Molecular mechanisms and genetic regulation in atherosclerosis

Ampadu-Okyere Jackson [a,b], Mugwaneza Annick Regine [a,b], Chakrabarti Subrata [c], Shiyin Long [d,*]

[a] Research lab of translational medicine, Medical school, University of South China, Hengyang, Hunan Province 421001, China
[b] International college, University of South China, Hengyang, Hunan Province 421001, China
[c] Department of Pathology and Laboratory Medicine, Western University, London, Ontario, Canada
[d] Department of Biochemistry and Molecular Biology, University of South China, Hengyang, Hunan Province 421001, China

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ABSTRACT

Atherosclerosis (AS) manifested by lipid accumulation, extracellular matrix protein deposition, and calcification in the intima and media of the large to medium size arteries promoting arterial stiffness and reduction of elasticity. It has been accepted that AS leads to increased morbidity and mortality worldwide. Recent studies indicated that genetic abnormalities play an important role in the development of AS. Specific genetic mutation and histone modification have been found to induce AS formation. Furthermore, specific RNAs such as microRNAs and circular RNAs have been identified to play a crucial role in the progression of AS. Nevertheless, the mechanisms by which genetic mutation, DNA and histone modification, microRNAs and circular RNA induce AS still remain elusive. This review describes specific mechanisms and pathways through which genetic mutation, DNA and histone modification, microRNAs and circular RNA instigate AS. This review further provides a therapeutic strategic direction for the treatment of AS targeting genetic mechanisms.

1. Introduction

Atherosclerosis (AS), resulting in lipid accumulation, extracellular matrix protein deposition, and calcification in the intima and media of the arteries causes arterial stiffness reducing its elasticity. It is generally accepted that globally AS causes increased morbidity and mortality [1,2]. Studies have shown that AS plaque is characterized by the accumulation of immune cells such as T-cell [3,4], monocyte/macrophages [5], dysfunctional endothelial cells (ECs) with endothelial-to-mesenchymal transition (EndMT). EndMT is a physiological process by which ECs develop mesenchymal phenotype to promote growth and development of vital organ such as the heart [6,7] and vascular smooth muscle cells proliferation, migration characterized by expression adhesion molecule Endothelial Selectin (E-selectin), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [8].

During AS plaque formation, inflammatory response by inflammatory cytokines from immune cells or defective vascular cells induce monocytes migrate into the intima where this matures to macrophages. Perpetual migration of monocytes and formation of macrophages promote secretion of chemokines such as MCP-1, 2, CXCL1,2,3 etc. which accelerate the recruitment of monocyte/macrophage leading to the formation of advanced vulnerable plaques susceptible to rapture enhancing thrombosis [3,4].

Moreover, ECs lining the inner layer of blood vessels promote homeostasis, prevent coagulation and clot formation. However, excessive secretion of inflammatory cytokines such as interleukin (IL)-1β, -6, -8, tumor necrotic factor-alpha (TNF-α), activation of phosphoinosol-3-kinese (PI3K), tyrosine activation kinase (Akt), mitogen-activated protein kinase (MAPK) etc., which activate inflammatory transcription factor such as nuclear factor kappa-B (NF-κB) leading to ECs inflammation, secretion of extracellular matrix (ECM) that serve a scaffold for the attachment of monocyte/macrophage, plasma proteins and other cell debris, collagen (I,II) and elastin. Furthermore, overexpression of various growth factors including fibroblast growth factors (FGF), transforming growth factor-β (TGF-β) etc., which activate NF-κB and Smad 2,3,4 respectively. Activated NF-κB and Smad 2,3,4 further stimulate twist and Snail transcription factors respectively, promoting ECs dysfunction, EndMT, vascular smooth muscle cells proliferation and migration into the intima and media. Furthermore increased ECM proteins such as collagen, elastin deposition causes increased intima media thickness (IMT) promoting the development of AS [6,7,9].

Recent studies indicate that the abnormal expression of specific genes play significant roles in the development of AS. Specific genetic mutations, DNA and histone modification have been demonstrated to accelerate the development of AS. Furthermore changes have been demonstrated in the miRNAs and circular RNAs in the context of AS [10]. However, the mechanism and pathway underlining these genetic regulations of AS still remains unclear.

This review describes specific mechanisms and pathways through which such genetic and epigenetic alterations lead to AS with an

* Corresponding author.
E-mail address: longshiyin@126.com (S. Long).

attempt to provide specific strategic direction for future therapeutic development.

1.1. Vascular endothelial abnormalities in atherosclerosis

Vascular endothelium prevents thrombosis and clot formation via the secretion of various anticoagulants and promoting antiplatelet mechanism. Recent studies have shown that ECs dysfunctions, lose of apical polarity, increased permeability, transition to mesenchymal-like cells, and apoptosis, promote development of AS [11,12]. Studies have shown that high glucose, oxidized low density lipoprotein (ox-LDL), excessive secretion of cytokines such as IL-1β, -6, -8, TNF-α, transforming growth factor-beta (TGF-β) etc., promote ECs dysfunction including apoptosis and cell transitions [13]. For instance, it has been observed that the abnormal secretion of inflammatory cytokines like IL-1β, -6, -8, TNF-α, etc., chemokines including MCP-1 induce vascular inflammation through PI3K/Akt/NF-κB pathway [14,15]. The occurrence of inflammation in the endothelium increases ECs adhesion via NF-κB pathway enhancing monocyte/macrophage-endothelial adhesion leading to the development of AS [16]. Moreover, ECs inflammation leads to ECs dysfunction. It has been reported that ECs dysfunction accelerates macrophage infiltration causing progression of AS [11]. Furthermore, EndMT is activated via IL-1β,-6,-8/PI3K/Akt/NF-κB/twist, endotherin-1(ET-1), fibroblast growth factor (FGF) and TGF-β/Smad2,3,4/Snail pathways. EndMT-derived mesenchymal cells increase adhesion molecule expression, binds to monocyte/macrophages, plasma protein and increase AS susceptibility [6].

It has been reported that EndMT-derived mesenchymal cells express high level of adhesion molecules which leads to monocyte/macrophage adhesion, ECM, collagen I,II, elastin deposition and migrate to the intima and media which promote IMT and AS progression [7,17,18]. Studies have demonstrated that genetic defect associated with metabolic syndrome such as dyslipidemia and hyperglycemia induces the accumulation of oxidized low-density lipoprotein (ox-LDL) and glucose respectively. Ectopic accumulation of ox-LDL and glucose further enhance inflammation, EndMT and monocyte/macrophage adhesion via NF-κB pathway leading to AS progression [19,20], indicating that AS can be triggered by multiple mechanisms. Targeting these mechanisms may provide a technique for the prevention of AS.

2. Abnormalities in DNA and histone in AS

2.1. Gene deletion studies altering inflammatory pathways

Previous studies have demonstrate that various genetic mutation, promote AS through multiple signaling pathways (Table 1) [21]. Recent studies have confirmed that DNA deletion play an important role in the development and progression of AS. For instance, deletion of hepatic phospholipid phosphatase 3 (PLPP3) gene, that encodes for a ubiquitous enzyme which dephosphorylates lipid substrates to promote lipolysis, enhances coronary arterial plaque formation by increasing serum low density lipoprotein (LDL), oxidized LDL (ox-LDL) accumulation, ECM protein deposition and AS development in mice [21]. Studies have shown that ox-LDL binds to its receptor, lectin-like oxidized low-density lipoprotein (LDL) receptor-1.

(LOX-1), stimulating PI3K/Akt which phosphorylate IκB-NF-κB complex to allow NF-κB's translocation to the nucleus. In the nucleus NF-κB stimulate the secretion of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6 transcription, adhesion molecules expression to allow the adhesion of monocyte/macrophage contributing to AS plaque formation [21–23]. Sirtuin (Sirt) proteins, on the other hand, induce vasorelaxation by enhancing the expression of vasodilation agents such as endothelial nitric oxide synthetase (eNOS) and Akt phosphorylation to inhibit NF-κB mediated inflammatory pathway and secretion of vasoconstriction proteins. This notion was supported by the finding that deletion of Sirt-3 [24] and Sirt-6 [25] genes significantly reduced eNOS production and increased vasoconstriction. Such manipulation further increased adhesion molecules expression through the activation of MCP-1/PI3K/Akt/NF-κB promoting AS plaque formation. On the other hand, SIRT-3 and SIRT6 overexpression reduced atherogenesis in mice. The deletion of TNF-α/β [26] and MCP-1 genes [27] prevented vascular inflammation, adhesion molecules expression, collagen (I, III), ECM protein deposition and AS plaque formation by inhibiting aforesaid pathways in mice [28–31]. Interestingly, overexpression of P2Y2 nucleotide receptor (P2Y2R), which regulates vascular inflammation and AS plaque formation, correlate with increased production of vascular adhesion molecule and inflammation by activating TNF-β/Akt/NF-κB pathway in the AS susceptible region in the aorta. Deletion of P2Y2R in contrast, inhibited TNF-β/Akt/NF-κB pathway, declined vascular adhesion molecule expression and AS plaque formation

Table 1
A table showing genetic mutation, associated pro-inflammatory cytokine, signaling pathway and transcriptional factors involved in atherosclerosis.

Gene mutation	Cytokine	Signaling pathway	Transcription factor	Study subject	Reference
Gene deletion					
PLPP3	TNF-α/β,IL-1β	Akt/PI3K	NF-κB	Mice	[21–23]
Sirt3,6	MCP-1	Akt/PI3K	NF-κB	Mice	[24,25,28–31]
MCP-1/HIF-α	–	Akt/PI3K	NF-κB	Mice	[34]
TNF-α		Akt/PI3K	NF-κB	Mice	[27]
P2Y2	TNF-α	Akt/PI3K	NF-κB	Mice	[32]
DNA/histone modification					
RID5B	INF-γ	Akt/PI3K	NF-κB	Human	[67,68]
BRCA-1 met	Ox-LDL	Akt/PI3K	NF-κB	Human	[65,66,120]
HDAC9	TNF-α/β,IL-1β	Akt/PI3K	EZH2	Mice	[70,71]
Metabolic dysfunction					
LDL	ox-LDL	Akt/PI3K	NF-κB	Human	[36,37]
apoB	ox-LDL	Akt/PI3K	NF-κB	Human	[37]
PCSK9	ox-LDL	Akt/PI3K	NF-κB	Human	[37,40–47]
ABCA1	ox-LDL	Akt/PI3K	NF-κB	Mice	[48–55]
HNF1A	HG,AngII,ET-1	Akt/PI3K	NF-κB	Mice	[59–61]
GCK	HG,AngII, ET-1	Akt/PI3K	NF-κB	Mice	[61]
RNAs					
miRNA-30e-3p/−455-3p/−155-5p	TNF-α, AngII, ET-1	Akt/PI3K	NF-κB,	ECs	[73,79]
miRNA-19b/−30c-5p/−126-5p/−30e-3p/−146a/b/146b-5p	TNF-α	Akt/PI3K	NF-κB	ECs, mice, Human	[80,81]
cirANRIL	–	p16^{INK4a}, p15^{INK4b}, p14^{ARF}	CDKN2A&B	Human	[7,82,84,85,121,122]
CirZNF609	–	–	MEFA2,Tie2	Human	[11,84–87]

in apoE deficient mice [32,33]. Researchers have also demonstrated that low shear stress activates expression of hypoxia inducible factor 1 alpha (HIF1α) and its target gene in the ECs isolated from AS prone site of apoE deficient mice. It was identified that aortic ECs, exposed to low shear stress activates RelA and p50 subunits of NF-κB and increased HIF1α inflammatory signaling, adhesion molecules expression and EC dysfunction. Overexpression of IκBα on the other hand inhibited NF-κB and other pathways mentioned above. These findings indicate that low shear stress stimulate HIF1α in NF-κB-dependent manner. This notion was confirmed by the finding that deletion of HIF1α prevents inflammation and AS plaque formation in apoE deficient mice [34,35] (Fig. 1A). Collectively, these data indicate that several pathways play a crucial role in the development of AS. Therefore, protecting anti-inflammatory genes and down-regulating the expression of inflammatory gene may lead to the prevention of AS.

2.2. Gene mutations causing metabolic abnormalities

2.2.1. Gene mutations and familial hypercholesterolemia

The development of AS has been closely related to genetic inheritance [36]. For instance, familial hypercholesterolemia (FH), an autosomal dominant inherited disease, occurs due to a loss-of-function T-to-A mutation in the LDL-receptor (LDLR) gene and C-to-G transversion along with G-to-A transversion in apolopoproteins (apoB) gene. The DNA base transversion leads to the conversion of amino acid arginine (Arg) to glycine (Gln), cysteine (Cys) to Arg, aspartic acid (Asp) to
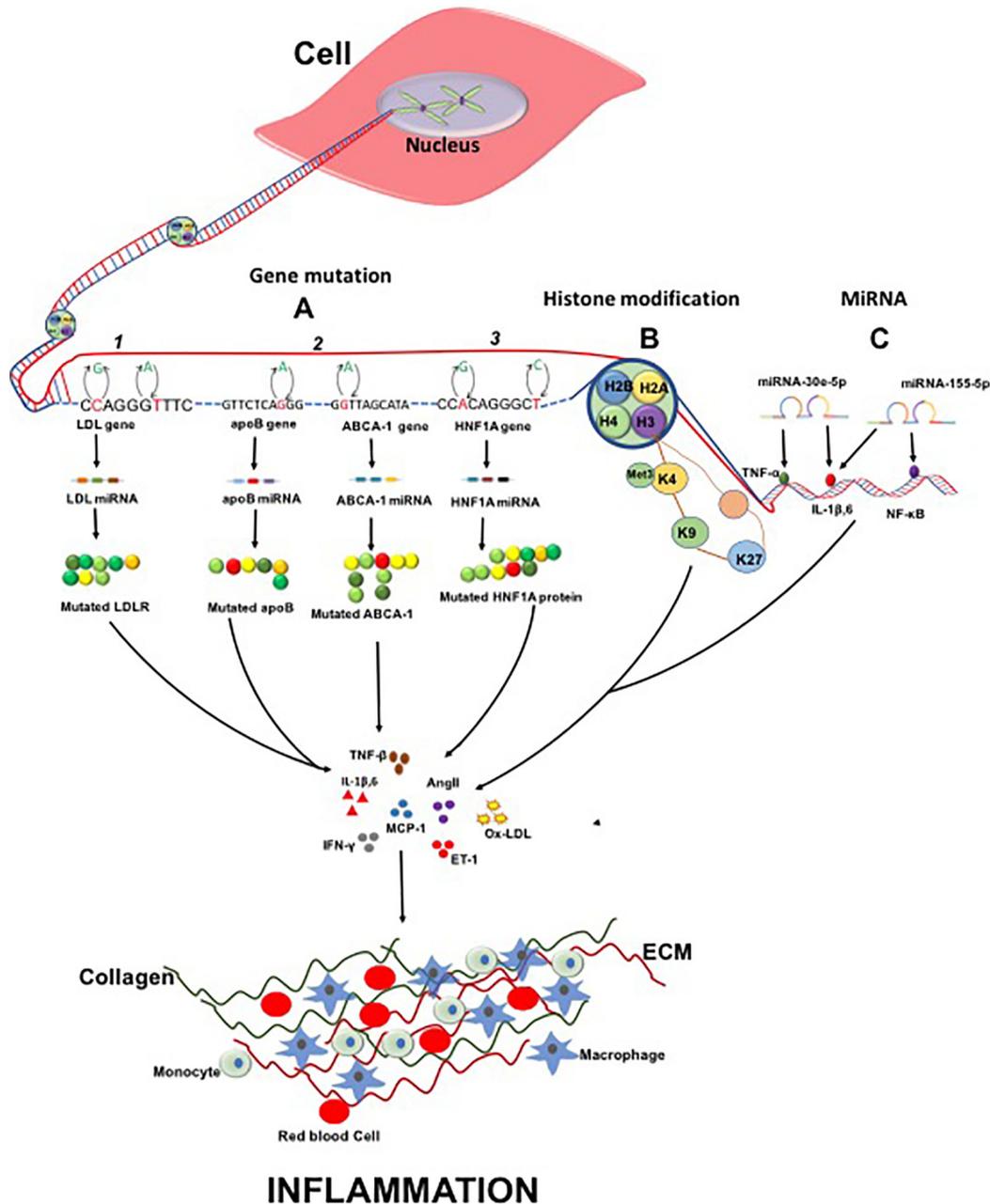

Fig. 1. Diagrammatic illustration of molecular mechanism in genetic regulation of atherosclerosis. The mutation C to G base transversion in LDL gene (A1), G to A transversion in apoB and ABCA1 genes(A2) reduce lipid uptake which increase ox-LDL accumulation, inflammatory cytokine secretion inducing vascular inflammation and AS plaque formation. In addition, A to G and T to C transition in HNFA1 (A3) promote β cell dysfunction increasing plasma glucose inducing vascular inflammation and AS plaque development C: The continuous loss of modified histone such as H3K4me3, H3K9me2, and H3K27me3 promote the secretion of inflammatory cytokines production, inflammation and atherosclerosis. D: The activation miRNA-30c-5p, miRNA-155-5p bind to TNF-α and IL-1β,6 promoter regions to increase the inflammatory and atherosclerotic activity of TNF-α and IL-1β,6.

asparagine (Asn), and Asp to glycine (Gly) in the binding domain of LDL leading to LDLR dysfunction [37]. The adhesion of LDL and LDLR and subsequent uptake and removal LDL from the circulation is reduced, thus promoting plasma retention of LDL, ox-LDL, vascular inflammation and AS plaque development [38,39]. Clinical studies indicate that the missense mutations in proprotein convertase substilisin/kexin type 9 (PCSK9), a gene that activate other serine protease in the secretory pathway, causes severe FH, suggesting additional factors beyond the loss-of-function mutation in the LDLR and apolopoprotein B (apoB) genes are of importance. Studies have shown that PCSK9 adheres to LDLR-LDL complex extracellularly and endocytosed via clathrin coated pits, directed toward the lysosome degradation to facilitate LDLR recycling. PCSK9 variant as a result of A to C base pair transversion leading Arg to Cys and Ser to Arg mutation exhibited higher LDLR affinity and reduce LDLR recycling. LDLR levels on the cell membrane and LDL uptake is decreased in this situation causing LDL accumulation and ox-LDL retention, a characteristic of FH trait in human [37,40–42]. PCSK9 associated FH has also been shown to induce vascular inflammation via ox-LDL/PI3K/Akt/NF-κB pathway, monocyte/macrophage recruitment, macrophage foam cell formation and accumulation, arterial stiffness and AS plaque progression in apoE deficiency mice [43,44]. Interestingly, other forms of PCSK9 mutation have been found to prevent FH and LDL accumulation from childhood. For instance, DNA base pair change from C-to-G in PCSK9 gene resulting from two nonsense mutations including tyrosine-to-X (any amino acid) and Cys-to-X cause increase the levels of cell surface LDLR and reduced LDL internalization. Moreover, C-to-T induced (leu-to-phe changes) reduce catalytic clavage activity of PCSK9 on LDLR which also reduces LDL retention leading to the inhibition of LDL/PI3K/Akt/NF-κB pathway in human [45–47]. Collectively, these data reveal that genetic mutations in PCSK9 promote AS. Hence, targeting PCSK9 variant to reduce LDL retention may future serve as therapeutic target for the treatment of AS.

Tangier disease (TD) is another hereditary disease associated with the mutation in ATP-binding cassette transporter (ABCA-1). ABCA-1 controls HDL-c efflux to reduce oxidation causing excessive lipid accumulation in the plasma [48]. Previous studies have indicated that TD occurs as a result of an A to G substitution leading to change of amino acid from glu-to-arg or arg-to-trp which reduce high density lipoprotein (HDL) efflux [49,50]. During ABCA1 activation, liver X receptor (LXR) and retinoid X receptor (RXR) form a heterodimer and bind to the promoter region of ABCA1 inducing its expression (51). However, it has been indicated that upregulating sterol regulatory element-binding proteins-2 (SREBP-2) inhibited LXLR-RXR heterodimer formation and prevent ABCA1 expression while inhibition of SREBP-2 by oxysterols promoted LXR-RXR heterodimer formation and increased ABCA1 expression in ECs [52]. These findings indicate that TD can occur as a result of excessive SREBP-2 transcription. Both inhibitions of LXR-RXR complex formation and ABCA1 activation promote HDL and LDL accumulation in the plasma, which increases OS and inflammation through ox-LDL/PI3K/MAPK/NF-κB pathway. Ultimately, these abnormalities lead to ECs adhesion molecules overexpression, macrophage foam cell formation, intima media IMT and AS plaque development [53–56] (Fig. 1A1–2). Hence, upregulation of LXR-RXR heterodimer formation and inhibition of SREBP-2 expression may terminate ox-LDL/PI3K/MAPK/NF-κB pathway, which may serve as a therapeutic target for the treatment AS in TD.

2.2.2. Gene mutations causing hyperglycaemia

Hyperglycaemia occurs as a result defective insulin production or action. Researchers have shown that maturity onset diabetes of the young (MODY), an autosomal dominant form of non-insulin-dependent diabetes mellitus, occurs by mutation in hepatocyte nuclear factor (HNF)-1α gene. [57,58]. MODY is associated with C to G, T to C and A to G mutation in the HNF1A and glucokinase (GCK) genes causing the changes of amino acid from proline (Pro)-to-alanine (Ala), Pro-to- serine (Ser), Ser-to-Arg, threonine (Thr)-to-Ala and methionine (Met)-to-Thr. It

was reported that such missense mutation causes insulin resistance, increasing the risk of developing type 2 diabetes, HG levels in the blood [59–61]. However, HG promotes endothelin-1 (ET-1) and angiotensin II (Ang II) activation which stimulates vascular inflammation via NF-κB pathways, endothelial dysfunction and adhesion molecule expression, increased ECM synthesis increasing arterial stiffness and AS plaque development [62–64] (Fig. 1A3). These data show that various mutations in HNF1A and GCK promote the accumulation of glucose lead the inflammation and AS development via several pathways. Targeting HNF1A and GCK may also serve as a therapeutic strategy for the prevention of AS in diabetic patients.

2.2.3. DNA and histone modification promote AS

Epigenetic modifications of DNA and histones associated with AS have recently gained attention [65]. DNA methylation at CpG dinucleotide sites is the most common genetic modification [66]. Macrophage polarization, the differentiation of anti-inflammatory macrophage (M2) to pro-inflammatory macrophage (M1) has been found to participate in the development of ECs inflammation, dysfunction and AS plaque formation. M1 macrophage induces inflammation, dysfunction and AS plaque formation by the secretion of inflammatory cytokines. Studies have shown that peroxisome proliferator-activated receptor-gamma (PPAR-γ) exhibit a potent anti-inflammatory activity in macrophages. It was demonstrated that methylation at PPAR-γ promoter region significantly reduces the expression of M2 cytokines such as IL-10 expression and increases M1 cytokines expression including IL-1β, -6 and TNFα.Inhibition of gene methylation and agonizing PPAR-γ with rosiglitazone, a specific PPAR-γ agonist, on the other hand significantly reduces M1 cytokine expression mice. In addition, increased level of PPAR-γ methylation, M1 macrophages, cytokine expression M2 macrophage cytokines was identified in peripheral blood monocytes from patient with AS [66]. These data indicate that PPAR-γ methylation induce the development of AS, by activating M1 macrophages to induce inflammation through NF-κB pathway. Methylation at CpG site in the promoter of breast cancer type 1 (BRCA1), a gene that regulate genome stability, cell-cycle control and lipogenesis, increases ox-LDL accumulation, inflammation via ox-LDL/PI3K/Akt/NF-κB pathway and AS plaque formation [65] [32]. Methylation of BRCA1 also diminishes lipogenesis and cause the excessive synthesis and accumulation of lipid. Such deregulated lipogenesis enhances excessive accumulation of ox-LDL, promotes vascular inflammation, expression of adhesion molecules, macrophage recruitment which leads to increased carotid IMT in human [65]. In addition, methylation of AT-rich interaction domain-5B (ARID5B), a transcription coactivator that forms a chromatin depressor complex with a histone H3K9Me2 demethylase has been found to reduce ARID5B expression and to prevent AS development. On the other hand, ARID5B demethylation increase ARID5B expression and AS development. Augmented expression of ARID5B decreased LDLR and ABCA1 levels resulting in the attenuation of lipolysis, macrophage migration inflammatory gene expression, carotid plaque formation and carotid arterial calcification in human. Increased ARID5B promoter methylation increased, lipolysis, inflammatory gene expression and carotid arterial calcification. These data suggest that ARID5B methylation prevent inflammation and AS plaque formation by inhibiting ox-LDL/PI3K/Akt/NF-κB pathway [67,68]. DNA methyltransferases (DNMT) -1 and -3A, enzymes catalyze the addition methyl group to cytosine, have been implicated in the development of AS plaque. Studies have reported that increased DNMT-1induced DNA cytosine-5 methylation promotes ECs dysfunction, migration, inflammation via connective tissue growth factor (CTGF)/PI3K/Akt/NF-κB pathway promoting monocytes and AS development. Inhibition of DNMT-1 on the other hand improved vascular function in the apoE deficient mice [69] Interestingly, overexpression of enhancer of Zeste Homolog 2 (EZH2), a histone-lysine N-methyltransferase enzyme that causes histone methylation and transcriptional repression, reduced H3K4me3 expression, recruited DNMT-1 to methylate CpG island of ABCA1 gene and caused its

inhibition. Such manipulation also enhanced lipid retention, vascular inflammation via ox-LDL/PI3K/Akt/NF-κB pathway and the development of AS [70]. Interestingly, histone deacetylase 9 (HDAC9) deletion increased H3 and H3K9 accumulation in ABCA1 promoter region downregulating inflammatory genes' expression and AS plaque progression in mice (Fig. 1B) [71,72]. These studies reveal that DNA and histone modification regulate atherogenesis, suggesting that targeting DNA and histone modification may provide a therapeutic strategy for the control of AS plaque formation.

2.3. RNAs

Lately, studies have shown that upregulation of some miRNA accelerate inflammation and AS while others prevent AS progression. For instance, it has been reported that overexpression of miRNA-155-5p and miR-155 exhibited AS effect by decreasing vasodilators such as eNOS, ox-LDL accumulation, increasing OS, TNF-α and NF-κB-dependent adhesion molecules in human umbilical vein EC (HUVEC) and mice respectively [73,74]. It has been observed that overexpression of miR-126 prevents ECs dysfunction, atherosclerotic plaque formation by inducing ECs repair and proliferation. The activation of miR-126 promoted ECs marker CD31 and proliferative transcription factor Notch. However, activation of miR-126-5p impaired ECs repair and proliferation by inhibiting Notch and upregulating delta like non-canonical notch ligand 1 (Dlk1) while silencing miR-126-5p reversed HUVEC dysfunction, increased repair and proliferation. In addition, upregulation of miR-126 reduced atherosclerotic plaque formation while the miR-126 knockout increased plaque formation in apoE deficiency mice. Additionally, miR-126-5p activation upregulated atherosclerotic plaque formation while miR-126-5p knockout downregulated AS in apoE deficiency mice [75]. The downregulation of miR-142-3p increased LDL accumulation, ox-LDL-induced ECs apoptosis, AS while miR-142-3p upregulation reduced LDL accumulation, ox-LDL-induced ECs apoptosis by increasing eNOS which led to the prevention of AS in apoE deficiency mice [76]. MiR-146a and miR-146b expression has been shown to exhibit anti-atherosclerotic effect by downregulating inflammatory cytokines, chemokines and NF-κB. The inhibition of miR-146a and miR-146b increased inflammation and AS while stimulation of miR-146a and miR-146b significantly downregulated AS in apoE deficiency mice [77]. Moreover, miR-217 upregulation increased lipid metabolic gene, reduced serum LDL level and upregulated HDL leading to the decline of inflammatory cytokines and IMT in apoE deficiency mice. Nevertheless, miR-217 deficiency mice expressed significant level of serum LDL, inflammation and IMT in the ascending aorta of apoE deficiency mice [78].

In addition, miRNA-30e-3p and miRNA-455-3p accelerate vascular inflammation and remodelling by increasing MAPK/NF-κB pathway in rats [79]. Additionally, up-regulation of miRNA-146b-5p and miRNA-19b increase vascular inflammation and AS via NF-κB activation, foam cell formation, ECM protein synthesis and deposition and plaque formation [80]. Additionally, downregulation of miRNA-30c-5p promoted macrophage foam cell formation and increased IMT while increased miRNA-30c-5p expression prevented such thickening in human [81]. Altogether, these data not only indicate that miRNAs play an important role in AS but also suggest that miRNAs may also serve as a potential therapeutic strategy for AS.

Circular RNAs (cirRNAs) is formed by back-splicing RNA and the coding exons are covalently joined at the 5′ and 3′ ends. It has been demonstrated the exons of ANRIL, a long non-coding RNA consisting of 19 exons, can circularized to for cirRNA (cirANRIL) to participate in the development of AS [82]. Furthermore, cirRNAs such as circANRIL promoted the binding to pescadillo homolog-1 [82], accelerate nucleolar stress and expression of apoptotic protein p16[INK4a], p15[INK4b] and p14[ARF], cyclin-dependent kinase inhibitors A and B (CDKN2A and B). These changes in turn, may alter expression levels of specific transcripts leading to ECs apoptosis, inflammation and AS plaque formation [82,83]. In addition, overexpression of cirZNF609 increases inflammatory

responses by elevating the secretion of IL-6 and TNF-α which aggravated vascular leakage and capillary degeneration in mice model of diabetic retinopathy. Further in vitro studies confirmed that cZNF609 acted as miR-615-5p, bonded to Ago2, the core part of RNA induced silencing complex (RISC), inhibited the expression of myocyte enhancer factor 2A (MEF2A) transcription factor and Tie2, a tyrosine-protein kinase that acts as cell-surface receptor for angiopoietins during angiogenesis, ECs survival, increased OS, ECs dysfunction and migration in HUVECs. However, researchers have shown that alteration of MEF2A and Tie2 accelerated vascular inflammation by activating proinflammatory signaling, macrophage infiltration, ECs dysfunction and AS in apoE deficiency mice [11,84–87].

(Fig. 1D). Other researchers have shown that the overexpression of circular RNAs including circHECTD1 and has-circ-0010729 upregulated EndMT characterized by excessive proliferation, migration, adhesion molecules expression, ECM and collagen (I,II) deposition in mouse microvascular lung (MML1) cells, mouse ECs line. However, whether cirRNAs accelerate the development of AS in human or animal model still remains unclear. Further studies in this area are needed.

3. Oxidative stress, inflammatory and nutritive factors promote atherosclerosis through molecular regulation

3.1. The molecular mechanism of oxidative stress promoting atherosclerosis

Oxidative stress (OS) occurs as a result of excessive accumulation of reactive oxygen species (ROS). Previous studies have shown that ROS can induce DNA damage at 8-oxo-7,8-dihydroguanine (8-oxo-G) site which promote inflammation [88]. The perpetual DNA lesions by OS increase MAPKs, PI3K and NF-κB expression. Treatment of 8-Oxoguanine-DNA glycosylase-1 (OGG1), an enzyme for repairing 8-oxo-G by DNA base excision repair pathway (OGG1-BER) on the other hand significantly reduce inflammation by inhibiting aforesaid mechanisms [88]. Anti-inflammatory cytokine IL-35 also regulates OS, inflammation, vascular adhesion molecules expression and AS plaque development. IL-35 inhibition increases AS in apoE deficient mice [89]. Toll-like receptor-9 (TLR-9) also increases expression of unmethylated CpG dinucleotides that promote secretion of pro-inflammatory cytokines. Interestingly, recent reports indicate that ox-LDL-LOX-1 axis decline OS, DNA damage and TLR9-induced inflammation by upregulating autophagy in (HUVECs) [90]. OS significantly increases the activation and phosphorylation of epithelial growth factor (p-EGFR) which led to the phosphorylation of PI3K/Akt, stimulation of inflammatory gene that induced ECs dysfunction, migration, SMCs proliferation, macrophage foam cells formation and IMT. It was further demonstrated that OS-induced p-EGFR, increased NF-κB activation causing col. (I, II) deposition, AS formation in apoE deficient mice. This notion was further supported by the finding that OS inhibition prevented IMT and AS plaque formation by abrogating PI3K/Akt/NF-κB pathway in apoE deficient mice [91]. Interestingly, N-acetyl cysteine (NAC) also exhibits reduced OS by up-regulating expression of apo-E gene expression and promote lipid efflux, reduced vascular inflammation and macrophage foam cell formation [92,93]. Collectively, these data indicate that OS promote genetic regulation of inflammatory associated AS. Augmenting the expression of NAC and protecting 8-oxo-G by increasing OGG1 may also be considered as anti-atherosclerotic therapeutic strategies to improve vascular function.

3.2. The molecular mechanism of inflammatory factors promoting atherosclerosis

Recent studies have identified gene that regulate vascular inflammation and moderated atherosclerosis. For instance, Sirt1, Sirt3 and, families of nicotinamide adenine dinucleotide (NAD+), have been shown to reduce progression of vascular inflammation and AS. Deletions of SIRT1 increase NF-κB sub-unit RelA/p65 acetylation, and MAPK activation leading to AS plaque formation in mice. On the other hand SIRT1

activation deacetylates NF-κB subunit RelA/p65 leading to the termination MAPK/NF-κB pathway and reduced inflammation [94], adhesion molecules expression and AS plaque formation [95–98]. Activation of SIRT3 suppressed the activity of nod-like receptor protein 3 (NLRP3) inflammasome preventing vascular inflammation and ECs dysfunction. SIRT3 deletion on the other hand, increases NLRP3 inflammasome activity and vascular inflammation [99]. SIRT6 overexpression also demonstrated to reduce inflammation, endothelial monocytes adhesion and expression of AS related transcripts, such as pentraxin 3 and TNF super family 4 transcription factors. Additionally, activation of SIRT6 increased proteins that participate in DNA repair such as several heat shock protein genes. Such approach further caused vasorelaxation and prevented AS plaque formation [96]. Recent studies have reported that the activation of PPARγ

prevented TNF-α/NF-κB-induce inflammation while PPARγ deletion induces NF-κB expression and carotid artery inflammation in mice [100]. Pigment epithelium-derived factor, an endogenous multifunctional cytokine with anti-inflammatory activity also decreased expressions of MAPK, NF-κB and reduced inflammation in mice while it's deletion drastically caused inflammation in mice [101] (Fig. 2). Altogether, these data suggest that activating anti-inflammatory molecules may serve a therapeutic strategy for the treatment of AS.

3.3. The molecular mechanism of nutritive factors promotes atherosclerosis

Lately, studies have reported that vitamins play significant role in the regulation of transcripts causing atherosclerosis. Researchers have
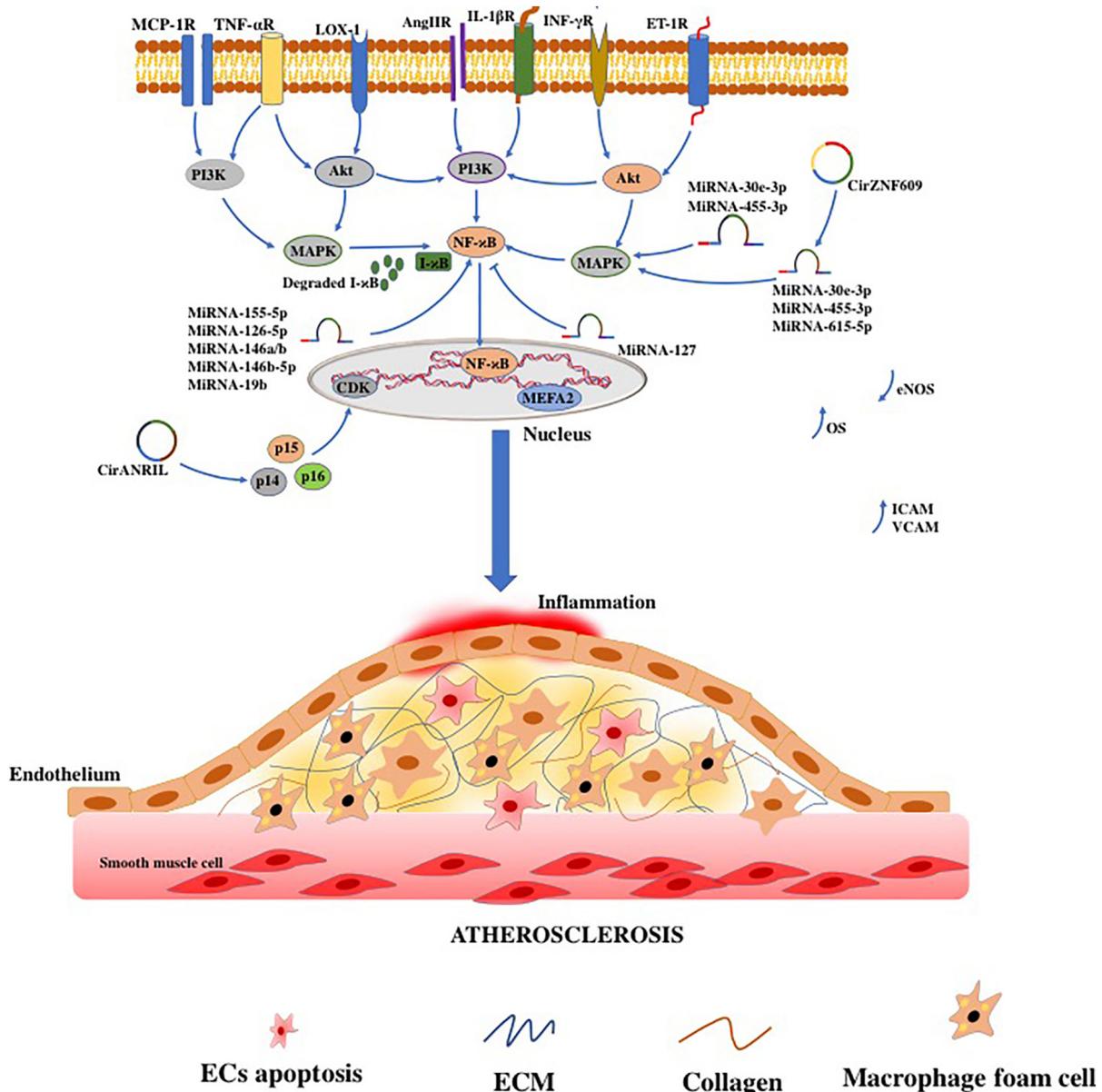

Fig. 2. A schematic illustration of signaling pathways involved in atherosclerosis: The altered levels of secreted cytokines including MCP-1, TNF-α, ox-LDL, AngII, IL-1β,6, INF-γ and ET-1 adhere to the respective membrane receptors. The interaction transduces signal to IKKB-NF-κB complex in the cytoplasm leading to the phosphorylation and degradation of I-κB to allow the nuclear translocation of NF-κB to activate the transcription of various cytokine which promote vascular inflammation and increase adhesion molecule expression to allow the binding of monocytes/macrophage leading to the formation of atherosclerosis. Moreover, miRNA-195, miRNA-30e-3p activate MAPK and Akt respectively to stimulate NF-κB vascular inflammatory activity and atherosclerosis. Furthermore, miRNA-155-5p, miRNA-126-5p, miRNA-146a/b,miRNA-146b-5p and miRNA-19b directly interact with NF-κB to promote vascular inflammation and atherosclerosis. However, MiRNA-30e-3p, MiRNA-455-3p, induce atherosclerosis by activating NF-κB via MAPK. Interestingly, MiRNA-127 prevent atherosclerosis by direct interaction and inhibition of NF-κB. In addition, the expression of CirANRIL upregulate p16[INK4a], p15[INK4b] and p14[ARF], inhibit CDK, promote inflammation and atherosclerosis. Additionally, CirZNF609 upregulate miRNA 615 that inhibit the expression of MEFA2. MEFA2 inhibition accelerates endothelial cell dysfunction, inflammation, migration and microphage infiltration the occurrence of atherosclerosis.

shown that vitamin B supplementation reduces pro-inflammatory cytokine secretion, adhesion molecules expression, MAPK/NF-κB activation and subsequent structural changes in human [102,103]. Vitamin C supplementation also exhibited high anti-atherogenic activity by promoting lipoprotein gene expression, reduced ox-LDL accumulation and pro-inflammatory gene expression [104]. Vitamin C acts by reducing expression of pro-inflammatory cytokines via inhibition of nuclear transport of NF-κB in ECs [105]. Moreover, vitamin D/vitamin D receptor axis activation reduced NF-κB expression and vascular inflammation via the increase of retinoid X receptor (RXR) which reduced glucose-induced ECs apoptosis and AS in mice [106–108]. In addition, supplementation of vitamin E reduced foam cell macrophage formation and expression of adhesion molecules transcripts as well as vascular inflammation by inhibition of Akt/NF-κB pathway in macrophage [109,110]. Collectively, these data indicate that several vitamins may be beneficial in this context.

3.4. Gene therapy for the treatment of atherosclerosis

The advancement in AS studies including imaging has provided the assessment of various plaque characteristics and their detrimental effect on the cardiovascular system. According to the stability, AS can be classified as either vulnerable or invulnerable. Vulnerable AS plaque has thin fibrous cap, susceptible to disruption, thrombosis and vascular occlusion while invulnerable plaques are characterized by thick fibrous cap, non-susceptibility to rupture and causing further vascular obstruction. The use of specific markers for diagnosing the development of AS, characterizing the vulnerability and invulnerability is vital for the management and treatment of AS in human and animals [111]. Recently, the accumulation of plasma lipid and inflammatory cytokines secretion have been used as markers for the diagnosis of AS. However, reduction or eradication of plasma lipids and inflammatory cytokines to control AS still remains a puzzle to be solved [112].

Lately, the use of statin and its derivatives such as Rosuvastatin as genetic intervention for FH associated AS. It was reported that patients with high genetic risk, greater subclinical AS burden exhibited clinical benefit from the statin therapy [113,114]. Nonetheless, studies have shown that patients with FH fail to achieve high LDL-C reduction despite high-intensity statin and progression of AS continues in this situation [115].

Researchers have shown that the use of Adeno-associated virus (AAV)-based gene therapy is promising for the treatment of severe FH. It was demonstrated that the intravenous administration of self-complementary (sc) AAV vectors resulted in apoA-I expression which led to the correction of the lipid metabolism abnormalities, reduced oxLDL-induced inflammation and AS plaque formation in inherited apoA-I deficiency and apoE deficient mice [116–118].

Recent studies have shown that diabetic mice treated with 17-dimethylaminoethylamino-17-demethoxygeldanamycin (DMAG) exhibited reduced level of glucose accumulation and atherosclerosis. It was observed that the administration of DMAG reduced the transcription of heat shock proteins (HSPs)-90, a key regulator of pathological mechanisms associated with diabetes, and inflammation via the inactivation of inflammatory transcription activity of NF-κB [119]. However large scale clinical studies are needed to validate such approach.

4. Conclusions

In this review, the mechanisms and pathways involved in AS are summarized with a focus on gene mutation. In general, this research showed that several genetic mutations promote AS mainly by activating vascular inflammation via NF-κB pathway. In addition, inhibition of NF-κB pathway significantly reduced the development of AS. Several gene mutations ultimately converge on the activation of NF-κB in AS. Hence targeting expression of NF-κB may provide a strategy to prevent vascular inflammation and AS plaque progression in both inherited and non-

inherited AS. However large scale long tern studies are required to support this notion.

Conflict of interest

The authors have indicated there are no conflicts of interest.

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