Role of Transcription Factors in Regulating Development and Progression of Atherosclerosis

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Abstract

Atherosclerosis is a chronic inflammatory disease of the vasculature that results in hardening of the vessel wall and narrowed lumen. Development of the atherosclerotic plaque starts from the deposition of the lipids in the fatty streak followed by its progression to atheroma, atheromatous plaque, and fibroatheroma. Diabetes mellitus (hyperglycemia), hypertension, smoking, obesity (hypercholesterolemia, dyslipidemia), male sex, family history of atherosclerosis, or genetic susceptibility are the risk factors for atherosclerosis. Chronic inflammation, immune cells infiltration, a bacterial or viral infection of the plaque, intraplaque hemorrhage, and endothelial and vascular smooth muscle dys regulation renders a stable plaque (rich in VSMC and collagen with few inflammatory cells) unstable (few VSMCs, more macrophages, and less collagen) which are prone to rupture. The role of various mediators of inflammation (damage associated molecular proteins), pro inflammatory cytokines (interleukin-1β, -6, -8, tumor necrosis factor-α etc.), and surface receptors (triggering receptors expressed on myeloid cell 1, Toll-like receptors, receptor for glycation end products etc.) in the pathogenesis of plaque development and rupture has been discussed in the literature. The mechanistic aspects of plaque progression have been discussed mainly at the protein level. The epigenetic regulation of atherosclerosis is a current area of interest to researchers. However, regulation of the development, progression, and rupture of the atherosclerotic plaque at the transcriptional level has not been studied in detail. This review emphasizes the role of transcription factors associated with atherosclerotic plaque progression and rupture.

Introduction

Atherosclerosis, a chronic inflammatory disease, is characterized by the formation of the atherosclerotic plaque and narrowed lumen of the vessel. Plaque formation starts with the inflammation in the fatty streak and deposition of excess lipids in the arterial intima as shown in Figure 1. Lipid deposition in the arterial intima is associated with inflammation, hyperglycemia, hyperlipidemia, and dys regulation of the angiotensin system [1-3]. Formation of the minimally-oxidized lipid (oxLDL) by the oxidation of deposited lipids results in the stimulation of the innate and adaptive immune responses. Induction of vascular smooth muscle and endothelial cells in the plaque area triggers the expression of adhesion molecules, growth factors, and chemo attractant which upon interaction with monocytes lead to homing and migration of immune cells as well as the differentiation of monocytes to macrophages and dendritic cells [1,4]. Chronically, fat deposition, inflammation, immune responses, secretion of pro-inflammatory cytokines, and Vascular Smooth Muscle Cells (VSMCs) proliferation leads to the increase in plaque size and renders the stable plaque into an unstable one followed by plaque rupture due to intraplaque hemorrhage, increased inflammation, and thinning of the fibrous cap [1,4,5]. Plaque rupture alleviates to thrombus formation and precipitates ischemic events including adverse cardiac events (myocardial infarction, angina), brain injury (ischemic stroke) and peripheral vascular disease [3]. Behavioral factors and some pathological conditions like Diabetes mellitus, smoking, hypertension, male sex, family history of atherosclerosis, or genetic susceptibility, add nuances to the disease presentation [3]. The pivotal role of various inflammatory cytokines (interleukin (IL)-6, IL1β, IL-8, tumor necrosis factor-α, interferon-γ) damage and pathogen-associated molecular patterns (HMGB-1, RAGE, ENRAGE, S100 proteins, and lipopolysaccharides), surface receptors including TREM-1, TLR-2, and TLR-4 in the atherosclerotic condition has already been discussed in detail by others [1,3,6-10]. Furthermore, the role of various signaling pathways involving inflammatory mediators, kinases (JNK, PI3K, MAPK, AMPK, etc.), and matrix metalloproteinases (MMP-1, -2, -9) in the pathogenesis of atherosclerosis has been very well established with the most common downstream
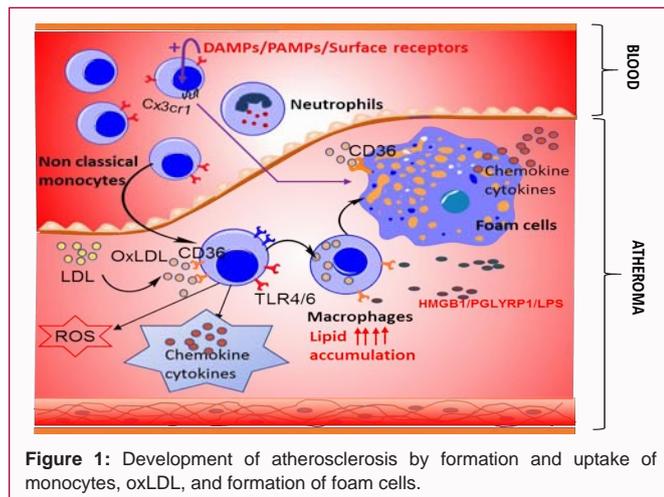
Figure 1: Development of atherosclerosis by formation and uptake of monocytes, oxLDL, and formation of foam cells.

signaling molecule, transcription factor nuclear factor-kappa beta (NF-κB) [8,11-15]. NF-κB's involvement in the pathogenesis of atherosclerosis has been extensively explored; however, the roles of other transcription factors are poorly understood. This review is envisioned to emphasize discussing the pathophysiological roles of various transcription factors in the development and establishment of atherosclerosis and atherosclerotic plaques.

Nuclear factor-kappa beta (NF-κB)

Activation of NF-kB has a crucial role in the increased secretion of pro inflammatory cytokines and activation of surface receptors which contribute positively to the progression of atherosclerotic lesions suggesting a proatherogenic role of NF-kB [16]. Various studies in the literature have suggested that inhibition of NF-kB subverted the expression of various cytokines and expression of inflammatory mediators, thereby modulating the inflammatory environment and progression of atherosclerotic lesions. Have reported that inhibition of NF-kB, JNK, and PI3K signaling pathways attenuates the expression of TREM-1, MMP-1, and MMP-9 in TNF-α treated vascular smooth muscle cells isolated from symptomatic carotid plaques compared to asymptomatic patients [8]. Guolan et al. have proposed that neferine could be beneficial in the early treatment of atherosclerosis due to its anti-inflammatory effect via modulation of MAPK and NF-κβ [13]. Suppression of p38, JNK/MAPK and NF-κB signaling pathways by; (a) Cinnamaldehyde protects vascular smooth muscle cells proliferation, their migration, inflammatory cytokine overproduction, and foam cell formation induced by ox-LDL as discussed by Li et al. [17], and (b) baicalin in ApoE⁻/⁻ mice fed with high-lipid diet model of atherosclerosis exhibited the anti-adipogenic, anti-oxidant, and anti-inflammatory effects in a dose-dependent manner as reported by Wu et al. [18]. Proliferation and migration of VSMCs are characteristic features of atherosclerotic lesions and Yu et al. have shown inhibition of proliferation and migration of Angiotensin II-induced VSMCs by attenuating NF-κB, p65, Akt, and Extracellular Signal-Regulated Kinase (ERK) signaling stimulations by Klotho genes [19]. Attenuation of chronic intermittent hypoxia-induced atherosclerosis in mice by selective inhibition of endothelial NF-kB signaling further suggested the atherogenic role of NF-kB in the pathogenesis of atherosclerosis [20]. These findings of transcription factor NF-kB's crucial role in the pathogenesis of atherosclerosis with its proatherogenic potential suggest that inhibition of NF-kB could be a potential therapeutic target in atherosclerosis.

v-ets erythroblastosis virus E26 oncogene homologue-1 (Ets-1)

Ets-1 proto-oncogene protein, a member of the Ets family of transcription factors with a highly conserved Ets domain, is involved in regulation of several biological processes including cell development, angiogenesis, and apoptosis. Recent studies by Rao et al. demonstrated that Epidermal Growth Factor (EGF), influenced Ets-1 overexpression and attenuated interstitial and basement membrane collagens in VSMCs increases the expression of MMP-1 and -9 and decreases collagen mRNA transcripts in VSMCs of patients with carotid stenosis. Inhibition of Ets-1 was found to increase the expression of mRNA transcripts for collagen I (α1) and collagen III (α1) and block induction of MMPs in symptomatic compared with asymptomatic carotid plaques. Conversely, inhibition of p38-MAPK and JNK-MAPK signaling decreased the expression of Ets-1, MMP-1, and -9 and increased the expression of collagen type I and III in EGF-treated VSMCs. These results outline the pivotal role of Ets-1 involving p38-MAPK and JNK signaling pathways in the pathogenesis of plaque destabilization in patients with carotid stenosis [15]. Li et al in their findings reported that 17β-Estradiol enhances expression of vascular endothelial miR-126-3p through ETS-1 in ApoE⁻/⁻ mice and Human Umbilical Vascular Endothelial Cells (HUVECs) atherosclerosis models. Dysfunctional endothelial cells initiate atherogenesis and one way of 17β-Estradiol to govern atherogenesis is by the vascular path up through endothelial proliferation and migration. The miR-126-3p is abundant in the endothelium and Ets-1 being a transcription factor for miR-126-3p is crucial for the regulation of endothelial proliferation and migration [21]. The endothelial cells apoptosis when induced by ox-LDL essentially modulates atherosclerosis where ox-LDL down regulated miR-221/222 expression through the suppression of Ets-1 as reported by Qin et al. [22] The miR-221/222 expression regulates endothelial inflammation and angiogenesis Its inhibition markedly enhanced apoptosis in ECs. Qin et al also proved that over-expression of miR-221/222 suppressed Ets-1 and partly improved the apoptotic cell death by ox-LDL treatment. These results suggest that Ets-1 can be an important target to modulate for the development of a novel therapeutic strategy against atherosclerosis.

PU.1

Transcription factor PU.1, a protein encoded by the SPI1 gene, is a member of Ets family transcription factors. The accumulation of lipid-loaded foam cells, derived from macrophages VSMCs in the sub endothelial space has an important role in the early development of atherosclerosis. After their recruitment to the intima of the arterial wall, VSMCs proliferate and change their phenotypes from a contractile to synthetic ones to engulf an excessive lipoprotein cholesterol to become foam cells and thus to transform stable plaque to unstable plaque. As reported by Inaba et al. VSMCs isolated from atherosclerotic lesions show the expression of macrophage colony-stimulating factor receptor encoded by the *c-fms* genes [23]. The stable expression of *c-fms* in normal vascular medial smooth muscle cells induced by platelet-derived growth factor-BB and epidermal growth factor was found to be PU.1 dependent. These factors were found to induce the expression of PU.1 mRNA in VSMCs. Further, growth factor-induced *c-fms* expression and foam cell formation were inhibited with PU.1 antisense oligonucleotides suggesting an essential role of transcription factor PU.1 in the phenotypic conversion of vascular smooth muscle cells on the pathogenesis of atherosclerosis. On the other hand reported that LXRα, that highly expresses in regressive plaques, and regulates macrophage arginase 1, is inversely

correlated with atherosclerosis progression, via PU.1 and IRF8 [24]. Liver X Receptors (LXRs), when activated, can regress existing lesions and thus inhibit the progression of atherosclerosis. Arg1 expression in the plaque was found to be LXRα-dependent. It was found that LXRα did not directly bind to the Arg1 promoter, however, it promoted the interaction between PU.1 and IRF8 transcription factors. This was further proved in IRF8 or PU.1 knockout macrophages where the LXRα strongly impaired the regulation of Arg1 expression in macrophage cells. These results, in turn, implicate the role of PU.1 in the pathogenesis of atherosclerosis.

Activator protein-1 (AP-1)

Transcription factor activator protein 1 (AP-1) controls cellular processes including differentiation, proliferation, and apoptosis and regulates gene expression in response to stimuli including cytokines, growth factors, stress, and bacterial and viral infections. As already mentioned earlier, an endothelial dysfunction and ox-LDL deposition play a crucial role in the pathogenesis of atherosclerotic lesions. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) also has a crucial role in endothelial dysfunction and atherosclerosis. Lee et al. reported that regulation of LOX-1 expression on endothelial cells is via fluid shear stress intensity as well as pattern and is mediated through the KLF2-AP1 pathway of mechano transduction [25]. Chronic inflammation and pro inflammatory cytokines do stir up the progression and rupture of plaques. Sha et al. [26] reported the role of inflammation-induced IL-35 in inhibiting LPS-induced endothelial cell activation by suppressing MAPK-AP1-mediated VCAM-1 expression. Here IL-35 also attenuated the LPS-induced secretion of pro inflammatory cytokines/chemokines indicating the possible role of IL-35 in controlling inflammation in the vasculature and if targeted, would be an attractive novel therapeutic remedy for cardiovascular diseases. The role of AP1 in atherosclerosis via *chlamydial pneumoniae* infection and its probable use as a target in gene therapy has also been discussed [27,28]. However, a clinical trial evaluating the profile of AP-1 activation histologically do not characterize AP-1 as a therapeutic target for progressive human atherosclerotic disease [29]. Having said this, one cannot negate the important role of AP1 in the pathogenesis of atherosclerosis if not as a promising target for atherosclerotic disease. Moreover, further detail investigations are inevitable to unwrap these contradictory results.

Krüppel-like factor 2 (KLF2)

Krüppel-like factor (Klf)-2 belongs to the zinc finger family of DNA-binding transcription factors. Studies have reported the protective role of KLF family transcription factor in vascular diseases [30,31]. KLFs govern cell activation and inflammatory responses in many cellular components of the vascular wall and plaque lesions. Alaiti et al. [31] have reviewed the role of various KLFs in atherosclerosis via regulating endothelial and VSMCs functions. Hu et al. [32] reported the protective role of KFL14 in atherosclerosis via NF-κB signaling inhibition. KFL14 attenuated the inflammation in the endothelial cells. Song et al. [33] showed that when treated with vascular endothelial growth factor there was a significant increase of endothelial markers in endothelial cells, migration and tube formation and this was observed to be associated with up regulation of KLF2. In endothelial cells, the KLF2 expression is controlled by MEF2 and HDACs, in p65 and TNF-α-dependent manner. Thus, they are a critical regulator of inflammation homeostasis under normal physiological condition. Up-regulation of KLF2 by AMPK activation promotes endothelial colony forming cells differentiation.

Interestingly, NF-κB and KLF2 both are antagonistic regulators of inflammation. In monocytes, KLF2 competitively interacts with PCAF and inhibits several inflammatory genes and cytokines expression by anchoring the transcriptional activity of NF-κB. KLF2 deficiency has been associated with chronic inflammatory diseases such as atherosclerosis and rheumatoid arthritis and may be explored as a therapeutic target to develop novel treatment of cardiac and inflammatory diseases [34,35].

Other transcription factors

Lipid accumulation and its oxidation, macrophage infiltration, and foam cell formation are associated with the development of atherosclerotic lesion. Nagy et al. [36] have reviewed the role of lipid-activated transcription factors in the pathogenesis of atherosclerosis. Recently, Erbilgin et al. [37] reported that with a hyper lipidemic low-density lipoprotein receptor-null background, inbred BALB/cJ mice carrying the mutant allele (carry a naturally occurring null mutation) for Zhx2 showed a 10-fold reduction in atherosclerotic lesion size as compared with wild-type allele. The group also reported that this effect of Zhx2 is partly mediated by monocytes/macrophages and macrophages from Zhx2 null mice showed significantly increased apoptosis. Bone-marrow and ChIPseq (chromatin immuno precipitation sequencing) studies suggested that roles for transcriptional repression and apoptosis. The study results indicated that macrophage survival promoted by Zhx2 leads to an increased proinflammatory function of macrophages and growth of the atherosclerotic lesions and mutation of Zhx2 is responsible for relative resistance to atherosclerosis. The role of activated activating transcription factor 4 (ATF4) pathway through the saturated fatty acid-induced endoplasmic reticulum stress and the involvement of the increased expression of proapoptotic transcription factor CCAAT enhancer–binding protein homologous protein (CHOP) in chronic kidney associated- vascular calcification has been documented [38]. Further, the role of liver-enriched transcription factor CREBH, which regulates plasma triglyceride clearance, in accelerating the diet-induced atherosclerosis was discussed by Park et al. [39]. Kouassi et al., have reviewed the role of triggering receptors expressed on myeloid cells-1 (TREM-1) in atherosclerosis and other cardiovascular diseases [10].

Macrophage infiltration, chronic inflammation, and cytokine production play a crucial role in plaque progression and destabilization. Murakami et al. [40] have discussed the transcriptional regulation of G2 accumulation (G2A), a G-protein coupled receptor, in monocytes/ macrophages. G2A mediates inflammatory process under oxidative conditions and plays a crucial role in atherosclerosis deterioration. The study demonstrated that transcription of G2A is dependent both on the chromatin structure around its Transcription Start Site (TSS), and on the binding of the transcription factors (c∕ÆBPα and β, Runx1 and Pu.1) to their cis-elements, located at the core promoter just upstream of TSS. Further, the role of macrophage transcription factor MafB in plaque instability and progression of atherosclerotic plaque has been reported [9]. An inflammatory and autoimmune response may be evoked by increased expression of Heat Shock Proteins (HSPs) in the vessel wall and contributes in the pathogenesis of atherosclerosis. Metzler et al. [41] reported the increased expression of HSP transcription factor (HSF1) in atherosclerotic lesions which gets activated by cytokines and disturbed mechanical stress to the vessel wall. Fan et al. [42] reported the involvement of transcription factor GATA6 in mTOR signaling pathway regulated cytokine-

induced endothelial inflammation through transcriptional and post-transcriptional mechanisms.

Endothelial cell dysfunction changed physiology, and endothelial-to-mesenchymal transition (EndMT) plays a crucial role in the development of atherosclerosis. The role of adaptor protein ShcA in the endothelial cells and its transcription regulation by the zinc-finger E-box-Binding homeobox 1 (ZEB1) and the Hippo pathway effector YAP, in protecting against monocyte-macrophage adhesion, LDL-oxidation, and atherosclerotic lesion formation has also been discussed [9]. Mahmoud et al. reported the essential role of transcription factor Snail in regulating the low shear stress induces dedifferentiation of endothelial cells through EndMT and its involvement in promoting early atherogenesis by enhanced vascular permeability [43]. Further, ZBTB46 is a shear-sensitive transcription factor which inhibits endothelial cell proliferation and plays an inhibitory role in angiogenesis by regulating the cell cycle proteins, however, its role in the pathogenesis of atherosclerosis has not been studied. Thus, further research is required to explore the potentiality of ZBTB46 as a therapeutic target in atherosclerosis [44].

Conclusion

Transcription factors play a crucial role in the pathogenesis of atherosclerotic plaque. The role of various transcription factors including NF-κB, Ets-1, PU.1, AP1, KLF2, KLF14, Zhx2, CHOP, CREBH, c∕EBPα, and β, Runx1, MafB, HSF1, ZBTB46, and ZEB1 has been discussed in the literature. These studies suggest that modulation of transcription factors alters the process of plaque progression and rupture. Thus, these transcription factors might be a good candidate as a therapeutic target. Although these results highlighted the importance of TF in the pathogenesis of atherosclerotic lesion, the role of TF in plaque development and progression is not well understood. Thus, there is a need for further research using modern techniques such as Chipseq and single cell RNAseq to identify more potential TF involved in the pathogenesis of atherosclerotic plaque as well as therapeutic targets.

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