, and GM-CSF) production in Natural Killer cells, suggesting a broad pro-inflammatory role of JMJD3 in regulating inflammation (Cribbs et al., 2018).

During the process of foam cell formation, the pro-fibrotic transcriptome signature is acquired. Using a high-throughput RNA-sequencing approach, Neele et al. (2017) recently observed decreased expression of pro-fibrotic genes in macrophage-derived foam cells in JMJD3-deficient cells, indicating the essential role of JMJD3 in regulating the pro-fibrotic transcriptome in foam cells. This study is in line with previous studies supporting the pro-inflammatory role of JMJD3 being a promising target to treat atherosclerosis (Neele et al., 2017). JMJD3 is also involved in foam cell formation during mycobacterial infection (Holla et al., 2016). In addition to foam cell formation, JMJD3 expression is increased by interleukin 4 (IL4) and is directly regulated by STAT6 in polarized M2 macrophages (Ishii et al., 2009). JMJD3 is also essential for macrophage differentiation and M2 macrophage polarization in response to helminth infection and chitin. Mechanistic studies indicate that transcriptional factor interferon regulatory factor 4 (IRF4) was the direct target of JMJD3 that controls the expression of gene sets responsible for M2 macrophages polarization (Satoh et al., 2010). Taken together, these findings suggest that JMJD3 is important for macrophage differentiation, foam cell formation, and M2 macrophage polarization, which are critical events in atherosclerosis (Satoh et al., 2010).

In addition to mediating various macrophages functions, JMJD3 is also involved in LPS induced endothelial cell inflammation. LPS stimulation increases the expression and nuclear accumulation of JMJD3 in human endothelial cells (Yu et al., 2017). LPS increases the recruitment of JMJD3, NF-κB, and H3K4me3, while decreasing the binding of H3K27me3 to promoters of multiple pro-inflammatory genes (TNFα, IL6, IL1 β etc), suggesting JMJD3 could synergize with NF-κB to drive inflammatory gene expression. JMJD3 expression can be regulated by anti-inflammatory agents. For example, in brain microvascular endothelial cells stimulated with TNFα, dexamethasone reduces the expression of JMJD3, via recruiting glucocorticoid receptor α and nuclear receptor co-repressor to JMJD3 gene promoters. Dexamethasone also induces the upregulation of claudin 5 and occludin genes (Na et al., 2017). These findings suggest that dexamethasone could preserve the endothelial cell integrity under inflammatory conditions (Na et al., 2017). In addition, JMJD3 gene expression and nuclear accumulation is increased in response to oxygen-glucose deprivation/reperfusion injury (OGD/RI) in mouse brain microvascular cells. Mechanistic studies suggest that JMJD3 is involved in OGD/RI induced IL6 upregulation via interaction with NF-κB (p65/p50 subunits) and CCAAT-enhancer-binding protein β (C/EBPβ) at the gene promoter of IL-6. The increased binding of JMJD3 and decreased binding of H3K27me3 to IL6 gene promoter upon OGD/RI, indicates that demethylase activity of JMJD3 is critical for IL6-mediated inflammatory responses (Lee et al., 2012).

These findings open avenues for future therapeutic intervention of inflammation and atherosclerosis by targeting JMJD3 using pharmacological inhibitors or gene deletion. However, a recent study has shown that plaques from LDLr$^{-/-}$ mice transplanted with myeloid cell-specific deletion of JMJD3 bone marrow showed more advanced plaques with increased plaque necrosis (Neele et al., 2018). Also, genetic (siRNA mediated knockdown) or pharmacological inhibition (by cell permeable prodrug GSKJ4) of JMJD3 reduces balloon injury and partial carotid ligation induced neointimal hyperplasia in rodents, suggesting the important role of JMJD3 in vascular remodeling (Luo et al., 2018). Although mounting evidence suggests that JMJD3 is involved in vascular dysfunction, it remain elusive whether or not pharmacological inhibition of JMJD3 can protect against atherosclerosis in pre-clinical models.

C. JMJD1 (KDM3a)

In a study of the role of H3K9 demethylase JMJD1 (KDM3a) in regulating VSMC function and associated neointimal hyperplasia, JMJD1 expression was increased, while global H3K9me2 level was decreased in diabetic vessels from rats fed high fat diet (Chen et al., 2017). After 4 weeks of balloon injury, JMJD1 overexpression exacerbates, while JMJD1 siRNA attenuates neointima formation in streptozotocin-induced diabetic rats. Mechanistically, JMJD1 regulated the transcription of Angiontensin II receptor 1 and Rho-associated coiled-coil containing protein kinase 2 by reducing H3K9me2 binding to the proximal promoters of both genes (Chen et al., 2017). This study identifies JMJD1 as a novel regulator of VSMC proliferation, migration and

formation of neointimal hyperplasia *in vivo*, providing the first evidence of the role of JMJD1 in vascular remodeling. Since neointimal hyperplasia is a preliminary stage of atherosclerosis, it is interesting to speculate that JMJD1 might represent a promising therapeutic target for treating atherosclerosis at early stage or atherosclerosis occurring in association with hyperglycemia or diabetes.

2.2.2. Histone acetylation/deacetylation

Histone acetylation is catalyzed by HATs, which acetylate conserved lysine residues on histone proteins. In mammalian cells, three categories of HATs have been identified: Gcn5-related N -acetyltransferases (GNAT), MYST, and CREB-binding protein (CBP)/p300 (Roth, Denu, & Allis, 2001). Generally, histone acetylation untightens chromatin structure and thus increases gene expression. Opposite to the functions of HATs, HDACs remove acetyl groups on histone substrates, thus tightening chromatin structure and repressing gene expression. Based on domain structure, biological functions, and sequence homology to the yeast orthologues, HDACs are classified in four classes (Dokmanovic, Clarke, & Marks, 2007) (Matouk & Marsden, 2008): Type I (HDAC1, HDAC2, HDAC3, HDAC8), Type II (IIa: HDAC4, HDAC5, HDAC7, HDAC9; IIb: HDAC6, HDAC10), Type III (Sirtuin 1-Sirtuin 7, NAD^+-dependent), and Type IV (HDAC11). The targets of HDACs include core histone proteins and some non-histone proteins. In the next section, we will overview the specific role of HATs (with a focus on p300) and individual HDAC isoforms (including sirtuins) in atherosclerosis *in vitro* and *in vivo*.

*2.2.2.1. Histone acetylation enzyme **p300**.* In the family of HAT proteins, p300 represents an important transcriptional coactivator and chromatin modifier that regulates gene transcription (Roth et al., 2001). Based on the current literature, p300 primarily acts pro-atherogenic by interacting with and regulating NF-κB-dependent expression of multiple pro-inflammatory gene in vascular cells (Khyzha et al., 2017). Clinically relevant, increased levels of acetylated H3K9 and H3K27 are observed in VSMCs, macrophages, and endothelial cells from human advanced atherosclerotic plaques, compared with healthy controls. The level of acetylated H3K9 in VSMCs and macrophages correlates with the extent of plaque severity (Greissel et al., 2015; Greissel et al., 2016). 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) is an oxidized lipid metabolite derived from 12/15-lipoxygenase that promotes multiple dysfunctional events in VSMCs. 12(S)-HETE promotes H3K9/14Ac recruitment to IL6 and MCP1 gene promoters, which is attenuated by PP2 (an inhibitor of Src) and 12/15-lipoxygenase deficiency (Reddy, Sahar, Villeneuve, Lanting, & Natarajan, 2009). Activation of 5' AMP-activated protein kinase (AMPK) by tool drug AICAR or a constitutively active mutant of AMPK (AMPK-CA) inhibits p300 acetyltransferase activity by promoting Ser89 phosphorylation, which decreases TNFα-induced p300-mediated acetylation of NF-κB. The outcome is reduced binding of NF-κB to promoters of pro-adhesive molecule VCAM1, and attenuated monocyte adhesion to endothelial cells (Zhang, Qiu, Wang, Zhang, & Xia, 2011). Total or VSMC-specific deletion of KLF15 also increased inflammatory responses, and diet-induced atherosclerosis by altering the level of acetylated NF-κB via interaction with p300 (Lu et al., 2013). In line with this evidence, cholesterol crystals and 15(S)-HETE induce p300 tyrosine phosphorylation via reactive oxygen species (ROS) production. The phosphorylated p300 promotes STAT1 acetylation and its interaction with PPARγ, thereby inducing CD36-dependent oxLDL uptake and foam cell formation (Kotla & Rao, 2015; Kotla, Singh, & Rao, 2017). While, curcumin**,** a pharmacological inhibitor of p300 (Balasubramanyam et al., 2004), has been reported to promote cholesterol efflux and display potent anti-inflammatory effects in macrophages via inhibiting JNK, NF-κB activation, while activating nuclear factor erythroid 2–related factor 2 (Nrf2) and LXRα pathway (Liu et al., 2014; Zhong, Feng, Fan, & Li, 2018). In summary, p300 is an important positive regulator of inflammation, oxidative stress, and macrophage-derived foam cell formation. Thus, p300 seems to be a promising target for reversing multiple cellular dysfunction in atherosclerosis.

2.2.2.2. Histone deacetylases.

A. HDAC3

HDAC3 is a member of class I HDAC. It is implicated in the differentiation of endothelial progenitor cells (Zeng et al., 2006). The first examination of HDAC3 in atherosclerotic conditions was performed by Zampetaki *et al.* (Zampetaki et al., 2010), who showed that HDAC3 expression is increased in arterial regions of disturbed blood flow. In cultured endothelial cells, disturbed flow induced the phosphorylation of HDAC3 at serine/threonine residues and increase the protein stability of HDAC3. Gain- and loss-of-function assays suggest that HDAC3 interacts and activates Akt phosphorylation and activity, thereby regulating endothelial cell survival. In aortic isografts of $ApoE^{-/-}$ mice depleted with HDAC3 (by shRNA), an increase in atherosclerotic plaque area and mortality rate was observed in shHDAC3-infected grafts (with signs of basement membrane rupture). This finding suggests that HDAC3 is an endothelial cell survival molecule in atherosclerosis development in response to disturbed hemodynamic forces (Zampetaki et al., 2010). In addition, HDAC3 also inhibits aspirin induced eNOS acetylation, ensuing NO production, and vasorelaxation (Jung et al., 2010). In macrophages, van den Bossche *et al.* have shown that HDAC3 inhibition in macrophages renders an atheroprotective phenotype, by increasing histone acetylation and accompanying gene expression of efflux transporters ABCA1 and ABCG1, as well as increasing anti-inflammatory and anti-apoptotic capacities (Van den Bossche et al., 2014). In human atherosclerotic plaques, HDCA3 is upregulated in ruptured plaques compared to stable plaques. Further study reveals that myeloid cell-specific deletion of HDAC3 (using bone marrow transplantation) favors plaque stability (by increasing plaque collagen content) in $LDLR^{-/-}$ mice fed an atherogenic diet (Hoeksema et al., 2014). Furthermore, HDAC3-deficient macrophages acquired an anti-inflammatory phenotype and showe less foam cell formation. Moreover, HDAC3 deletion lead to pro-fibrotic program via epigenetic regulation of TGFβ1, which allows VSMCs to generate collagen to stabilize the plaques (Hoeksema et al., 2014). Taken together, this evidence suggests the necessity to employ macrophage specific deletion of HDAC3 (without influencing the pro-survival effects in endothelial cells) as a promising strategy to prevent atherosclerosis development.

B. HDAC5

HDAC5 belongs to the family of class IIa HDAC. A previous study (Xu et al., 2007) has found that Ang-II stimulates protein kinase D (PKD)-dependent HDAC5 phosphorylation (at Serine259/498 residues), and promotes HDAC5 nuclear export, thus mediating Ang-II-mediated VSMC hypertrophy. Mechanistic studies indicate that HDAC5 is recruited to histone H4 at the smooth muscle-alpha-actin promoter (Yoshida, Gan, & Owens, 2008). Laminar blood flow can also promotes phosphorylation-dependent nuclear export of HDAC5 and derepress the expression of KLF2 and downstream gene eNOS in endothelial cells (Kwon, Wang, Xu, & Jin, 2014; Wang et al., 2010). Although direct evidence of HDAC5 in atherosclerosis is lacking, this evidence suggests that HDAC5 inhibition may confer protective effects against neointimal hyperplasia, and atherosclerosis.

C. HDAC9

HDAC9 belongs to the family of class IIa HDAC. Recent genome-wide association studies (GWAS) have identified several genetic variants of HDAC9 associated with carotid intima-media thickness, peripheral arterial disease, CAD, and ischemic stroke of large vessel (Hacke & Grond-Ginsbach, 2012; Malik et al., 2017; Markus et al., 2013; Matsukura et al., 2015; Shroff et al., 2018; Wang et al., 2016). By immunohistochemical staining, HDAC9 was mainly expressed in VSMCs and

endothelial cells of cerebral and systemic arteries. More importantly, HDAC9 gene expression was upregulated in carotid plaques from patients compared with plaque-free control arteries (Markus et al., 2013). Although GWAS shows potential role of HDAC9 in atherosclerosis, the direct evidence of HDAC9 in atherosclerosis was demonstrated by Cao et al. (2014), who observed that HDAC9 expression is induced upon monocyte differentiation to macrophages and systemic deletion or hematopoietic cells-restricted deletion of HDAC9 attenuated atherosclerosis in LDLr$^{-/-}$ mice fed an atherogenic diet. The mechanism is linked to reduction of pro-inflammatory genes, and an increase of M2 macrophage polarization. HDAC9 deletion also promotes cholesterol efflux from macrophages via increasing acetylated H3 and H3K9 to efflux related gene promoter. The pro-atherogenic role of HDAC9 was later confirmed by others using ApoE$^{-/-}$ mice, another well-established model of atherosclerosis (Azghandi et al., 2015). Studies in cultured cells also show that HDAC9 expression is increased in endothelial cells exposed to apoptosis-inducing dose of oxLDL. HDAC9 depletion reverses oxLDL-induced endothelial cell apoptosis and the inflammatory responses (by reducing TNFα and MCP1 expression) (Han, Han, Wang, Shen, & Dong, 2016). These findings collectively suggest that targeted inhibition of HDAC9 represents a novel promising strategy to reduce atherosclerosis.

D. Other HDACs

HDAC1 (type I HDAC) expression is increased and H3K9 acetylation (H3K9ac) is decreased in the aorta of ApoE$^{-/-}$ mice challenged with high methionine diet to induce hyperhomocysteinemia. HDAC1 overexpression decreased global H3K9ac level and promoted lipid accumulation in foam cells (Zhao et al., 2017). **HDAC2** (type I HDAC) overexpression (but not HDAC 1, 3, or 8) in human aortic endothelial cells suppresses arginase 2 (Arg2) expression, while, HDAC2 depletion by siRNA increase the expression of Arg2. HDAC2 regulates Arg2 by direct binding to Arg2 gene promoter. Overexpression of HDAC2 functionally blocked oxLDL induced impairment of endothelium-dependent vasorelaxation (Pandey et al., 2014). Similarly, in human aortic endothelial cells, oxLDL increases global level of protein NEDDylation (a post-translational modification of proteins linked to ubiquitination and degradation) and reduces HDAC2 expression. Further studies indicate that HDAC2 is a substrate for NEDD8 conjugation. Whereas, treatment with MLN4924 (an inhibitor of protein NEDDylation), prevented oxLDL induced HDAC2 downregulation and Arg2 upregulation, thereby improves endothelial function (Pandey et al., 2015). These findings suggest that HDAC2 activation represents a novel therapy for endothelial dysfunction and atherosclerosis. **HDAC4 (**Class IIa HDAC). A multiethnic association study indicates a robust association of a single-nucleotide polymorphism (rs3791398) in HDAC4 with carotid intima/media thickness (Lanktree, Hegele, Yusuf, & Anand, 2009). Further evidence showing the involvement of HDAC4 in neointimal hyperplasia and atherosclerosis is lacking. **HDAC6 (**Class IIb HDAC) expression/activity was selectively increased in oxLDL-treated human aortic endothelial cells, and selective inhibition of HDAC6 by tubacin and HDAC6 siRNA increased CSE-dependent H_2S production, and prevented oxLDL-induced oxidative injury in endothelial cells (Leucker et al., 2017). This evidence suggests HDAC6 may represent a promising therapeutic target to prevent endothelial dysfunction and atherosclerosis development. The specific role of HDAC6 in atherosclerosis warrants further studies in experimental animal models using genetic and/or pharmacological inhibition of HDAC6.

E. SIRT1

Sirtuins (SIRTs) are class III NAD$^+$-dependent histone deacetylases, which catalyze deacetylation/deacylation reactions on histone and protein substrates. This type of deacetylation generates deacetylated substrate, O-acetyl-ADP-ribose, and nicotinamide (Finkel, Deng, & Mostoslavsky, 2009). Some members of SIRTs also have mono-ADP-ribosylation activity (Hassa, Haenni, Elser, & Hottiger, 2006). SIRTs are activated during calorie restriction and are implicated in many pathophysiological processes, including aging and cell metabolism. To date, seven members of SIRTs have been identified: SIRT1 to SIRT7 (Finkel et al., 2009). SIRTs share the conserved catalytic domain implicated in substrate deacetylation, but differ as to tissue distribution, intracellular localization, and substrate of choice and cellular functions. SIRT1, SIRT6 and SIRT7 are found mainly in cell nuclei, while SIRT3, SIRT4 and SIRT5 are localized in the mitochondria, and SIRT2 is localized only in the cytosol. Among SIRTs, SIRT1, SIRT2, SIRT3, and SIRT6 provide protective effects against atherosclerosis (D'Onofrio et al., 2018; Sosnowska et al., 2017; Vitiello et al., 2017; Winnik et al., 2015; Xu, Bai, & Jin, 2016).

SIRT1 is the best characterized nuclear-localized SIRT that has broad cardiovascular protective actions and metabolism-regulating effects (Chang & Guarente, 2014). Well-established substrates of SIRT1 include histones (such as acetylated H3K9, and H3K56) and non-histone proteins (such as NF-κB, forkhead transcription factors (FOXOs), p53, peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α), LXRα, 66-kDa Src homology 2 domain-containing protein (p66shc), eNOS, and several DNA damage repair proteins (Ku70 and DNA-PK)) (Kitada, Ogura, & Koya, 2016; Kumar et al., 2017). In the vasculature, SIRT1 negatively regulates vascular inflammation, endothelial dysfunction, VSMCs proliferation and migration, ROS generation, foam cell formation, impaired autophagy, DNA damage response, and senescence, thereby preventing vascular aging, intimal hyperplasia, and atherosclerosis (D'Onofrio et al., 2018; Sosnowska et al., 2017; Vitiello et al., 2017; Winnik et al., 2015; Xu, Bai, & Jin, 2016). SIRT1 protein expression is decreased in mouse models of atherosclerosis and human patients (Gorenne et al., 2013). SIRT1 deficient mice in ApoE$^{-/-}$ background increases atherosclerosis development (Stein et al., 2010; Stein et al., 2010). In addition, endothelial cell-(Wen et al., 2013), and VSMC-specific (Gorenne et al., 2013) ablation of SIRT1 increases atherosclerosis development in mice. Macrophage-specific knockout of SIRT1 increased the incidence and severity of abdominal aortic aneurysm formation (induced by Ang-II) by increasing macrophage inflammation and modulating M1/M2 macrophage polarization (Zhang et al., 2018). Pharmacological inhibition of SIRT1 by EX-527 promotes atherosclerosis in ApoE$^{-/-}$ mice through autophagy impairment (Yang et al., 2017). In contrast, pharmacological activation of SIRT1 by resveratrol (Berbee et al., 2013; Fukao et al., 2004; Howitz et al., 2003; Norata et al., 2007), SRT1720 (Chen, Zhang, Cai, Zhao, & Dai, 2015), SRT3025 (Miranda et al., 2015) inhibits experimental atherosclerosis. Also, endothelial cell-specific SIRT1 transgene attenuates atherosclerosis in ApoE$^{-/-}$ mice (Zhang et al., 2008). This evidence suggests an overall atheroprotective role of SIRT1 and that SIRT1 activation or overexpression may serve as a novel therapeutic strategy for treating atherosclerosis despite some controversy (Qiang et al., 2011).

SIRT1 and endothelial function. SIRT1 exerts endothelial protective effects by increasing eNOS-dependent NO production (Mattagajasingh et al., 2007), anti-inflammatory pathways (Liu et al., 2017; Pan, Yu, Huang, & Zhu, 2016), reducing oxidative stress (Zhang et al., 2017), reducing endoplasmic reticulum (ER) stress (Kassan et al., 2017), limiting inflammasome activation (Li et al., 2016; Li et al., 2017), reducing senescence (Li et al., 2016), and improving autophagy dysfunction (Liu et al., 2015; Zhang et al., 2016). Pharmacological activation of SIRT1 by SRT1720 attenuated LPS-induced lung injury, by decreasing endothelial tight junction permeability (Fu et al., 2018; Zhang et al., 2017). Also, SIRT1 activation was responsible for Ginkgolide B mediated anti-inflammatory effects in oxLDL-stimulated human endothelial cells via reducing LOX-1 and ICAM1 expression (Ma et al., 2013). SIRT1 activation is also responsible for Apelin mediated protective effects against Ang-II mediated endothelial cell senescence (Yang et al., 2018) as well as for chlorogenic acid mediated protective effects against H_2O_2-induced endothelial apoptosis and mitochondrial dysfunction (Tsai et al., 2018). Endothelial-mesenchymal transition (EndoMT) is an important mechanism contributing to atherosclerosis (Souilhol,

Harmsen, Evans, & Krenning, 2018). SIRT1 inhibits TGFβ-induced EndoMT via direct deacetylation of Smad4 (Li et al., 2018). SIRT1 activation by red wine polyphenol resveratrol inhibits high glucose-induced oxidative stress, mitochondrial dysfunction and ensuing apoptosis in human endothelial cells (Wang, Wang, Zhao, & Li, 2017), underscoring the therapeutic potential of SIRT1 activation in treating the cardiovascular complications of diabetes. SIRT1 expression is decreased in circulating monocytes from patients with CAD, associated with upregulation of LOX-1-dependent oxidative stress, apoptosis, and increased monocytes adhesion to endothelial cells (Chan et al., 2017).

SIRT1 and VSMC function. In VSMCs, SIRT1 expression is gradually lost during advanced aging process in humans (Thompson, Wagner, & Rzucidlo, 2014). SIRT1 protects against oxidative DNA damage and inhibits atherosclerotic plaque development in hyperlipidemic mice, partially through activating Nijmegen breakage syndrome-1 (NBS-1) (Gorenne et al., 2013) and 8oxoG DNA glycosylase I (OGG1) (Shah et al., 2018). In contrast, VSMC-specific SIRT1 transgene attenuates Ang-II as well as injury induced vascular remodeling in mice (Li et al., 2011; Liu et al., 2014). In addition, SIRT1 transgene or pharmacological activation reduces MMP-2 production (induced by platelet activating factor (PAF)) via decreasing expression of PAF receptor in VSMCs, indicating the role of SIRT1 in preventing plaque destabilization (Kim, Bae, Lee, Park, & Kim, 2015). Pharmacological activation (by resveratrol and SRT1720) or VSMC-specific overexpression of SIRT1 attenuates arterial stiffness induced by high-fat high-sucrose diet by reducing NF-κB dependent VCAM1 expression and vascular oxidative stress (Fry et al., 2016). SIRT1 also inhibits Ang-II-induced VSMC hypertrophy (Li et al., 2011) and associated inflammation, as well as migration of VSMC-derived foam cells after oxLDL stimulation (Yang et al., 2017; Zhang et al., 2016).

SIRT1 and macrophage function. SIRT1 is a master regulator of inflammatory responses in macrophages by chromatin modulation, as macrophage specific deletion of SIRT1 leads to the hyperacetylation of NF-κB and dependent inflammatory genes expression *in vitro* and *in vivo* (Schug et al., 2010). Macrophages from SIRT1$^{+/-}$ApoE$^{-/-}$ mice show reduced oxLDL uptake and macrophage-derived foam cell formation. The mechanism is related to decreases in LOX-1 expression *via* suppressing the NF-κB pathway (Stein, Lohmann, et al., 2010). On the other hand, SIRT1 inhibits foam cell formation by deacetylating and activating liver X-receptor (LXR)-dependent ABCA1 and ABCG1 expression, thereby promoting the reverse cholesterol transport (Zeng et al., 2013). The net outcome of these effects is the retardation of foam cell formation in macrophages. More recently, Du et al. (2018) have shown that CSE/H_2S treatment increases SIRT1 deacetylase activity and activated target proteins p53, p65, and SREBPs, thereby reducing vascular inflammation, inhibiting macrophage cholesterol uptake and hepatic cholesterol synthesis. Mechanistic studies show that CSE/H_2S induces SIRT1 sulfhydration at zinc finger domains and prevents SIRT1 degradation (Du, Lin, et al., 2018), indicating a new mechanism of regulating SIRT1 protein expression/activity via H_2S dependent sulfhydration. In addition, SIRT1-mediated effects on upregulating ABCA1-mediated cholesterol efflux and resultant foam cell formation can be induced by several pharmaceutical agents, such as berberine (Chi, Peng, Pan, Hu, & Zhang, 2014), curcumin (Lin et al., 2015) and Tanshindiol C (Yang et al., 2018). In addition, SIRT1 also promotes efferocytosis of oxLDL-induced apoptotic macrophages via inducing autophagy (Liu, Zhang, Guo, Li, & Xu, 2014).

In summary, SIRT1 is a deacetylase that regulates a plethora of important metabolic and physiologic processes including cellular metabolism, stress resistance, apoptosis and senescence. Its upregulation reduces inflammation in atherosclerotic lesions, reverses cholesterol transport, formation of macrophage-derived foam cells, and reduces overall risk for development of cardiovascular diseases (D'Onofrio et al., 2018; Sosnowska et al., 2017; Vitiello et al., 2017; Winnik et al., 2015; Xu, Bai, & Jin, 2016). In aging research, SIRT1 is one of the so-called longevity markers. The expression of SIRT1 gradually decreases with aging. Thus, SIRT1 activation represents a promising therapeutic strategy to treat multiple cardiovascular disorders including atherosclerosis (Paneni, Diaz Canestro, Libby, Luscher, & Camici, 2017).

F. SIRT2

SIRT2 is a SIRT member localized in the cytosol. Several genetic variants of SIRT2 are associated with acute myocardial infarction (Yang et al., 2017). More recently, Zhang *et al.* (Zhang, Ma, & Xiang, 2018) used gain- and loss-of-function studies to study the role of SIRT2 in atherosclerosis using LDLr$^{-/-}$ mice. The authors observed that SIRT2 attenuates and stabilizes atherosclerotic plaques. SIRT2 overexpression also decreased markers of macrophage infiltration (MOMA-2 staining) and apoptosis (TUNEL staining). Mechanistically, lentivirus-SIRT2 infection reduces the expression of M1 macrophage marker-iNOS, while increases that of M2 macrophage marker Arg1. This new finding suggests an atheroprotective role of SIRT2 by fine-tuning the macrophage polarization process (Zhang, Ma, & Xiang, 2018). Further studies are warranted to understand the deacetylation targets of SIRT2 in regulating macrophage polarization program.

G. SIRT3

SIRT3 is a SIRT member exclusively localized in mitochondria. SIRT3 regulates multiple aspects of mitochondrial functions, such as mitochondria biogenesis, autophagy and tissue homeostasis, particularly under stress conditions. SIRT3 knockout mice are normal at birth, but exhibit hyperacetylation of multiple mitochondrial proteins, such as manganese-dependent superoxide dismutase (Mn-SOD, also known as SOD2). SIRT3$^{-/-}$ mice have disorder in lipid metabolism, and aberrant hepatic accumulation of triglycerides and acylcarnitines under fasting conditions. SIRT3 protects against exaggerated oxidative stress by directly deacetylating and activating Mn-SOD. However, SIRT3 deficiency only mildly impairs endothelium-dependent relaxation under challenge with an atherogenic diet (Winnik et al., 2016). Also, in a diet-induced atherosclerosis model in LDLr$^{-/-}$ mice, SIRT3 deficiency does not affect lesion formation, nor plaque instability, despite hepatic protein hyperacetylation in the mitochondria and elevated circulating level of malondialdehyde (an index of lipid peroxidation) (Winnik et al., 2014). SIRT3 deficiency accelerates thrombus formation by increasing tissue factor activity and the formation of neutrophil extracellular traps in a combined model of carotid thrombosis by a laser and LPS challenge (Gaul et al., 2018). Of clinical relevance, reduced SIRT3 expression was observed in CD14^{+} leukocytes from patients with ST-elevation myocardial infarction (Gaul et al., 2018). Therefore, increasing SIRT3 expression/activity may provide protection against thrombotic complications in patients with myocardial infarction.

H. SIRT6

SIRT6 has overlapping cellular localization and biological functions with SIRT1, in terms of regulating endothelial cell senescence, leukocyte adhesion, macrophage-derived foam cell formation, macrophage polarization, lipid metabolism, and inflammatory responses (D'Onofrio et al., 2015; D'Onofrio et al., 2018; Sosnowska et al., 2017; Vitiello et al., 2017; Winnik et al., 2015; Xu, Bai, & Jin, 2016). Reduced SIRT6 expression is observed in hypercholestrolemic ApoE$^{-/-}$ mice (Liu, Wang, Huang, Li, & Liu, 2016) as well as in carotid atherosclerotic plaques from patients with atherosclerosis with (Balestrieri et al., 2015) or without diabetic conditions (Zhang et al., 2016). SIRT6 alters gene expression by deacetylating epigenetic marks of H3K9, H3K18, and H3K56 on histones and several non-histone protein substrates (D'Onofrio et al., 2015; D'Onofrio et al., 2018; Sosnowska et al., 2017; Vitiello et al., 2017; Winnik et al., 2015; Xu, Bai, & Jin, 2016). For example, hepatic SIRT6 deficiency increases LDL-cholesterol in mice by regulating important genes in regulating lipid metabolism, such as PCSK9 and sterol-regulatory element binding protein 2 (SREBP2), by deacetylating H3K9 and H3K56 at promoters of PCSK9 (Tao, Xiong, DePinho, Deng,

& Dong, 2013a) and SREBP2 (Tao, Xiong, DePinho, Deng, & Dong, 2013b).

The direct atheroprotective role of SIRT6 in atherosclerotic plaque development has been documented in several animal models of atherosclerosis. SIRT6 heterozygous ($SIRT6^{+/-}$) mice show an increase in atherosclerotic lesions by upregulating the expression of natural-killer group 2 member D (NKG2D) ligand in macrophages and endothelial cells. This effect leads to the activation of natural killer cells and augmented production of inflammatory cytokines (Zhang, Ren, et al., 2016). $SIRT6^{+/-}/ApoE^{-/-}$ and SIRT6 depleted $ApoE^{-/-}$ mice also show increased atherosclerotic lesion area, impaired endothelium-dependent vasodilation, and upregulation of VCAM-1 (Liu, Wang, Huang, et al., 2016; Xu et al., 2016; Zhang, Ren, et al., 2016). Additional evidence suggests that SIRT6 deacetylates H3K9 at promoters of atherosusceptible gene-tumor necrosis factor superfamily member 4 (TNFSF4) and reduce the expression of TNFSF4 (Xu, Yin, et al., 2016).

In vitro, when ECs are exposed to high-glucose media, SIRT6 expression was downregulated, accompanied by hyperactivation of NF-κB-dependent pro-inflammatory pathway (Balestrieri et al., 2015). SIRT6 has been shown to reduce atherosclerosis by inhibiting foam cell formation. Specifically, under oxLDL stimulation, macrophage-derived foam cell formation is reduced by SIRT6 *via* induction of autophagy and cholesterol efflux (He et al., 2017). In particular, overexpression of SIRT6 in foam cells increases the levels of ABCA1 and ABCG1, activates cholesterol efflux, and reduces the level of miR-33. Indeed, transfection of miR-33 mimics into cells overexpressing SIRT6 reduces foam cell formation and reverses autophagy flux induction (He et al., 2017). Given that cholesterol efflux is regulated by the LXR/ABCA1 (G1) pathway, and SIRT1 interacts, deacetylates and activates LXR activity (Li et al., 2007) to repress foam cell formation, it merits further exploration whether SIRT6 can also attenuates foam cell formation by deacetylating and activating LXR in the nuclear. In addition to regulating foam cell formation, a recent study has shown that myeloid cell-specific deletion of SIRT6 drives NF-κB hyperactivation, followed by IL6 production and STAT3 activation. This effect drives macrophage polarization toward M1 type, underscoring the important role of macrophage-derived SIRT6 in preventing diet-induced inflammation and insulin resistance (Lee et al., 2017). Independent of the promising results about the atheroprotective role in atherosclerosis in mice models and *in vitro*, it still remains to be seen, whether SIRT6 overexpression and/or modulation by specific activators are able to rescue vascular inflammation and retard atherosclerotic plaque development in humans.

To date, there is no literature regarding the direct roles of other SIRTs, such as SIRT4, and SIRT5, and SIRT7 in atherosclerosis. It remains elusive whether these SIRTs also play a role in regulating vascular functions and atherosclerosis.

2.3. RNA-based mechanisms

In addition to DNA methylation and histone modifications, recent researches convincingly demonstrate the diverse biological functions of several RNA-based mechanisms, including non-coding RNAs (ncRNAs). Some ncRNAs contain small open reading frames which encode functional peptides. Based on size difference, non-coding RNAs are categorized into: (1) small non-coding RNAs (<200 bp), including microRNAs (miRNA), and PIWI-interacting RNAs (piRNA); (2) long non-coding RNAs (lncRNAs, >200 bp) including long intergenic non-coding RNA (lincRNA), circular RNA (circRNAs), natural antisense transcripts (NATs), and enhancer RNAs (eRNAs) (Boon, Jae, Holdt, & Dimmeler, 2016). Mounting evidence has demonstrated that ncRNAs represent another important epigenetic mechanism in the development of atherosclerosis and its vascular complications. The detailed role of ncRNAs in cardiovascular health and diseases is recently reviewed elsewhere (Aryal & Suarez, 2018; Das, Samidurai, & Salloum, 2018; Lucas, Bonauer, & Dimmeler, 2018). In this section, we will briefly discuss the updated role of miRNAs, and lncRNAs (including circRNAs) in atherosclerosis.

2.3.1. miRNA

miRNAs are highly conserved, small ncRNAs of 20 ~ 40 nucleotides that emerged as key post-transcriptional regulators of gene expression which act by binding to the 3′-untranslated region of target mRNA, thereby degrading mRNA transcripts or blocking protein translation or inducing gene degradation (Lucas et al., 2018). DNA methylation and demethylation is also important for miRNA regulation in various types of cancer (Ahmad, Li, Bao, Kong, & Sarkar, 2014). More than a half of all miRNA genes are related with CpG islands, thus susceptible to methylation. Other miRNAs are regulated by histone modifications with or without concurrent DNA methylation (Wang et al., 2013).

The contribution of miRNAs to atherosclerosis has been extensively investigated in the past decade. As can be seen from Table 2, miRNAs are important in regulating multiple cellular functions involved in atherosclerosis, such as endothelial function/dysfunction, cholesterol metabolism, cell fate, inflammation, and oxidative stress. In macrophages, miRNAs mediate inflammatory responses, cholesterol uptake, cholesterol efflux, monocyte differentiation, and M1/M2 polarization. In ECs, miRNAs regulate inflammation, leukocyte adhesion, eNOS-dependent NO production, and EndoMT. In VSMCs, miRNAs regulate VSMC differentiation, phenotypic switch, calcification, inflammation, apoptosis, proliferation, and migration. Accumulating evidence has also indicated that miRNAs can serve as a novel class of diagnostic or prognostic markers in atherosclerotic plaque progression and instability (Feinberg & Moore, 2016; Laffont & Rayner, 2017; Leeper & Maegdefessel, 2018; Poller et al., 2018; Schober & Weber, 2016). As circulating miRNAs can be detected in peripheral blood components (such as leukocytes), and urine, miRNAs can be explored as potential biomarkers for the development of atherosclerosis as well as the severity of atherosclerosis (Feinberg & Moore, 2016). These atherorelevant miRNAs can be regulated by different disease-associated stimuli or pharmacological agents. Evidence implicating miRNA in the development of atherosclerosis was recently the subject of multiple excellent systematic reviews elsewhere (Feinberg & Moore, 2016; Laffont & Rayner, 2017; Leeper & Maegdefessel, 2018; Poller et al., 2018; Schober & Weber, 2016).

2.3.2. Long non-coding RNAs (LncRNAs)

LncRNAs represent a family of non-protein coding transcripts >200 nucleotides, which occupy a large portion of the human genome. lncRNAs have long been considered as “dark matter” of the human genome with unknown biological functions (Uchida & Dimmeler, 2015). A growing body of evidence draws however a conclusion that lncRNAs play critical roles in regulating multiple pathophysiological processes in cardiovascular diseases (Das, Samidurai, & Salloum, 2018; Simion, Haemmig, & Feinberg, 2018; Uchida & Dimmeler, 2015; Weirick, Militello, & Uchida, 2018). A subset of lncRNAs might be exploited as useful biomarkers for cardiovascular diseases. A recent study (Arslan et al., 2017) has analyzed the expression levels of five lncRNAs known to be associated with CAD, including ANRIL (antisense noncoding RNA in the INK4 locus), MIAT (myocardial infarction associated transcript), MALAT1 (metastasis associated lung adenocarcinoma transcript 1), KCNQ1OT1 (KCNQ1 overlapping transcript 1), and aHIF, by real time-PCR. The authors observed that ANRIL and MIAT expression was higher, while MALAT1 expression was lower in atherosclerotic coronary artery plaques, compared with non-atherosclerotic internal mammary artery. These studies suggest that some lncRNAs are strongly associated with human atherosclerosis, raising the therapeutic possibility to treat atherosclerosis by targeting de-regulated lncRNA expression (Arslan et al., 2017).

LncRNA can regulate gene expression (either activating or suppressing) via transcriptional, post-transcriptional, and epigenetic mechanisms. Compared with miRNAs, lncRNAs have more diverse functions

by acting as chromatin regulators, sponge, decoy, guide, molecular scaffold, and enhancers (Uchida & Dimmeler, 2015). LncRNAs also mediate signal transduction, such as protein phosphorylation, and protein trafficking (Gomes et al., 2017; Lucas et al., 2018). Emerging studies in the past 2–3 years have shown that lncRNAs are important regulators of vascular homeostasis and function in cardiovascular health and disease (Table 3). More and more lncRNAs have been identified and functionally characterized in response to pathophysiological stimuli or in different models of vascular disease states. However, our knowledge of the mechanisms whereby these lncRNAs control gene expression and regulate important cellular functions is still in its infancy.

Like miRNA, lncRNAs not only regulate gene expression but also participate epigenetic regulation like DNA methylation and histone modifications (Khalil et al., 2009; Voelter-Mahlknecht, 2016). Furthermore, lncRNA expression is tissue and cell specific, and is developmentally regulated. Many lncRNAs are associated with chromatin remodeling complexes to guide them to specific locations inside the genome (Khalil et al., 2009). PRC2 seems to be particularly involved in establishing heterochromatin states by recruiting H3K27me3 mark to target gene promoters. Consequently, PRC2 together with lncRNA might serve as transcriptional repressing complex by silencing specific genomic loci. Khalil et al. (Khalil et al., 2009) suggested that lncRNA TUG1 may function in such epigenetic mechanism. The authors propose that following DNA damage, TUG1 is induced through direct binding to p53, which then binds PRC2 and may thus repress various cell-cycle related genes.

In terms of vascular function, LncRNAs regulate endothelial function and dysfunction (such as proliferation, migration, apoptosis, angiogenesis, and EndoMT) (e.g. STEEL (Man et al., 2018), MALAT1 (Michalik et al., 2014; Zhang, Tang, Hamblin, & Yin, 2018), MEG3 (Boon et al., 2016; Ruan et al., 2018), MANTIS (Leisegang et al., 2017)). LncRNAs also modulate VSMC phenotypes (Simion et al., 2018) (phenotypic switch, proliferation, migration, apoptosis) (e.g. H19 (Zhang et al., 2018a), ANRIL (Congrains et al., 2012), SMILR (Ballantyne et al., 2016), SENCR (Bell et al., 2014), MYOSLID (Zhao et al., 2016)). A large body of evidence also implicated lncRNAs in regulating monocyte/macrophage functions, such as inflammation (e.g. lincRNA-Cox2 (Yu et al., 2016), linc00305 (Zhang et al., 2017), THRIL(Li et al., 2014)), foam cell formation (e.g. LeXis (Tontonoz et al., 2017), MeXis (Sallam et al., 2018), and NEAT1 (Huang-Fu, Cheng, Wang, Li, & Wang, 2018)), and M1/M2 polarization (e.g. GAS5(Ito, Asai, Suzuki, Kobayashi, & Suzuki, 2017)), and lipid handling (e.g. H19 (Han, Ma, Wang, & Wang, 2018)). Several lncRNAs may serve as biomarkers for CAD (e.g. LncRNA-GAS5 (Zhang, Wang, et al., 2016), ENST00000444488.1 (Li et al., 2018), Upperhand (Li et al., 2018), H19 (Zhang et al., 2017), LIPCAR (Zhang, Gao, et al., 2017), LncPPARδ (Cai et al., 2016), and CoroMarker (Cai et al., 2016)). Biological functions and molecular mechanisms of lncRNAs implicated in atherosclerosis from cell culture studies, experimental animal models and human patients are summarized in Table 3. Recently, Miao *et al.* (Miao et al., 2018) has shown that an enhancer-associated lncRNA that enhances eNOS expression (LEENE, also known as linc00520) regulate eNOS expression, NO production, and monocyte adhesion. LEENE recruits RNA Pol II to eNOS gene promoter, thereby enhancing eNOS nascent RNA transcription (Miao, Ajami, et al., 2018). LncRNAs expression can also be modulated by therapeutic agents (such as melatonin (Zhang et al., 2018) and statins (Miao, Ajami, et al., 2018)), atherosclerosis-causing stimuli (oxLDL (Bao et al., 2018)), and biomechanical factors (such as shear stress (Huang et al., 2017) and cyclic strain (Yao et al., 2017)).

Circular RNAs (circRNAs) is a large category of ncRNAs ubiquitously expressed in eukaryotic cells (Szabo & Salzman, 2016). For a long time, the biological functions of circRNAs were underestimated. Deep-scale sequencing has enabled the identification of disease-associated circRNAs. Recently, a circRNA-miRNA-mRNA network has been described in a rabbit model of atherosclerosis (Zhang et al., 2018). This circRNA atlas identified seven dysregulated circRNAs which have primary function in mediating cell adhesion/activation as well as immune response (Zhang, Zhang, Zhang, et al., 2018). Different from conventional linear RNAs, circRNAs are formed by so called backsplicing, which allow for exonuclease resistance and high stability (Fu, Jiang, Li, Hu, & Guo, 2018). Emerging evidence has shown that circRNAs are involved in the development of atherosclerosis. For example, ANRIL on chromosome 9p21 modulates ribosome RNA maturation and atherosclerosis in humans (Holdt et al., 2016). ANRIL binds to pescadillo homologue 1 (an essential assembly factor in 60S-preribosome), and affects exonuclease-mediated pre-ribosomal RNA processing and ribosome biogenesis in VSMCs as well as macrophages. By doing so, ANRIL induces p53 activation, causing apoptosis and growth inhibition (Holdt et al., 2016). Another example is human circ0003575, which is increased in response to oxLDL-stimulation in endothelial cells. Depletion of circ0003575 increases the proliferation and capillary-like tube-forming ability of HUVECs (Li, Ma, & Yu, 2017). The role of circRNA in epigenetic regulation of gene expression, as observed for miRNAs or lncRNAs has yet to be elucidated. For a detailed review of the lncRNAs (including circRNAs) in atherosclerosis, we refer readers to several topical reviews recently (Das, Samidurai, & Salloum, 2018; Simion et al., 2018; Weirick et al., 2018).

The comparison of differentially expressed lncRNAs between control and human atherosclerotic patients, will help identify disease-associated lncRNAs. With the recent advances of novel technologies, such as RNA-sequencing, lncRNA arrays, more atherosclerosis-associated lncRNAs (defined as "Athero-lincs") are being discovered and biologically characterized. For example, a recent study (Li, Wang, Li, et al., 2018) has identified over 1000 aberrantly expressed lncRNAs in peripheral blood mononuclear cells isolated from patients with CAD at transcriptome-wide level. Loss of function studies suggest that some of these lncRNAs control the expression of several inflammation-related genes. There have appeared several promising strategies to modulate lncRNA expression to intervene in atherosclerosis, such as using adeno-associated virus (AAV) as expression vectors to deliver lncRNA locally or systemically, or using small interfering RNAs (siRNAs), GapmeRs locked-nucleic acid technology, or CRISPR/cas9-based genome-editing to deplete target lncRNAs. Deepened understanding of lncRNAs in atherosclerosis will provide conceptual and mechanistic insights into pathophysiology of atherosclerosis and accelerate the discovery of novel disease biomarkers and/or therapeutic targets (Simion et al., 2018). Future studies will be focused on identification of novel "atherolincs" and new therapeutic drugs that target these lncRNAs for atherosclerosis therapeutics.

3. Cardiovascular risk factors and epigenetic regulation

The human epigenome can be influenced by dynamic changes in modifiable risk factors during our life-time to modulate gene expression and functional states of the body. In this regard, multiple cardiovascular risk factors (Fig. 4) are associated with DNA methylation and histone modifications (Baccarelli et al., 2010; Zhong et al., 2016). These risk factors include dyslipidemia (Braun et al., 2016; Dekkers et al., 2016; Wang et al., 2017), hyperglycemia (Ling & Groop, 2009), hypertension (Wise & Charchar, 2016), overweight/obesity (Demerath et al., 2015), hyperhomocysteinemia (Zhou, Zhang, & Xu, 2014), aging (Lowe & Raj, 2014), environmental pollution (Chi et al., 2016), and lifestyle options (e.g., smoking (Joehanes et al., 2016), diet (Loche & Ozanne, 2016; Muka et al., 2016), and physical inactivity (Grazioli et al., 2017)). In view of the important roles of these risk factors in the development of CVD, AHA adopts "Life's Simple 7" to track progress toward the 2020 Impact Goal, and these seven factors include not-smoking, physical exercise, a healthy diet regimen, controlled body weight, cholesterol level, blood pressure, and blood glucose level (http://www.heart.org).

4. Trans-generational inheritance and trained immunity

Epigenetic alternations are generally reset during passage through germline transmission. Epigenetic programming can be transmitted to the next generation or even several generations in a gender-specific

Table 2
Role of miRNAs in the development of atherosclerosis.

Endothelial function and dysfunction (including mechanosensing, vascular tone, inflammation, senescence, apoptosis, pyroptosis, DNA damage, injury, and cell adaptation etc): miR-10a, miR-21, miR-22, miR-27a/b, miR-30-5p, miR-34a, miR-92a, miR-101, miR-103, miR-126, miR-135a, miR-142-3p, miR-143/miR-145, miR-146a, miR-155, miR-181b, miR-217, miR-211/222, miR-223, miR-365, miR-383-3p, miR-483, miR-633, miR-712
VSMC phenotypic switch, proliferation and migration, apoptosis, and inflammation: miR-21, miR-26a, miR-29b, miR125b, miR-181a; miR-221/222, miR-143/145
Monocyte differentiation, macrophage inflammation, foam cell formation, and M1/M2 macrophage polarization: miR-19a, miR-21, miR-26, miR-27a, miR-33, miR-98a, miR-106, miR-124, miR-125a, miR-128-1, miR-130b, miR-135a, miR-144, miR-146a, miR-147b, miR-148a, miR-155, miR-183, miR-212, miR-214, and miR-223, miR-301b, miR-302a, miR-let7a, miR-758
Biomarkers of CVD: miR-10b, miR-17, miR-19a, miR-29a, miR-30e-5p, miR-92a, miR-96, miR-122, miR-125a, miR-126, miR-145, miR-150, miR-155, miR-181b, miR-185, miR-211, miR-222, miR-342, miR-378, miR-484
Cholesterol homeostasis and lipid metabolism: miR-26, miR-27, miR-33, miR-92a, miR-106, miR-122, miR-128-1, miR-144, miR-145, miR-148a, miR-185, miR-223, miR-758
Atherosclerotic plaque stability/vulnerability: miR-19b, miR-21, miR-24, miR-29, miR-33, miR-133b, miR-143, miR-145, miR-155-5p, miR-210, miR-221/miR-222, miR-322, miR-451a, miR-483-5p, miR-494, miR-638, miR-4530,

Due to space limitations, atherosclerosis related miRNAs (Athero-miR) are summarized numerically based on several recent reviews (Das, Samidurai, & Salloum, 2018; Donaldson, Lao, & Zeng, 2018; Feinberg & Moore, 2016; Laffont & Rayner, 2017; Leeper & Maegdefessel, 2018; Lucas et al., 2018; Poller et al., 2018; Schober & Weber, 2016; Zhang, Price, & Fernandez-Hernando, 2018), and updated with most recent literatures as of the time of submission (Dai, Wu, Dai, Li, & Mehta, 2018; Du, Lu, & Sha, 2018; Eken et al., 2017; Hartmann et al., 2016; Jin et al., 2018; Katano, Nishikawa, Yamada, Yamada, & Mase, 2018; Li et al., 2017; Li et al., 2018; Li et al., 2018; Li, Ching, Luk, & Raffai, 2015; Li, Zhang, & Mao, 2018; Lian, Lv, Yu, & Wang, 2018; Luque, Farwati, Krupinski, & Aran, 2018; Ma et al., 2016; Markus et al., 2016; Miao, Zeng, & Gong, 2018; Natarelli et al., 2018; Qin et al., 2018; Sun et al., 2014; Ulrich et al., 2016; Wang et al., 2017; Wezel et al., 2015; Yang et al., 2018; Yilmaz, Isbir, Kunt, & Isbir, 2018; Yue, Lv, Zhang, & Kang, 2018; Zhong et al., 2018).
Abbreviations: VSMC, vascular smooth muscle cells; CVD, cardiovascular diseases; miR, micro-RNA.

manner. This phenomenon leads to the occurrence of transgenerational epigenetic inheritance, which can be caused by prenatal/perinatal exposure to environmental factors or alternations of nutritional status (Gabory, Attig, & Junien, 2009). Transgenerational epigenetic inheritance is often very common in the development of atherosclerosis (Leentjens et al., 2018). For example, ApoE deficiency and postnatal exposure to hypercholesterolemic environment causes altered histone methylation patterns in the vasculature (Alkemade et al., 2010). Recently, Trenteseaux et al. (2017) evaluated the effect of perinatal hypercholesterolemia on atherosclerosis development in the offspring of ApoE−/− mice. The authors observed that perinatal hypercholesterolemia exacerbates atherosclerosis in their offspring by epigenetically modulating several genes implicated in the metabolism of trimethylamine-N-oxide and bile acids via DNA methylation (Trenteseaux et al., 2017).

It has been known that monocytes/macrophages can acquire a long-term pro-inflammatory and pro-atherogenic phenotype after prior exposure to inflammatory stimuli via regulating histone methylation alternations at pro-inflammatory gene promoters. This phenomenon is termed 'trained immunity' (Bekkering, Joosten, van der Meer, Netea, & Riksen, 2013; Leentjens et al., 2018). Commonly used in *vitro* stimuli of monocyte/macrophage training are: oxLDL, β-glucan, and the bacillus Calmette-Guérin vaccine (Bekkering et al., 2016). In 2006, Groeneweg *et al.* (Groeneweg et al., 2006) first observed that, prior treatment with oxLDL increases LPS-induced TNFα and IL6 expression, while it decreases anti-inflammatory cytokine IL10 expression in bone marrow-derived macrophages. However, the epigenetic basis of this observation is unknown. Eight years later, a similar phenomenon was observed in monocytes primed with oxLDL (Bekkering et al., 2014). Those trained monocytes have an augmented production of a set of inflammatory mediators (including IL6, IL8, IL18, TNFα, MCP1, and MMP2/MMP9) when re-stimulated with TLR ligands 6 days after initial priming. oxLDL training also promotes foam cell formation via increasing the expression of lipid-uptake genes-CD36 and SRA, while decreasing the expression of cholesterol efflux related genes-ABCA1 and ABCG1. Mechanistic studies show increased H3K4me3 in gene promoters of pro-inflammatory genes 6 days after oxLDL. Furthermore, oxLDL-induced pro-inflammatory response is reduced by treatment with a histone methyltransferase inhibitor (Bekkering et al., 2014). This phenomenon of trained immunity may also exist for other priming factors, such as high glucose and AGEs (van Diepen et al., 2016) or possibly exist in other cell types, such as endothelial cells and VSMCs. For example, El-Osta and colleagues (El-Osta et al., 2008) reported that transient hyperglycemia exposure (for 16 h) induced long-lasting (6 days after returning to normoglycemia) epigenetic changes in human aortic endothelial cells by inducing SET7-dependent H3K4me1 binding to promoters of genes downstream of NF-κB pathway (MCP1 and VCAM1). In addition, high glucose can induce "senescent memory" in endothelial cells, which can be corrected by treatment with resveratrol and metformin (Zhang et al., 2015).

In addition, feeding with western-type diet also induces NLRP3-dependent trained immunity. A recent report by Christ *et al.* (Christ et al., 2018), has shown that myeloid cell responses toward innate stimuli remained increased after diet switch from western diet to normal diet. However, this pattern of systemic inflammation and trained immunity was not seen in NLRP3$^{-/-}$/LDLr$^{-/-}$ double knockout mice, indicating a central role of NLRP3/IL-1β in mediating trained immunity after western diet feeding. This finding agrees with the promising findings in the recent CANTOS trial, which showed IL1β blockade reduces cardiovascular risk and usher a new direction of new therapeutic interventions for CVD (Ridker et al., 2017). In agreement with this evidence, mevalonate can induce trained immunity in human monocytes via activation of IGF1 receptor (IGF1R) and mTOR. More clinically relevant, monocytes from patients with mevalonate kinase deficiency (who accumulate mevalonate) recapitulated the trained phenotype. Further, statins, which block mevalonate generation are capable of preventing the trained immunity phenotype (Bekkering et al., 2018). The identification of mevalonate in regulating trained immunity via epigenetic mechanisms will help the quest for novel therapeutic targets and drugs for treating atherosclerosis. Further studies in this direction are necessary to elucidate the comprehensive role of trained immunity and epigenetic reprograming in atherosclerosis and develop novel pharmacologic targets for disease therapy (Leentjens et al., 2018).

5. Epigenetic drugs in treating atherosclerosis

The reversible nature of epigenetic modifications (DNA/RNA/histone modifications in particular) has sparked intense interest of 'epigenetic therapy' as a treatment option for atherosclerosis. The purpose of epigenetic therapy is to reverse "abnormal" (or disease-causing) epigenetic alternations that occur in atherosclerosis, thus restoring a "normal" cardiovascular epigenome (Sharma et al., 2010). Many epigenetic drugs have been identified in the past decade that effectively prevented or treated atherosclerosis in several translational animal models, raising the possibility to combat atherosclerosis by targeting epigenetic processes also in humans (Table 4).

5.1. DNMT inhibitors (DNMTi)

DNMTi are among the first epigenetic drugs that are used in cancer therapeutics (Sharma et al., 2010). DNMTi can be classified as nucleoside-based and non-nucleoside inhibitors. 5-Azacytidine and 5-Aza-2′-deoxycytidine are FDA-approved nucleoside-based DNMTi that inhibit DNA methylation in actively dividing cells by trapping DNMTs in the target gene promoters and thus re-activate gene transcription. Both drugs are used for treating myelodysplastic syndromes and acute myeloid leukemia (Sharma et al., 2010). Several elegant studies have recently shown that 5-Aza-2′-deoxycytidine effectively inhibits

Table 3
Role of long non-coding RNA in vascular pathophysiology.

LncRNA	Mechanism	Cell type	Function	Reference
LncRNA 00113	p-PI3K/p-Akt/p-mTOR, Bcl-2	EC, VSMC	↑Proliferation, ↑Survival, ↑Migration	(Yao, Yan, Zhang, Li, & Wan, 2018)
Linc00341	VCAM1	EC	↓Inflammation ↓Monocyte adhesion	(Huang, Wang, et al., 2017)
SMILR	HAS2	VSMC	↓Proliferation	(Ballantyne et al., 2016)
LincRNA-p21	MDM2/p53	VSMC, Mφ	↓Proliferation ↑Apoptosis, ↓Neointimal hyperplasia	(Wu et al., 2014)
MYOSLID	p-smad2, MKL1	VSMC	↑VSMC differentiation ↓VSMC proliferation	(Zhao et al., 2016)
XIST	miR-320/NOD2	EC	↑oxLDL induced injury, apoptosis	(Xu, Ma, Liu, Duan, & Zhang, 2018)
SENCR		EC	↑Mesodermal and endothelial commitment ↑Proliferation, migration and angiogenesis ↑Cell cycle progression	(Boulberdaa et al., 2016; Sun, Wang, & Song, 2018)
SENCR	Myocardin	VSMC	↓Smooth muscle cell migration ↑Contractile phenotype	(Bell et al., 2014)
STEEL	KLF2, eNOS	EC	↑Angiogenic microvessels	(Man et al., 2018)
MALAT1		EC	Mechanosensitive	(Qiao et al., 2016)
MALAT1	Cell cycle regulators	EC	Hypoxia responsive ↑Angiogenesis	(Michalik et al., 2014; Zhang, Tang, Hamblin, & Yin, 2018)
MALAT1	β-catenin/CD36	Mφ	↑Foam cell formation	(Huangfu et al., 2018)
MALAT1		Mφ, splenocytes	↑Atherosclerosis lesion in MALAT1$^{+/-}$; ApoE$^{-/-}$ mice ↑Immune system dysregulation ↓TNFα, iNOS	(Gast et al., 2018)
MALAT1	miR-155	EC	↓ox-LDL mediated inflammation and apoptosis	(Li et al., 2018)
Linc00657	miR-590-3p	EC	↑Proliferation, migration, and tube formation ↑Angiogenesis	(Bao et al., 2018)
MeXis	LXR/ABCA1; DDX17	Mφ	↑Cholesterol efflux and atheroprotection	(Sallam et al., 2018)
H19	miR-148b/WNT/β-catenin	VSMC	↑Proliferation ↓Apoptosis	(Zhang, Cheng, Yue, et al., 2018a)
H19	miR-130b	Mφ	↑Lipid accumulation ↑Inflammation	(Han et al., 2018)
H19	miR-29a	EC	↑Angiogenesis	(Jia et al., 2016)
H19		Plasma	Biomarker of CAD risk	(Zhang, Gao, et al., 2017)
H19	p38, NF-kB	EC	↑Apoptosis ↓Proliferation	(Pan, 2017)
H19		EC	Aging	
H19	HIF1α	VSMC	↑Abdominal aortic aneurysm ↑VSMC apoptosis	(Li et al., 2018)
LncRNA-RP11-714G18.1	LRP2BP	EC, VSMC	↓ Migration ↓ Monocyte adhesion to EC ↓ Angiogenesis ↑Nitric oxide	(Zhang, Zhang, Zhang, et al., 2018)
TUG1	miR-133a/FGF1	VSMC, Mφ	↑Cell proliferation ↑Migration ↓Apoptosis ↑Atherosclerotic lesion ↑Inflammation, hyperlipidemia	(Zhang et al., 2018b)
lincRNA-p21	LOX-1	EC	↑Apoptosis ↑Cholesterol efflux	(Zhou & Chen, 2017)
LeXis	LXR/SREBPs	Mφ	↓ Atherosclerotic lesion ↓TC, TG	(Sallam et al., 2016; Tontonoz et al., 2017)
Linc00305	miR-136	EC	↑Hypoxia-induced EC apoptosis	(Zhang, Jin, & Zhao, 2017)
ANRIL		EC	↑Inflammation, apoptosis, coronary atherosclerosis	(Song et al., 2017)
NEAT1	CD36, NF-κB	Mφ	↑Expression upon oxLDL stimulation ↓ CD36, DiI-oxLDL uptake ↓ p65 phosphorylation, inflammation	(Huang-Fu et al., 2018)
NEAT1	miR-128	Mφ	↓Proliferation, ↑apoptosis ↑CD36, oxLDL-induced foam cell formation ↑Inflammation (IL-6, IL-1β, and TNF-α) ↑ROS	(Chen, Hui, Zhang, & Chang, 2018)
NEAT1	miR-342-3p	Mφ	↑Inflammation (IL-6, IL-1β, TNFa) ↑CD36-dependent lipid uptake ↑ Lipid accumulation (TC, TG)	(Wang et al., 2018)
NEAT1	WDR5	VSMC	↑ Proliferation and migration ↑ Neointima formation	(Ahmed et al., 2018)
HOTAIR		EC	Decrease in EC from human atherosclerotic plaques ↑Proliferation, migration, ↓Apoptosis ↓oxLDL induced EC injury	(Peng et al., 2017)
HOTAIR	miR-330-5p	Mφ	↑oxLDL induced oxidative stress ↑oxLDL induced inflammation ↑CD36-mediated oxLDL uptake ↑TC, TG	(Liu, Huang, & Ke, 2018)

Table 3 (*continued*)

LncRNA	Mechanism	Cell type	Function	Reference
Linc00305	LIMR/AHRR-NF-κB	Monocytes	↑Inflammation ↑VSMC phenotypic switch	(Zhang, Wang, et al., 2017)
MANTIS	BRG1	EC	↑Angiogenic sprouting ↑Alignment of endothelial cells in response to shear stress	(Leisegang et al., 2017)
HOXC-AS	HOXC6	Macrophage	↓Lipid accumulation	(Huang et al., 2016)
ANRIL	Pescadillo homologue 1	VSMC, Mφ	↑Apoptosis ↓Proliferation ↑Nucleolar stress and p53 activation,	(Holdt et al., 2016)
HULC	miR-9	EC	↓ TNFα-induced apoptosis	(Ma et al., 2016)
MIAT	miR-150-5p	EC	↑Pathological angiogenesis ↑Diabetes mellitus-induced retinal microvascular dysfunction	(Yan et al., 2015)
RP5-833A20.1	miR-382-5p/NFIA	Mφ	↑Cholesterol uptake ↑Inflammation ↓ Cholesterol efflux	(Hu et al., 2015)
Lnc-Ang362	miR-221 and miR-222	VSMC	↑Proliferation	(Leung et al., 2013)
GATA6-AS	LOXL2/periostin and COX2	EC	↑EndoMT ↓Vessel formation	(Neumann et al., 2018)
LEENE (Linc00520)	eNOS	EC	↑eNOS, NO ↓Inflammation	(Miao, Ajami, et al., 2018)
HOTTIP	Wnt/β-catenin	EC	↑Proliferation, migration	(Liao et al., 2018)
HOTTIP	Wnt/b-catenin	EC	↑Proliferation, migration	(Liao et al., 2018)
XR007793	STAT2, lmo2, IRF7	VSMC	↑Proliferation, migration	(Yao et al., 2017)
Dnm3os	Nucleolin and ILF-2	Mφ	↑Inflammation, phagocytosis, and diabetic vascular complications	(Das et al., 2018)
MEG3		EC	Increase in senescent ECs ↓Angiogenic sprouting	(Boon, Hofmann, et al., 2016)
MEG3	VEGFR2	EC	↑Migration, angiogenesis	(Ruan et al., 2018)
MEG3	miR-223/NLRP3	EC	↑Pyroptosis	(Guo et al., 2018)
MEG3	miR-21	EC	↓Proliferation and migration ↓Collagen I, V, and proteoglycan expression	(Wu et al., 2017)

Abbreviations: ABCA1, ATP binding cassette subfamily A member 1; ANRIL, antisense non-coding RNA at the INK4 locus (also known as CDKN2B antisense RNA 1); CD36, cluster of differentiation 36; DDX17, DEAD-box helicase 17; Dnm3os, DNM3 opposite strand/antisense RNA; EC, endothelial cells; eNOS, endothelial nitric oxide synthase; EndoMT: endothelial to mesenchymal transition; FGF1, fibroblast growth factor 1; GATA6-AS: antisense transcript of GATA6; HAS2, hyaluronan synthase 2; H19, imprinted maternally expressed transcript; HIF1α, hypoxia inducible factor 1, alpha subunit; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA transcript at the distal tip; HOXC-AS, HOXC cluster antisense RNA; HULC, hepatocellular carcinoma up-regulated long non-coding RNA; IRF7, Interferon regulatory factor 7; ILF-2, interleukin enhancer-binding factor 2; iNOS, inducible nitric oxide synthase; KLF2, kruppel like factor 2; LEENE, enhancer-associated lncRNA that enhances eNOS expression; LIM domain only 2; LOX-1, lectin-like oxidized LDL receptor 1; LRP2BP, LRP2 binding protein; LOXL2, lysyl oxidase like 2; LXR, liver X receptor; MALAT1, metastasis associated lung adenocarcinoma transcript 1; Mφ, macrophages; MANTIS, lncRNA n342419; MEG3, maternally expressed 3; MDM2, MDM2 proto-oncogene; MIAT, myocardial infarction associated transcript; MKL1, MYOCD-related transcription factor A; MYOSLID, MYOcardin-induced Smooth muscle LncRNA, Inducer of Differentiation; NEAT1, nuclear paraspeckle assembly transcript 1; NFIA, nuclear factor I A; NF-kB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; NOD2, nucleotide binding oligomerization domain containing 2; SENCR, Smooth muscle and endothelial cell-enriched migration/differentiation-associated long non coding RNA; SMILR, Smooth Muscle Enriched Long Noncoding RNA; STEEL, spliced-transcript endothelial-enriched lncRNA; TC, total cholesterol; TG, triglycerides; TNFa, tumor necrosis factor-alpha; VCAM1, vascular cell adhesion molecule 1; WDR5, WD Repeat Domain 5; VSMC, vascular smooth muscle cells; XIST, X-inactive specific transcript.

atherosclerosis development in several well-established animal models of atherosclerosis, including diet induced atherosclerosis in ApoE$^{-/-}$ mice, LDLr$^{-/-}$ mice and ApoE$^{-/-}$ mice undergoing carotid partial ligation (Cao, Wang, et al., 2014; Dunn et al., 2014; Zhuang et al., 2017). One disadvantage of these nucleoside inhibitors is the cytotoxic effect on normal cells as these drugs are irreversibly incorporated into DNA (Sharma et al., 2010). An alternative approach is to develop non-nucleoside DNMTi, which potently and selectively inhibit DNA methylation by targeting catalytic/cofactor-binding sites of DNMTs or DNMTs gene and protein expression, without being incorporated into DNA (Sharma et al., 2010). Small-molecule DNMTi of this kind include SGI-1027, RG108 and MG98 (Sharma et al., 2010) and several natural products (i.e., quercetin (Hayek et al., 1997; Leckey et al., 2010; Lee, Shim, & Zhu, 2005; Shen et al., 2013), curcumin (Ghosh, Bie, Wang, & Ghosh, 2014; Liu et al., 2009; Zhang, Zou, Li, Zheng, & Feng, 2018) and EGCG (Lee et al., 2005; Pan et al., 2018)). Although the current literature has proven that some of the naturally occurring non-nucleoside DNMTi are capable of inhibiting atherosclerosis in mice, it is unknown how far their specific mechanism of action and the DNMTs inhibiting effects of these compounds contribute to their atheroprotective effects.

5.2. TET2 activators

Vitamin C (or ascorbic acid) is a classical and potent dietary antioxidant that has been tested both pre-clinically and clinically to treat atherosclerosis. The potential atheroprotective mechanisms of vitamin C include inhibition of LDL oxidation, improving endothelial dysfunction and arterial stiffness, modulation of lipid profile, inhibition of platelet activation, and many others (Lynch, Gaziano, & Frei, 1996). Mounting evidence from animal studies, epidemiological and clinical studies has supported vitamin C supplementation in preventing atherosclerosis progression and reducing the incidence of CVD events, although with some controversy (Lynch et al., 1996; Moser & Chun, 2016; Salonen, et al., 2003). The antioxidant-independent cardiovascular actions of vitamin C are however remain incompletely understood. Recent studies have demonstrated that vitamin C can also function as an epigenetic drug that activates TET2-dependent DNA demethylation, thereby regulates gene transcription (Yin et al., 2013). The TET2 activating effects of vitamin C have been validated in multiple cell types and *in vivo* (Agathocleous et al., 2017; Cimmino et al., 2017; Qu et al., 2017). More recently, another potential TET2 activator from natural sources, vicenin-2, has been identified to ameliorate high glucose induced endothelial inflammation (including hyperpermeability, leukocyte adhesion, ROS production, and NF-kB dependent adhesion molecules expression) (Ku & Bae, 2016), as well as LPS induced macrophage inflammation (TNFα, IL1β, and IL18) (Hassan et al., 2018), underscoring the potential of TET2 activators to prevent atherosclerosis development. Further studies are necessary to validate, whether TET2 activation directly contribute to these compounds-mediated atheroprotection.

5.3. Histone deacetylase inhibitors (HDACi)

HDACi, such as suberoylanilide hydroxamic acid (SAHA), trichostatin A (TsA), phenylbutyrate and valproic acid are widely used in cancer biology and therapeutics (Mottamal, Zheng, Huang, & Wang, 2015). The pharmacological effects of HDACi are mediated through the reactivation of silenced genes by preventing histone deacetylation on target gene promoters. The pan-HDAC inhibitor SAHA, a clinically-used drug for treating T cell cutaneous lymphoma, attenuates vascular inflammation and atherosclerosis lesion development in ApoE$^{-/-}$ mice fed a western-type diet (Xu et al., 2017). Part of the anti-atherosclerotic mechanism of SAHA is related to pharmacological activation of KLF2, a promising target for treating atherosclerosis (Xu et al., 2017). In addition, the pan-HDAC inhibitors, phenylbutyrate and valproic acid, which also demonstrated therapeutic effects in attenuating experimental atherosclerosis in mouse models (Huang et al., 2017). Interestingly, both 4-phenylbutyrate and valproic acid also target ER stress and GSK3α/β, which render them as dual function HDACi that confer atheroprotection (Huang, Young, et al., 2017). TsA, another pan-HDAC inhibitor, upregulates SR-BI expression and promotes SR-BI-dependent cholesterol efflux (Bao et al., 2009) and inhibits VSMC proliferation via inducing the expression of p21 (WAF1) expression and cell-cycle arrest (Okamoto et al., 2006). However, TsA accelerates macrophage infiltration, foam cell formation, and atherosclerosis development in LDLr$^{-/-}$ mice by upregulating scavenger receptor CD36 (Choi et al., 2005). Probably, the atheroprotective effects of TsA may be surpassed by its pro-atherogenic effects. This phenomenon suggests that HDAC inhibition-dependent and -independent mechanisms must be explored when assessing the pharmacological effects of pan-HDACi.

5.4. Sirtuin activating compounds (STAC)

Based on the overall atheroprotective functions of SIRT1 and SIRT6, several natural and synthetic SIRT1 and SIRT6 activators have been developed and demonstrated considerable efficacy in attenuating experimental atherosclerosis. One well-studied SIRT1 activator is the wine-derived natural product resveratrol, which displays multiple atheroprotective effects in several mouse models of atherosclerosis, including ApoE$^{-/-}$ mice, ApoE$^{-/-}$; LDLr$^{-/-}$ mice, and ApoE*3-Leiden. CETP mice (Berbee et al., 2013; Fukao et al., 2004; Howitz et al., 2003; Norata et al., 2007). Other synthetic STACs, such as SRTT1720 (Chen, Zhang, et al., 2015), SRT3025 (Miranda et al., 2015), and SRT2104 (Venkatasubramanian et al., 2013; Venkatasubramanian et al., 2016) also demonstrate atheroprotective functions. Similar as SIRT1 activators, four SIRT6 activators have been reported to have atheroprotective properties, namely, Icariin (from Chinese medicine *Epimedium brevicornum Maxim*) (Chen et al., 2015), Fucoidan (from marine-derived brown seaweeds) (Rahnasto-Rilla et al., 2017), Cyanidin (from plant-derived anthocyanidins) (Rahnasto-Rilla et al., 2018), and Fluvastatin (Kim, Lee, Kim, & Kim, 2018). Since most of these natural products display multiple cardiovascular actions in addition to SIRT activation, it remains to be elucidated, whether the atheroprotective functions are dependent on SIRT activation.

5.5. HMTi (such as EZH2 inhibitors)

The effect of HMT inhibitors (HMTi), such as EZH2 inhibitors, have been intensively explored in cancer therapies. One such EZH2 inhibitor in clinical trial, is GSK343. It is a potent and EZH2 specific inhibitor selectively targeting H3K27me3 in cancer cells (Verma et al., 2012). GSK343 treatment improves aortic performance in Fbn1C1039G/+ mice (an animal model of Marfan Syndrome), concordant with restoration of SM22α, an important contractile protein expressed in VSMCs (Lino Cardenas et al., 2018). Several atheroprotective drugs (statins (Ishikawa et al., 2014), fish oil (Dimri, Bommi, Sahasrabuddhe, Khandekar, & Dimri, 2010), metformin (Tang et al., 2018)) inhibit EZH2 expression in cancer cells and some anti-atherosclerotic treatments (fluid shear stress (Maleszewska et al., 2016; Xu, Xu, et al., 2018)) decrease EZH2 protein expression in endothelial cells. Although most of these findings are performed in cancer cells, the utility of specific or repurposed EZH2 inhibitors in atherosclerosis remains to be assessed. Nevertheless, the current findings reinforce the concept that EZH2 inhibitors may exert cardiovascular protective actions *in vivo*.

5.6. BET inhibitor (BETi)

The bromodomain and extra-terminal domain (BET) family of proteins are composed of two tandem bromodomains ("readers" of lysine acetylation) and one extra-terminal domain. Mammalian BET proteins have four members, BRD2, BRD3, BRD4, and BRDT. BET family proteins orchestrate gene transcription through interactions with acetylated lysine residues on target proteins via its bromodomains (Taniguchi, 2016). RVX-208 (also known as apabetalone) is an orally bioavailable and novel epigenetic targeting drug that increases the levels of ApoAI and HDL, thereby increasing HDL functionality (such as cholesterol efflux and anti-inflammatory effects) (Bailey et al., 2010) by selective binding to BD2 domain (second bromodomain) of BRD4, thereby preventing protein-protein interaction between BET proteins and acetylated lysine residues and transcription factors (McLure et al., 2013). RVX-208 selectively inhibits LPS induced IL6 expression in U937 cells, but not TNFα mRNA (McLure et al., 2013). It also inhibits TNFα induced upregulation of MCP1 and VCAM1 in human aortic endothelial cells (Jahagirdar et al., 2014). Patients receiving RVX-208 have lower levels of circulating inflammatory cytokines and lower incidence of major adverse cardiac events (Gilham et al., 2016). RVX-208 (150 mg/kg, oral administration, for 12 weeks) also reduces atherosclerosis in hyperlipidemic ApoE$^{-/-}$ by increasing HDL level while decreasing LDL level (Jahagirdar et al., 2014). (+)-JQ1 is another BET bromodomain inhibitor which has anti-inflammatory effects by displacing BET proteins from chromatin via binding to bromodomain in a competitive manner (Filippakopoulos et al., 2010). (+)-JQ1 (50 mg/kg, 10 weeks) has been demonstrated to dampen inflammatory responses in activated endothelium and decrease leukocyte adhesion to activated endothelium as well as reduced atherosclerosis in hyperlipidemic ApoE$^{-/-}$ mice (Brown et al., 2014). In addition, (+)-JQ1 also attenuates Ang-II-induced hypertension, and inflammation in mice (Das et al., 2017). These studies collectively suggests that BET inhibitors could provide potential atheroprotective effects *in vivo*.

5.7. miRNA-based therapeutics

As discussed earlier, atherosclerosis is a multifactorial disease involving multiple mechanisms and diverse cell types. The nature of this complex regulatory network renders miRNA as a promising therapeutic target for treating atherosclerosis by delivering miRNA mimics or inhibitors locally or systemically (Lucas et al., 2018). Recent findings from Maegdefessel group have shown the advantage of local delivery of mimics of miR-21 (Jin et al., 2018) and miR-210 (Eken et al., 2017) to increase plaque stability and potentially prevent the incidence of atherothrombotic vascular events. However, a major hurdle in the miRNA-based therapeutic field is the question of efficient miRNA delivery strategies. Therefore, development of new vectors (such as nanoparticles, ultrasound-targeted microbubbles etc.) for targeted delivery of miRNAs or miRNA inhibitors to the desired targeted vascular cell type is of the utmost importance to achieve site-specific drug delivery and therapeutic effects in the future (Sharma et al., 2010).

6. Concluding remarks and future perspectives

The past decade has witnessed unanticipated progress in deciphering various epigenetic mechanisms in gene regulation, with far-reaching implications for understanding cardiovascular development, biology, and

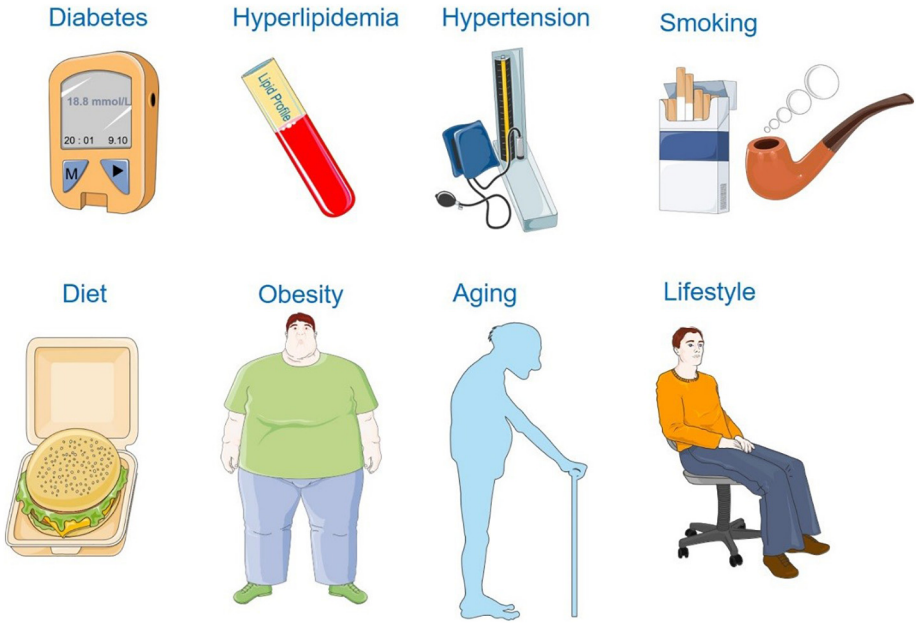

Fig. 4. Major risk factors for atherosclerosis. The development of atherosclerosis is influenced by multiple risk factors, which affects different epigenetic mechanisms in atherosclerosis. Some risk factors have effects on transgenerational inheritance and epigenetic memory effects, highlighting the necessity of epigenetic drugs.

diseases. The overall consensus is that individual epigenetic regulation of atherosclerosis is very complex. Cell type- and isoform- specific role of epigenetic enzymes does exist at different stages of atheroprogression. The epigenetic-based hypothesis of atherosclerosis has deepened the understanding of the molecular mechanisms of atherosclerosis, which is traditionally viewed as a chronic inflammatory and lipid disorder with genetic codes as the key determinant (Libby, Tabas, Fredman, & Fisher, 2014). Advances in cardiovascular epigenetics, especially the epigenome-wide association studies help us to appreciate the intricate interplay of epigenetics in regulating lipid metabolism, inflammation, and redox status in atherosclerosis.

Epigenetic processes are often influenced by environmental and lifestyle factors, such as air pollution, physical inactivity, unhealthy diet, and smoking, which are well-known risk factors for CVD (Abdul, Yu, Chung, Jung, & Choi, 2017). Atherosclerotic patients are likely to develop systemic inflammation and cardiovascular complications even after intensive lipid-lowering therapies (by statins). The residual risk of vascular inflammation presents major challenges for treating atherosclerosis. In this scenario, cardiovascular drugs targeting epigenetics hold great promise for cardiovascular therapeutics as they may complement standard statin treatment and PCSK9 inhibitor-based hypolipidemic therapy in clinical practice.

Future directions in the field of cardiovascular epigenetics include:

1. Exploratory research on novel molecular biomarkers of CVD. It is important to identify specific biomarkers associated with disease (and/or disease severity), such as novel secreted lncRNAs and miRNAs (He, Chen, Hao, & Qian, 2018).
2. New bioinformatic tools to predict the lncRNA-disease associations, such as e.g. LncDisease (Wang et al., 2016) developed by the Cui lab (http://www.cuilab.cn/). These tools are helpful in identifying the biological functions of emerging new lncRNAs in disease prevention, diagnosis and management.
3. The improvement of precision in cardiovascular medicine. The Institute of Precision Cardiovascular Medicine at AHA (https://precision.heart.org) aims to find a cure for coronary heart disease and improving cardiovascular health. This possibility creates new therapeutic opportunities by modulating disease risk, as well as targeting selected disease through epigenetic mechanisms (Costantino et al., 2017). Epigenetics may also explain why individuals with similar genetics and risk factors respond differently to treatment. Gender is an important determinant of the incidence of CVD. A recent study (Hassan et al., 2018) has shown that estrogen can promote phosphorylation-dependent EZH2 degradation via PI3K/Akt pathway, suggesting that sex hormone-dependent modulation of chromatin modifiers could be partially responsible for sex dimorphism.
4. The role of RNA methylation in atherosclerosis. RNA N6-methyladenosine methylation (m^6A) (Yue, Liu, & He, 2015) is an emerging new epigenetic mechanism that has been recently intensively investigated in cancer biology. This new type of modification is dictated by m^6A methylation "writers" and can be reversed by demethylases that serve as "erasers". The role of this new type of RNA modification in cardiovascular biology is unknown and warrants further studies.
5. New translational animal models for characterizing the pharmacological actions of epigenetic cardiovascular drugs: To date, $ApoE^{-/-}$ or $LDLr^{-/-}$ mice are the two most widely used mouse models for studying atherosclerosis via pharmacological intervention or gene engineering (Emini Veseli et al., 2017). The development of atherosclerosis in both models can be accelerated by challenging with Western-type diet or high cholesterol diet for several months. The use of other translational pre-clinical models of atherosclerosis, such as partial carotid ligation in $ApoE^{-/-}$ mice (Nam et al., 2009), or AAV8-mPCSK9D377Y mutant injection (Bjorklund et al., 2014; Goettsch et al., 2016; Kumar, Kang, Rezvan, & Jo, 2017) will significantly shorten the experimental time frame, and potentially accelerate the discovery of new epigenetic drugs targeting chromatin modifiers.
6. Research on new epigenetic pharmaceuticals by drug repurposing/repositioning. Besides seeking new therapeutic strategies, identifying new epigenetic targets of FDA-approved small molecule drugs (such as statins which function at least partially through epigenetic mechanisms (Allen & Mamotte, 2017)) and repurposing them as new therapies for atherosclerosis, is potentially a safe and cost-efficient avenue of future cardiovascular drug discovery.
7. Cocktail or combinatorial epigenetic therapy. Since different epigenetic mechanisms, especially DNA methylation and histone methylation/acetylation coordinate to regulate gene expression networks, HDACi and DNMTi combination therapies are attractive. This type of epigenetic "cocktail" therapy may synergistically derepress

Table 4
Therapeutic drugs that target epigenetic processes in atherosclerosis and associated vascular diseases.

Compound Name	Category	Subjects or Animal models	Pharmacological effects	Reference
Resveratrol	Natural SIRT1 activator	1. ApoE$^{-/-}$/LDLr$^{-/-}$ mice 2. ApoE$^{-/-}$ mice+HFD 3. ApoE$^{-/-}$ mice+ND 4. ApoE*3-Leiden.CETP mice+HCD 5.Fbn1 C1039G/+ Marfan syndrome mouse	↓Atherosclerosis lesion ↓Thrombosis ↓Inflammatory chemokines ↑Plaque stability ↓Vascular inflammation ↓Aortic root dilation	(Berbee et al., 2013; Fukao et al., 2004; Hibender et al., 2016; Howitz et al., 2003; Norata et al., 2007)
SRT1720	SIRT1 activator	1. ApoE$^{-/-}$ mice +Ang-II infusion 2. HFHS diet	↓Atherosclerosis lesion ↓Blood pressure, inflammation ↓NF-κB and STAT3 activation ↓ Arterial stiffness	(Chen, Zhang, et al., 2015; Fry et al., 2016)
SRT2104	SIRT1 activator	Cigarette Smokers Patients with T2DM	Improved lipid profile ↓Augmentation pressure	(Venkatasubramanian et al., 2013; Venkatasubramanian et al., 2016)
SRT3025	SIRT1 activator	ApoE$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↓PCSK9 secretion ↑LDLr expression	(Miranda et al., 2015)
Icariin	Natural SIRT6 activator	1. ApoE$^{-/-}$ mice+HFD 2. Rabbits+HFD	↓Atherosclerosis lesion ↑eNOS/NO-pathway ↓ROS ↓Macrophage infiltration ↓Platelet adhesion and aggregation	(Chen, Sun, et al., 2015; Li, Li, Cole, McLaughlin, & Du, 2018; Wang et al., 2016; Xiao, Sui, & Lu, 2017; Zhang, Bai, Zheng, Xie, & Yuan, 2013)
Fucoidan	Natural SIRT6 activator	ApoE$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↓Hepatic steatosis ↓Foam cell accumulation	(Rahnasto-Rilla et al., 2017; Yokota, Nomura, Nagashima, & Kamimura, 2016)
Cyanidin	Natural SIRT6 activator	ApoE$^{-/-}$ mice+STZ injection	↓Atherosclerosis lesion ↑Endothelial repair	(Rahnasto-Rilla et al., 2018; Zhang, Wang, Wang, Liu, & Xia, 2013)
SAHA	HDAC inhibitor	ApoE$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↓Monocyte adhesion to EC ↑KLF2 expression	(Xu et al., 2017; Ye, Zhao, Lu, Long, & Zhang, 2018)
5-aza-2′-deoxycytidine	DNMT inhibitor	1. ApoE$^{-/-}$ mice+HFD 2. LDLr$^{-/-}$ mice+HFD 3. ApoE$^{-/-}$ mice +Partial carotid ligation	↓Atherosclerosis lesion ↓Neointima ↓TET2 methylation ↓Macrophage inflammation and chemotaxis ↓Macrophage ER stress ↓Macrophage adhesion to EC ↑LXRα and PPARγ	(Cao, Wang, et al., 2014; Dunn et al., 2014; Zhuang et al., 2017)
Quercetin	Natural DNMT inhibitor	1. ApoE$^{-/-}$ mice+HFD 2. LDLr$^{-/-}$ mice+HFD	↓LDL uptake, aggregation ↓LDL oxidation ↓Endothelial dysfunction ↑eNOS and HO1	(Hayek et al., 1997; Leckey et al., 2010; Lee et al., 2005; Shen et al., 2013)
EGCG	Natural DNMT inhibitor	ApoE$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↑LXRα and LXRβ ↓SREBP1	(Lee et al., 2005; Pan et al., 2018)
Curcumin	Natural inhibitor of CBP/p300	1. ApoE$^{-/-}$ mice+HFD 2. LDLr$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↓TLR4, NF-kB ↓IL-1β, TNFα, VCAM1, ICAM1	(Ghosh et al., 2014; Liu et al., 2009; Zhang, Zou, Li, et al., 2018)
Statins	EZH2 inhibitor	1. ApoE*3-Leiden mice +HCD 2. Aged ApoE$^{-/-}$ 3. ApoE$^{-/-}$ mice +HFD 4. LDLr$^{-/-}$ mice+HFD 5. Patients with atherosclerosis	↓Atherosclerosis lesion ↓Macrophage content ↓TF and MCP1 ↓CD36 and calpain-1	(Bea, Blessing, Shelley, Shultz, & Rosenfeld, 2003; Ishikawa et al., 2014; Kang, Wu, & Li, 2004; Kleemann et al., 2003; Lin et al., 2015; Yin et al., 2017)
Vitamin C	TET2 activator	1. Rabbits+HCD 2. ApoE$^{-/-}$ mice	↓Atherosclerosis lesion ↓ Aortic VEGF, VEGFR2	(Das, Ray, Snehlata, Das, & Srivastava, 2006; Nespereira et al., 2003; Qu et al., 2017; Yin et al., 2013)
Valproic acid	HDAC inhibitor	1. ApoE$^{-/-}$ + STZ 2. LDLr$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↓Hepatic GSK-3β activity	(Bowes, Khan, Shi, Robertson, & Werstuck, 2009; Huang, Young, et al., 2017)

Table 4 (*continued*)

Compound Name	Category	Subjects or Animal models	Pharmacological effects	Reference
			↓Hepatic GSK-3β Activity ↓ER stress	
Phenylbutyrate	HDAC inhibitor	LDLr$^{-/-}$ mice+HFD	↓Atherosclerosis lesion ↓Necrotic core size	(Huang, Young, et al., 2017)
RVX-208 (Apabetalone)	BET inhibitor	1. ApoE$^{-/-}$ mice+HFD 2. CAD patients	↓Atherosclerosis lesion ↓Adverse cardiovascular events ↓Adhesion molecules ↓hsCRP ↑HDL-C	(Bailey et al., 2010; Jahagirdar et al., 2014; McLure et al., 2013; Nicholls et al., 2018)
(+)-JQ1	BET inhibitor	1. LDLr$^{-/-}$ mice+HFD 2. Ang-II infused mice	↓Atherosclerosis lesion ↓Macrophage and T cell infiltration ↓Leukocyte adhesion ↓Blood pressure	(Brown et al., 2014; Das et al., 2017).
GSKJ4	JMJD3 inhibitor	1. Rats carotid artery balloon injury 2. Mouse left carotid artery partial ligation	↓Neointimal hyperplasia ↓VSMC proliferation, migration, inflammation	(Luo et al., 2018)

Abbreviations: Ang-II, angiotensin II; ApoE, apolipoprotein E; BET, bromodomain and extra-terminal motif; CAD, coronary artery disease; CD36, cluster of differentiation 36; DNMT, DNA methyltransferase; EC, endothelial cells; EGCG, Epigallocatechin gallate; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; EZH2, Enhancer of zeste homolog 2; HFD, high fat-diet; GSK-3β; glycogen synthase kinase 3 beta; HCD, high cholesterol diet; HDAC, histone deacetylase; HDL-C, high-density lipoprotein-cholesterol; HFD, high-fat diet; HO1, heme oxygenase 1; hsCRP, high-sensitivity C reactive protein; ICAM1, intercellular adhesion molecule 1; IL-1β, interleukin-1 beta; JMJD3, JmjC domain-containing protein 3; KLF2, kruppel like factor 2; LDL, low-density lipoprotein; LDLr, low density lipoprotein receptor; LXR, liver X receptor; MCP1, monocyte chemoattractant protein-1; NF-kB, nuclear factor-kappa B; NO, nitric oxide; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; TET2, Tet methylcytosine dioxygenase 2; EC, endothelial cells; PPAR, peroxisome proliferator-activated receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; ROS, reactive oxygen species; SAHA, suberanilohydroxamic acid; SIRT, sirtuin; SREBP1, sterol regulatory element-binding protein 1; STAT3, signal transducer and activator of transcription 3; T2DM, type 2 diabetes mellitus; TF, tissue factor; TNFα, tumor necrosis factor-alpha; TLR4, toll like receptor 4; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; VSMC, vascular smooth muscle cells.

atheroprotective gene expression, thereby reducing drug dosages and potentially side effects in atherosclerotic patients. To date, several epigenetic drugs such as DNMTi, EZH2i, BETi, and HDACi have been (or being tested in clinical trials) used in treating cancers (Bennett & Licht, 2018). However, there are up to date very few reports of epigenetics "cocktail" therapy for treating CVD.

8. Targeting 'trained immunity' by epigenetic drugs. Lipid-lowering statins are the cornerstone for treating atherosclerosis. Recent studies (Ridker et al., 2017) have shown that anti-inflammatory therapy with Canakinumab (a monoclonal antibody that targets IL-1β) reduces recurrent cardiovascular events in high-risk patients, highlighting the importance of targeting inflammation as a second treatment option to improve cardiovascular outcome. Despite these therapeutic advances, residual cardiovascular risk remains very high, which might be due to the "epigenetic memory" effects elicited by abnormal lipid profile and/or pro-inflammatory cytokines in addition to low statin responses in certain human patient populations. The emergence of epigenetic drugs could fill this gap to abrogate the trained immunity effects conferred by pro-atherogenic insults and complement lipid-modulating and anti-inflammatory therapies.

In this review, we timely overviewed the epigenetic mechanisms and targeted therapeutics of atherosclerotic cardiovascular disease. The use of epigenetic drugs in CVD is likely to further energize clinicians, translational scientists, and the pharmaceutical industry to identify new chemical entities that may target selected chromatin "readers", "writers" and "erasers". Future epigenetic studies in cardiovascular medicine will improve our understanding of the molecular pathogenesis of CVD and most importantly, facilitate novel biomarker identification, improved disease prevention, and new therapeutic strategies in managing CVD. It can be envisaged that the deepened understanding of epigenetic regulation in cardiovascular health and disease will yield novel therapeutic interventions precisely tailored to patients' precise disease conditions.

Conflict of interest

The authors declare they have no conflicts of interest.

Author contributions

S.X. draft the manuscript; S.X., and Z.G. J. conceptualize the manuscript; P.J.L., D.K., S.N., J.P., and Z.G. J. proofread and revise the manuscript.

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