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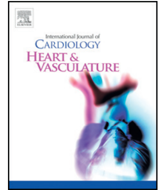
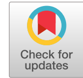


Molecular mechanisms and genetic regulation in atherosclerosis



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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.

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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

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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	–	$p16^{INK4a}$, $p15^{INK4b}$, p^{14ARF}	CDKN2A&B	Human	[7,82,84,85,121,122]
CirZNF609	–	–	MEFA2,Tie2	Human	[11,84–87]

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