

Review

# The Role of Transcription Factors in Coronary Artery Disease and Myocardial Infarction

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## Abstract

Coronary artery disease (CAD) and its main complication, myocardial infarction (MI), is a complex disease caused by environmental and genetic factors and their interaction. Family-based linkage analysis and genome-wide association studies have indicated many of genetic variations related to CAD and MI in recent years. Some are in the coding sequence, which mediates the coding protein, while others are in the non-coding region, which affects the expression of adjacent genes and forms differential gene expression. These variants and differential expressions will have varying degrees of impact on the development of the cardiovascular system and normal heart electrical activity function, subsequently leading to CAD and MI. Among these affected genes, some Transcription Factors (TFs), as important means of transcriptional regulation, have a key role in the pathogenesis of coronary artery disease and myocardial infarction. The GATAs binding protein 2 (GATA2) enhances monocyte adhesion and promoted vessel wall permeabilization through vascular EC adhesion molecule 1 (VCAM-1) upregulation, further revealing its atherosclerosis-promoting role. Myocyte enhancer factor 2 (MEF2) has a role in fostering many functions of the atherosclerotic endothelium and is a potential therapeutic target for atherosclerosis, thrombosis, and inflammation. Nuclear factor-kappa B (NF- $\kappa$ B) is an important promoter of vascular endothelial growth factor (VEGF)-driven angiogenesis, and its pathway has a key role in atherosclerosis-related complications such as angiogenesis, inflammation, apoptosis, and immune effects. Activating transcription factor 3 (ATF3) may be a novel prognostic biomarker and therapeutic target for atherosclerosis. The important role of signal transducer and activator of transcription 3 (STAT3) (especially in mitochondria) in endothelial cells (EC) dysfunction, inflammation, macrophage polarization and immunity in atherosclerosis.

**Keywords:** transcription factors (TF); myocardial infarction (MI); coronary artery disease (CAD); GATA2; MEF2A; NF- $\kappa$ B; ATF3; STAT3

## 1. Introduction

### 1.1 Health Hazards of CAD

Coronary artery disease (CAD) is the primary reason for death globally [1–3]. The most common type of heart disease in the Western world is CAD. More than 13 million Americans are estimated to be affected by CAD, among the primary causes of mortality in the United States [4,5]. Coronary artery disease (CAD) is the most serious complex disease with the highest mortality and disability in the world. It is not only the leading cause of morbidity and mortality in the world but also the main cause of sudden death. The sequelae of heart failure and arrhythmia seriously affect patients' quality of life and bring a huge economic burden to society. The pathogenesis of coronary artery disease is caused by known factors such as smoking, diabetes, hypertension, obesity, lack of exercise, drinking, psychological status and so on. Currently, coronary

artery disease is primarily treated with drug therapy, which includes lipid-lowering medications, coronary artery dilating medications, and anti-platelet aggregation medicines; interventional therapy, which provides for placing coronary artery, stents and creating percutaneous transluminal coronary arteries; and surgery, which includes coronary artery bypass grafting. Coronary artery disease (CAD) is a research hotspot, and many scientists have focused on it and made some progress.

### 1.2 The Relationships between Atherosclerosis, CAD and Myocardial Infarction

A complex, fatal and multi-factorial condition, atherosclerosis, is the primary agent for developing CAD [6,7], and myocardial infarction (MI) is one of the associated complications of CAD. The cause of CAD is atherosclerosis in the coronary artery walls. This pathogenic process is caused by blood monocyte binding



to the endothelium activated by inflammatory molecules and oxidized low-density lipoprotein (LDL) cholesterol [8–13]. The bound monocytes then mobilize and pass through the endothelium to enter the intima area and transform into macrophages, which then take up particles of modified lipoproteins, and form foam cells, creating early lesions of atherosclerosis and initiating the build-up of plaques [8–13]. Plaques form primarily due to vascular smooth muscle cell growth and migration to the lesion site, arterial extracellular matrix (collagen) degradation, and the deposit of apoptotic cell debris and degraded products.

Central to atherosclerotic diseases is dysfunction of the endothelium that results in chronic and sustained inflammation of the vascular tissue and subsequently initiates atherosclerotic lesion formation and associated complications [14]. Dysfunction of endothelial cells (EC), expressed in areas of the arterial vasculature that are susceptible to lesions, results in low-grade inflammation, the earliest noticeable changes in the life cycle of an atherosclerotic lesion [14]. Because of blood flow dynamics, vascular curvatures and branch-point regions are vulnerable to atherosclerotic plaque development, substantially contributing to atherosclerotic cardiovascular disease (CVD) pathophysiology [14]. The inflammation and other injuries may subsequently disrupt the endothelial barrier, causing frank rupture or plaque fissure and erosion, accompanied by the release of tissue factors, thrombosis, platelet activation, and MI [8–13]. The effects of vascular inflammation are well-known in atherosclerosis, including characteristic changes in the wall of the vessel, activation of EC, formation of a sticky surface that easily attracts immune cells and circulation of monocytes. These inflammation effects lead to the thickened artery wall and impede arterial blood flow, which is the primary pathological condition underlying cerebrovascular disease and CAD leading to stroke and heart attack, respectively. Changes in arterial single-cell layer endothelium are deemed to be important to the occurrence of atherosclerosis [14].

As a disease condition of the arterial wall, atherosclerosis is characterized by chronic inflammation and leads to atherosclerotic plaque development, forming a hardened and narrowed artery lumen. Risk factors of the cardiovascular system, including hypertension, smoking, and hyperlipidemia, that stimulate vascular inflammation may initiate and maintain the formation of plaques [15–17]. Coronary atherosclerotic heart disease is a kind of heart disease caused by coronary artery stenosis or obstruction caused by atherosclerotic lesions, resulting in myocardial ischemia, hypoxia or necrosis, often called “coronary artery disease”. On the other hand, the extent of coronary artery disease may be more extensive, including inflammation, embolism and other causes of lumen stenosis or blockage.

### 1.3 Mechanism of Myocardial Infarction

According to the World Health Organization, coronary artery disease is divided into five categories: asymptomatic myocardial ischemia (occult coronary artery disease), angina pectoris, myocardial infarction, ischemic heart failure (ischemic heart disease) and sudden death. Clinically, it is usually categorized as an acute coronary syndrome and stable coronary artery disease. Coronary artery disease (CAD) is caused by the formation of coronary artery wall plaques (atherosclerosis, AS), which leads to vascular stenosis, resulting in an insufficient supply of blood, oxygen and nutrients to the heart, chest pain (angina pectoris), shortness of breath or other signs and symptoms of coronary artery disease. The blood supply disturbance of coronary artery circulation is proportional to myocardial damage. Complete coronary artery obstruction can cause a heart attack, called a myocardial infarction (MI) [1].

Adaptive and innate immunity have crucial roles in the rupture of plaques. The most abundant immune cell type is macrophages in atherosclerotic lesions. Each stage of atherosclerosis has essential functions, such as initiating lesions to the rupture of plaques. In macrophages exhibiting key effects promoting atherogenesis, their accumulation may lead to the break of plaques. A key characteristic of atherosclerosis is producing foam cells from macrophages in the vascular intima [15,18]. Atherosclerosis is also fueled by the persistent occurrence of foam cells in the artery’s walls [15,19]. Atherosclerosis underlies several CVDs, including MI [20], peripheral artery disease [21], and CAD [22], contributing to the majority of deaths due to CVDs.

### 1.4 Genetic Factors for CAD

Despite marked evidence of a complex genetic contribution of CAD and its associated risk factors [4,5], it is not as per Mendelian segregation for inheritance. Complex genetic disorders typically include multiple inherited genetic mutations that combine with environmental factors to promote the disease state [4,5]. Genome-wide association studies (GWAS) have identified more than 50 loci or genomic variants associated with CAD and MI [8–13]. GWAS also found another significant CAD risk variant, SNP rs17465637, in an intron of the *MIA3/TANGO1* gene encoding ARNT or TANGO1 [23]. We replicated this finding in the Caucasian population of the US gene bank [24] and the Gene ID population of the Chinese [1]. A large meta-analysis of 7263 CAD patients and 8347 controls from five Asian people also found a significant association between SNP rs17465637 and CAD and MI. In the first genetic analysis of coronary artery disease in the Chinese Han population, we used the GeneID database for the first time to find a single nucleotide polymorphism (genomic variation) SNP rs6903956 in intron 1 of the *C6orf105* gene (now known as *ADTRP*), which significantly increased the risk of CAD and MI, and was associated with decreased expression of *ADTRP* [25]. Other groups also replicate this association [26–29].

Genomic variants of *ADTRP* and *TFPI* have been reported to be significantly associated with the risk of CAD and myocardial infarction [10,30]. We found 39 variants in the *POU1F1* gene and their upstream and downstream 2 kb in the CADRDioGRAMplusC4D GWAS database, including 60,801 CAD cases and 123,504 controls [10,30]. Nine variants were nominally associated with the risk of CAD ( $p < 0.05$ ) [10]. We then replicated 9 variants from the most recent GWAS database from UK Biobank (GeneAtlas), including 33,387 CAD cases and 418,877 controls [10,31]. Three of the nine variants, including rs11127975, rs7637388 and rs9822911, continued to show a significant correlation with the risk of CAD ( $p < 0.006$  to 0.05) after being corrected by Bonferroni in multiple trials [10,31]. The Meta-analysis of two groups of GWAS data showed that the correlation signals of all three variants were stronger and the  $p$  value was better. The signal associated with rs9822911 (OR = 1.03,  $p_{\text{meta}} = 2.0 \times 10^{-4}$ ), a variant located in intron 2 of *POU1F1*, is the best [10]. By analyzing the GTEx database [32], we found that the risk allele C of rs9822911 variation was significantly associated with the expression of *POU1F1* in three tissues, including arterial tissue (tibial artery,  $p = 1.9 \times 10^{-7}$ ), skeletal muscle ( $p = 4.1 \times 10^{-7}$ ), and colon ( $p = 3.0 \times 10^{-5}$ ) [10,32].

For the first time, our study showed that three variants of *POU1F1*, including rs11127975, rs7637388 and rs9822911, were significantly associated with the risk of CAD after adjusting for multiple trials (ORs = 1.024–1.025,  $p = 2.0 \times 10^{-4}$ – $3.1 \times 10^{-4}$ ) [10]. We also found that the risk allele C of lead variant rs9822911 was associated with increased expression of *POU1F1* [10]. Our data show for the first time that *POU1F1* variation is related to CAD risk. More interestingly, the acquisition of functional variation in *POU1F1* is associated with the risk of CAD [10]. We establish a link between *POU1F1* and cardiovascular disease for the first time by demonstrating a relationship between genetic variation in *POU1F1* and the risk of coronary artery disease [10].

### 1.5 The Roles of Transcriptional Factors for Atherosclerosis

Until now, transcriptional regulation of the inflammation of the vascular endothelium is not well-understood [14, 33–35]. It is found that some transcription factors (GATA2, MEF2A, ATF3, NF- $\kappa$ B, STAT3) are closely related to CAD. Qin *et al.* [15] analyzed datasets of atherosclerosis from the NCBI-GEO (Gene Expression Omnibus) database. They found that expression levels of ATF3 were lower in macrophages from ruptured atherosclerotic plaques than from stable atherosclerotic plaques. Expression levels of ATF3 correlated with the stability of atherosclerotic plaques [15]. This novel step in the characterization of the effects of ATF3 in macrophages indicated a potential function for ATF3 in contributing to the development of ruptured atherosclerotic plaques in mice [15].

These observations by Connelly *et al.* [4] show that GATA2 is a novel susceptibility gene for coronary artery disease. Studying this transcription factor and its downstream targets may uncover a regulatory network important for coronary artery disease inheritance. Izadpanah *et al.* [36] have shown that a very interesting gene in this regard is GATA-binding protein 2 (GATA2), an important regulator of various gene expressions in vascular endothelial cells. As a result, the relationship between different GATA2 polymorphisms and CAD and MI has already been assessed.

MEF2 (Myocyte Enhancer Factor 2) is essential for endothelial homeostasis and the atheroprotective gene expression program. Previous studies proposed that MEF2 is necessary for promoting an anti-thrombotic, anti-inflammatory, and anti-proliferative endothelium. MEF2 is a compelling therapeutic target for atherosclerosis, thrombosis, and inflammation [37]. Oxidative stress and inflammation are present in coronary artery disease (CAD) and are linked to the activation of the transcription nuclear factor-kappa B (NF- $\kappa$ B). To attenuate these complications, transcription factors like nuclear factor erythroid 2-related factor 2 (Nrf2) and peroxisome proliferator-activated receptor- $\beta/\delta$  (PPAR $\beta/\delta$ ) can be activated to inhibit NF- $\kappa$ B. However, the available data on the expression of NF- $\kappa$ B, Nrf2 and PPAR $\beta/\delta$  in CAD patients is limited [38]. STAT3 regulates monocyte-to-macrophage differentiation, and inhibiting STAT3 activity reduces inflammation and monocyte-to-macrophage differentiation [39].

These findings indicate the importance of identifying markers for prognosis and potential drug targets for personalized treatments [15]. Recently, gene profiling through bioinformatics analysis has revealed new biomarkers and potential therapeutics for various diseases [15,40]. Bioinformatic tools aid in screening all genes in a specific sample and time point, and provide meaningful biomarkers and target agents [15].

GATA binding protein 2 (GATA2), myocyte-specific enhancer factor subtype 2A (MEF2A), transcriptional nuclear factor-kappa B (NF- $\kappa$ B) and activating transcription factor 3 (ATF3), signal transducer and activator of transcription 3 (STAT3), play a relatively clear and important role in coronary artery disease. Understanding the pathophysiology of coronary artery disease and identifying targets for its prevention and therapy will be facilitated by thoroughly examining the correlation between transcription factors and coronary artery disease. This review focuses on the possible role of the following transcription factors detected by GWAS in MI and CAD: GATA binding protein 2 (GATA2), myocyte-specific enhancer factor subtype 2A (MEF2A), transcription nuclear factor-kappa B (NF- $\kappa$ B), activating transcription factor 3 (ATF3), signal transducer and activator of transcription 3 (STAT3), which are very important in the occurrence and development of atherosclerosis or cardiovascular disease.

## 2. Transcriptional Factors

### 2.1 The GATA Binding Protein 2 (GATA2)

Early-onset CAD is also associated with a gene, *GATA2* [4,36]. GATA2 protein, a member of the GATA family, is a zinc finger transcription factor that also harbors GATA1-6 proteins. These proteins are expressed as specific to tissues and have non-redundant functions. GATA1–3 shares more sequence homology and is expressed mainly in the hematopoietic system, while GATA4–6 is expressed primarily in the gonads and cardiovascular system [41, 42]. Characteristically, the transcription factors of the GATA group, are specific to the zinc finger motif and the (T/A)GATA(A/G) sequence [36,43], joining these sequences on DNA and acting as activators of transcription [36,44,45]; in addition, the gene encoding for GATA2 maps to 3q21.3, and participates in the aortic wall neovascularization, hematopoiesis, and in adipogenesis [36,46]. Various biological processes are regulated by GATA2 to indirectly or directly affect the progression of atherosclerosis, including aortic neovascularization, hematopoiesis, adipogenesis, and inflammation [36,43]. At the transcriptional level, GATA2 regulates eNOS (endothelial nitric oxide synthase) and other EC-specific genes, von Willebrand factor, Down syndrome critical region 1, VCAM-1 (vascular EC adhesion molecule 1), PECAM-1 (platelet/EC adhesion molecule 1), and KDR (kinase insert domain receptor) [36,43]. It is important for the functioning of ECs, aortic smooth muscle cells and the maintenance of progenitor/hematopoietic cells [43,47]. Furthermore, phosphorylation of GATA2 mediated by Akt-triggers differentiation of preadipocytes and lowers the inflammation of adipose tissue [43,48], whereas the unphosphorylated form of GATA2 inhibits PPAR- $\gamma$ , stalls adipogenesis, and retains the preadipocytes in an inflammatory macrophage-like state [43,48]. This suggests a connection between atherosclerosis and obesity. By upregulating VCAM-1, GATA2 also improves monocyte adherence and promotes diapedesis through the arterial walls, demonstrating its pro-atherosclerotic action [43,48]. GATA2 diapedesis is significant because *ADTRP* also promotes the adhesion of monocytes and transmigration via the vascular EC layer by upregulating *MIA3/TANGO1* genes related to MI, the *PIK3R3/AKT* pathway, and CAD [12,43]. The *GATA2-ADTRP* pathway is associated closely with the endothelium's activation and function and thus drives atherosclerosis development.

### 2.2 Myocyte-Specific Enhancer Factor Subtype 2A (MEF2A)

The *MEF2A* gene is present in the chromosomal 15q26 region and encodes a transcription factor [49,50]. MEF2A is a member of the transcription factor family MEF2 (myocyte enhancer factor-2), which includes other members such as MEF2B, -2C, and -2D [49,50]. The MEF2 factors function as hetero- or homodimers that bind to their MEF2 target DNA (rich in A–T sequences) in several reg-

ulatory regions of muscle-specific genes and direct transcription [49,50]. Initially, MEF2A was identified as a gene specific to muscles. However, later it was found to be expressed at high levels in coronary artery endothelium [49,51].

In the endothelium of coronary arteries, MEF2A is highly expressed. To prevent myogenesis, MEF2A interacts with the myogenic regulatory factors, such as transcription factors like TWIST and transcriptional activators [52], by negatively regulating transcription repressors interacting with MEF2 associated with histone deacetylases [52–54], the myocyte enhancer factor 2 (MEF2) family of transcription factors is not only important for controlling gene expression in normal cellular programs, like muscle differentiation, T-cell apoptosis, neuronal survival, and synaptic differentiation but has also been linked to cardiac hypertrophy and other pathological conditions. HDAC3 efficiently deacetylated MEF2D *in vitro* and *in vivo*. HDAC3 is associated with the acetyltransferases p300 and p300/CBP-associated factor (PCAF) to reverse autoacetylation. Supporting the physical interaction and deacetylase activity, HDAC3 repressed MEF2-dependent transcription and inhibited myogenesis [53].

As a result of the role of MEF2A in morphogenesis, changes in its sequence may negatively affect the regulatory mechanisms of these processes, possibly developing vascular disorders. Thus, the role of the *MEF2A* gene is indicated in CAD [49,52,55,56], although a few other studies have invalidated such a role in vessel disease [52,57–64]. To further verify this, *MEF2A* gene variants were identified by angiography in a study in the patient cohort from Saudi Arabia and were found to be associated with CAD [52]; they also identified both variants of the gene and a haplotype that confer risk and reinforce the role of MEF2A independently as a CAD susceptibility gene [52].

Bhagavatula *et al.* [49] identified a seven-amino acid deleted region of MEF2A that segregates along with CAD/MI. The seven-amino acid deletion (mentioned previously in this text) of MEF2A is a mutation that disrupts MEF2A transcriptional activation activity through a dominant-negative mechanism [49,51]. Bhagavatula *et al.* [49] subsequently identified and characterized the function of three newly detected MEF2A missense mutations in four (out of 207) patients with CAD. They represented these three as loss-of-function mutations, indicating that MEF2A mutations can lead to MI/CAD through various biochemical mechanisms [49].

These results strongly indicate that MEF2A is the autosomal dominant type of CAD1 [49]. According to studies comparing genotype and phenotype, the dominant-negative mutation in individuals may lead to CAD with a more severe form and a high incidence of MI when compared to loss-of-function mutations. Preliminary research has also calculated the frequency of MEF2A mutations in a patient cohort with CAD and MI [49].

Their results support the notion that MEF2 has roles in many of the functions that promote an atheroprotective endothelium [49]. MEF2 is a potentially promising treatment target for atherosclerosis, thrombosis, and inflammation [49].

### 2.3 Transcription Nuclear Factor-Kappa B (NF- $\kappa$ B)

The transcription factor NF- $\kappa$ B belongs to the 'Rel' family representing a vital signal transduction system participating in various inflammatory conditions including atherosclerosis [65]. NF- $\kappa$ B exists in its dimer form and, like other 'Rel' family members, it harbors a highly conserved RHD (Rel-homology domain), which interacts with the I $\kappa$ B (inhibitory kappa B) proteins, binds DNA, and involves in the nuclear translocation of NF- $\kappa$ B [65,66]. I $\kappa$ B proteins (I $\kappa$ B  $\alpha$ ,  $\beta$ , and  $\gamma$ ) regulate the transcriptional activity and nuclear translocation NF- $\kappa$ B by binding to it via ankyrin repeats.

Signal transduction pathways mediated by NF- $\kappa$ B activation have been established in different stages of atherosclerosis from the formation of plaques to its destabilization and ultimate rupture. NF- $\kappa$ B pathways also have key roles in atherogenesis related complications like angiogenesis, inflammation, apoptosis, and immune effect [65,67]. Studies involving the inhibition of these pathways may reduce the occurrence of atherosclerosis. For example, developing specific inhibitors over I $\kappa$ B kinase  $\alpha$  or  $\beta$ , may help establish treatments that attenuate atherogenesis and prevent associated complications, such as angiogenesis [65].

As a dynamic process, angiogenesis involves the degradation of the extracellular matrix of ECs, the migration, proliferation, differentiation of ECs, and the invasion of ECs into capillaries [68]. Monocytes are widely known to play an important function in controlling this process. Monocyte-secreted factors increase the proliferation, homing, and mobilization of bone marrow-derived ECs [69]. Besides monocytes, activated macrophages also facilitate angiogenesis by generating promoters including fibroblast growth factor-2 and VEGF (vascular endothelial growth factor) [70]. It is worth noting that NF- $\kappa$ B is a crucial promoter of VEGF-driven angiogenesis [71].

Although pathways mediated by NF- $\kappa$ B are usually proangiogenic, they may also exhibit regulating properties in anti-angiogenesis [72]. NF- $\kappa$ B may also be a proapoptotic Fas ligand activator, increasing the recruitment of acetylated histones H3 and H4 and HAT p300. In contrast, NF- $\kappa$ B may increase histone deacetylase 1, act as a pro-survival cellular FLICE-like inhibitory protein (cFLIP) repressor, reduce the transcription factor nuclear factor of activated T-cells (NFAT) recruitment, and decrease p300 and histone acetylation [73]. Therefore, targeting NF- $\kappa$ B signaling by pathway inhibitors has been suggested to potentially suppress tumor growth, vascularization, and metastasis [74,75].

### 2.4 Activating Transcription Factor 3 (ATF3)

ATF3 is a member of the family of mammalian activation transcription factor/CREB (cAMP-responsive element-binding). The translation of ATF3 is conducted by an immediate-early gene, with weak expression in various cells; nevertheless, it can be induced in several types of stressed tissues, such as injured peripheral nerves, heart tissue deprived of blood, and atherosclerotic plaques [15, 76]. ATF3, a crucial transcriptional regulator, controls chemokine and cytokine expression to suppress inflammatory responses, indicating a beneficial effect in stressed tissues. The Western lifestyle has increased in popularity, increasing the worldwide burden of atherosclerosis [15,77,78]. Its function in innate immunity and inflammation suggests its relationship with atherosclerosis. Qin W *et al.* [15] analyzed atherosclerosis datasets from the database NCBI-GEO (Gene Expression Omnibus). They observed lower ATF3 expression in macrophages present in ruptured atherosclerotic plaques compared to those from stable atherosclerotic plaques. ATF3 levels correlate with atherosclerotic plaque stability. Kyoto Encyclopedia of Genes and Genomes analysis of DEGs (different expression genes) between stable and ruptured atherosclerosis plaques was carried out by the Metascape database [15]. The formation of ruptured plaques of atherosclerosis may be through the PI3K-AKT pathway. Mice (apoE<sup>-/-</sup>) with atherosclerosis induced by a high-fat diet—were categorized into an ATF3 over-expression group and a model group [15]. Evaluations of atherosclerotic plaques developed in the aortic root indicate that the lack of ATF3 and a higher number of macrophages may be the risk factors for ruptured atherosclerotic plaque formation. They found reduced lesion areas in aortic arch branches and aortic roots, and an increase in Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL)-positive areas and lesions of macrophages [15]. Consistently, suppression of Matrix metalloproteinases (MMPs) expression and activation of transduction pathway protein PI3K/AKT reduced the incidence of elastic plate cracks and degradation. Thus, ATF3 functions as a signaling molecule to mediate the stability and progression of atherosclerotic plaques. ATF3 may be a novel prognostic biomarker and a treatment target for atherosclerosis [15].

Qin W *et al.* [15] acquired three original datasets, GSE41571, GSE70126, and GSE9874, from the online GEO database and notable indications of the vital role of ATF3 in the PI3K-AKT pathway. Then, they used a mouse model and an *in vitro* culture system for macrophages to examine ATF3 function and expression in macrophages [15]. This novel form of ATF3 characterization indicated its possible role in the development of ruptured plaques of atherosclerosis in mice [15].

In atherosclerotic lesions, the most abundant type of immune cells are macrophages, which have important roles in each stage of the disease, from initiation of lesions to

rupture or plaques [15,79]. A hallmark of atherosclerosis is macrophage foam cell formation in the vascular intima [15,80]. Macrophages in the lesions can induce inflammatory responses, oxidative stress, and enzymes that catalyze the degradation of the matrix to facilitate the progression of atherosclerosis, degradation of plaque structure, and formation of the necrotic core.

The role of smooth muscle cells in atherosclerosis is primarily protective through the secretion of extracellular matrix and collagen, and the formation of fibrotic caps. ATF3 decreased macrophage content [15]; accordingly, increased collagen content and reduced apoptosis-positive areas indicate that ATF3 modulates macrophages and plays a protective role in atherosclerosis [15].

The aortic elastic lamina is eventually damaged or broken by atherosclerosis plaques, disrupting the integrity of arteries susceptible to atheroma and causing aneurysms and rupture [15,81]. The primary causes of this are MMPs produced by macrophages [15,82]. Consecutive and severe breakage of aortic elastic lamina was observed in mice models, successfully protected by overexpression of ATF3 in terms of severity and incidence [15].

A bioinformatics study suggested that ATF3 and the Akt-PI3K-Akt signal pathway, may be related. Additionally, the Akt-PI3K pathway's augmentation of Akt phosphorylation in response to ATF3 overexpression had an impact on radioresistance; likewise, the amount of ATF3 could be raised by inhibiting the PI3K/Akt signaling pathway in radioresistant breast cancer cells [15]. The PI3K-Akt pathway was found to enhance MMPs expression [15,83,84].

Bioinformatics analysis by Qin *et al.* [15] and a few earlier studies suggest the close relation between ATF3 and the PI3K-Akt activation, although whether the association of ATF3 with the PI3K-Akt pathway is via MMPs is not known. The western blot analysis conducted by Qin *et al.* [15] revealed a substantially decreased level of MMP-2 and -9, the most robust enzymes for matrix-degradation that degrade arterial elastin and lesion collagen, concurrently with reduced phosphorylation of Akt and PI3K [15].

### 2.5 Signal Transducer and Activator of Transcription 3 (STAT3)

STAT3 belongs to the STAT family. There are seven members in the STAT family including STAT1, -2, -3, -4, -5a, -5b, and -6 [85–89]; these have transcriptional regulation and signal transduction functions. STAT3 was identified for the first time by two separate groups in 1994 [90,91]. It has received great attention for its vital roles in several biological processes, such as cell differentiation, proliferation and survival, immunity, inflammation, and angiogenesis [92]. The oncogenic role of the gene encoding STAT3 (*Stat3*) was first reported in 1999 [93] and had thus become the research focus as a possible target for anticancer agents. STAT3 has been found to participate essentially in diseases, including malignancy [94], ischemic injury of the

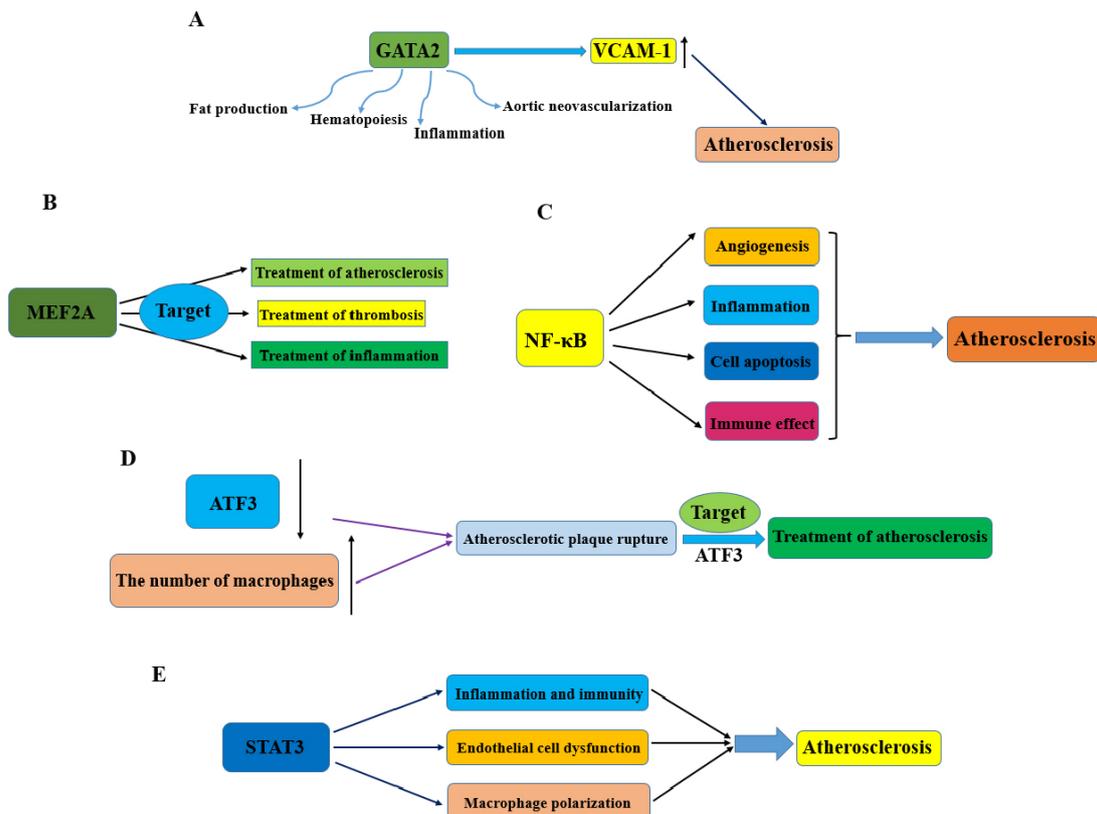
myocardium [95], stroke [86], as well as obesity [96]. With more focused research on cardiovascular and cerebrovascular diseases, STAT3 has key roles in various cardiovascular diseases, including heart hypertrophy, arteriosclerosis, and heart failure [97–100]. While atherosclerosis is deemed the critical pathological basis of most cerebrovascular and cardiovascular diseases, there are no specific reviews on the association of STAT3 and atherosclerosis. The study by Chen *et al.* [39] aimed to fill this gap.

STATs are generally present in their inactive form in the cytoplasm and can be activated through stimulation by various growth factors and cytokines [39,101]. JAKs (Janus-activated kinases), as well as other tyrosine kinases, phosphorylate the tyrosine residues present on the cytoplasmic domain of STATs, activating them [39,102–105]. JAKs, a group of receptor-associated cytoplasmic tyrosine kinases, were identified over two decades ago and have received significant attention for their crucial roles in activating STAT [39,106,107]. Until now, four JAK family members have been characterized, namely, JAK1, -2, -3, and TYK2, and their sizes are 120–140 kDa. Each member has seven conserved domains, namely JH1-7 (Janus homologs 1-7) that consist of three parts: (1) a FERM (4.1 protein, ezrin, radixin, and moesin) domain, and an -SH2 domain in the N-terminal region (JH3-7), which are responsible for the interactions between JAKs and various cytokine receptors [39,92], (2) a pseudokinase domain (JH2), which is important for maintaining the inactive state of JAK and critical for JH1 activity regulation [39,95,104], (3) a C-terminal tyrosine kinase domain (JH1), which can activate JAKs. Although *STAT* genes are significantly homologous, the functions of STAT proteins vary. Other than STAT5b, other members of the STAT family have different roles in atherogenesis. STAT1, -4, and -5a were shown to participate in inflammation in the atherosclerotic condition [39,86,108,109], while STAT2 can exclusively mediate interferon signaling [39,99] and STAT6 participates in lipid accumulation and immune activity and affects atherosclerosis [39,98]. The most studied among these seven proteins is STAT3 in atherosclerosis for its effects on EC dysfunction and all the activities mentioned above [39].

In the review by Chen Q *et al.* [39], the crucial role of STAT3 has been highlighted in atherosclerosis; they have also discussed STAT3 inhibitors for potentially treating atherosclerosis. They have described STAT3 in terms of its function, structure, and regulation, and its role in atherosclerosis through three related but independent biological processes, inflammation and immunity, EC dysfunction, and macrophage polarization [39]. They further summarized the currently available STAT3 inhibitors and explored their effects on atherosclerosis treatments, some possible complications and their solutions [39]. Their review adds to the available information using STAT3 as a novel treatment target for atherosclerosis [39].

**Table 1. List of these selected transcription factors' role in CAD and MI.**

Gene symbol	Transcription factor	Function
<i>GATA2</i>	The GATA binding protein 2 (GATA2)	Various biological processes are regulated by GATA2 to indirectly or directly affect the progression of atherosclerosis, including aortic neovascularization, hematopoiesis, adipogenesis, and inflammation. It is important to function ECs and aortic smooth muscle cells and maintain progenitor/hematopoietic cells. GATA2 also enhances the adhesion of monocytes and facilitates diapedesis through the vascular walls by the upregulation of VCAM-1, further revealing its pro-atherosclerotic effect. The GATA2-ADTRP pathway is associated closely with the endothelium's activation and function and thus drives atherosclerosis development.
<i>MEF2A</i>	Myocyte-specific enhancer factor subtype 2A (MEF2A)	MEF2 has roles in many functions that promote an atheroprotective endothelium and is a potentially promising treatment target for atherosclerosis, thrombosis, and inflammation.
<i>NF-κB</i>	Transcription nuclear factor-kappa B (NF-κB)	NF-κB is a crucial promoter of VEGF-driven angiogenesis; NF-κB pathways have key roles in atherogenesis-related complications like angiogenesis, inflammation, apoptosis, and immune effect.
<i>ATF3</i>	Activating transcription factor 3 (ATF3)	ATF3 may be a novel prognostic biomarker and a treatment target for atherosclerosis. ATF3 decreased macrophage content, increased collagen content, and reduced apoptosis-positive areas. It modulates macrophages and exerts a protective role in atherosclerosis.
<i>STAT3</i>	Signal transducer and activator of transcription 3 (STAT3)	STAT3 was found to have key roles in various cardiovascular diseases, including hypertrophy of the heart, arteriosclerosis, and heart failure. It plays a role in atherosclerosis through three related but independent biological processes, inflammation and immunity, EC dysfunction, and macrophage polarization. The significant roles of STAT3 (particularly in mitochondria) in EC dysfunction, inflammation, macrophage polarization, and immunity in atherosclerotic conditions.



**Fig. 1. Shows the functional pattern illustrations of five TF related to coronary artery disease. (A) The function and pattern of TF GATA2. (B) MEF2A TF function and pattern. (C) NF-κB TF function and pattern. (D) ATF3 function and pattern. (E) TF STAT3 function and pattern analyses.**

STAT3, particularly its aberrant expression, has been observed to play a key role in atherosclerosis occurrence and development. Therefore, the research on inhibitors of STAT3 is a topic of great interest [39]. The significant roles of STAT3 (particularly in mitochondria) in EC dysfunction, inflammation, macrophage polarization, and immunity in the atherosclerotic condition were described by Chen *et al.* [39]; they also summarized a STAT3 inhibitor classification, which could offer possible approaches for the treatment of atherosclerosis. Furthermore, Chen *et al.* [39] highlighted a few challenges that hinder the development of medicines that use STAT3 inhibitors to treat atherosclerosis and potential solutions to these issues. As a result, their review may be valuable in the future for developing STAT3 inhibitor-based treatment methods for atherosclerosis.

### 3. Conclusions and Perspectives

We investigated the function and mechanism of these five selected transcription factors in the incidence and progression of atherosclerosis based on a substantial body of earlier research. The five transcription factors' roles in the occurrence and progression of atherosclerosis and myocardial infarction (MI) have been briefly summarized (Table 1 and Fig. 1). For example, the expression level of ATF3 is related to plaque stability. ATF3 encodes a member of the mammalian transcription factor/cAMP response element binding protein family [101]. The expression of ATF3 was low in resting cells and increased under stress conditions (including injury, ischemia, ischemia/reperfusion or exposure to chemical toxins). It is considered an adaptive response gene that participates in cellular processes to adapt to extracellular and/or intracellular changes and transmits signals from different genes to activate or inhibit gene expression. It plays a role in inflammation and innate immunity [110]. Lack of ATF3 and increase of macrophages may be risk factors for the formation of ruptured atherosclerotic plaques. ATF3 is a signal molecule that mediates the progression and stability of plaques [110]. ATF3 might be a novel prognostic biomarker and a possible therapeutic target for treating atherosclerosis [111].

GATA2 regulates various biological processes to affect the progression of atherosclerosis, including aortic neovascularization, hematopoiesis, adipogenesis, and inflammation indirectly or directly. At the transcriptional level, GATA2 regulates eNOS (endothelial nitric oxide synthase) and other EC-specific genes, von Willebrand factor, Down syndrome critical region 1, VCAM-1 (vascular EC adhesion molecule 1), PECAM-1 (platelet/EC adhesion molecule 1), and KDR (kinase insert domain receptor) [43,47]. It is important for the functioning of ECs, aortic smooth muscle cells, and the maintenance of progenitor/hematopoietic cells [48]. GATA2 also enhances the adhesion of monocytes and facilitates diapedesis through the vascular walls by the upregulation of VCAM-1 further revealing its pro-atherosclerotic effect [47]. The GATA2-

ADTRP pathway is associated closely with the activation and function of the endothelium, and thus drives the development of atherosclerosis [36,43].

MEF2A was formerly thought to be a gene unique to muscles; however, it was later discovered to be highly expressed in the endothelium of coronary arteries. In a patient cohort study, angiography was used to identify *MEF2A* gene variations and found that they were connected to CAD [52,61]. MEF2 has roles in many of the functions that promote an atheroprotective endothelium [55]. MEF2 is a potentially promising treatment target for atherosclerosis, thrombosis, and inflammation [61].

NF- $\kappa$ B pathways are key contributors in atherogenesis-related complications like angiogenesis, inflammation, apoptosis, and immune effect. Studies involving the inhibition of these pathways may reduce the occurrence of atherosclerosis [67]. Nucleosome, chromatin, transcription, DNA repair, etc. Angiogenesis requires the degradation of the extracellular matrix of ECs, the migration, proliferation, differentiation of ECs, and the invasion of ECs into capillaries [38,73]. It is well known that monocytes play a significant role in directing this process. NF- $\kappa$ B is a crucial promoter of VEGF-driven angiogenesis [38].

With more focused research on cardiovascular and cerebrovascular diseases, STAT3 was found to have key roles in various cardiovascular diseases, including hypertrophy of the heart, arteriosclerosis, and heart failure [39]. The crucial role of STAT3 has been highlighted in atherosclerosis; discussed STAT3 inhibitors for potentially treating atherosclerosis [65,75]. The significance of STAT3 in atherosclerosis through three related but distinct biological processes inflammation and immunity, EC dysfunction, and macrophage polarization and its function, structure, and regulation [39]. The significant roles of STAT3 (particularly in mitochondria) in EC dysfunction, inflammation, macrophage polarization, and immunity in atherosclerotic conditions [39,85].

Studies over the past few decades have clarified various mechanisms of atherosclerosis, such as endothelial dysfunction, oxidative stress, chronic inflammation, lipid deposition and epigenetic disorders [112]. Although great progress has been made in the pathogenesis and emerging drug treatment of atherosclerosis, atherosclerosis and its clinical sequelae are still the main causes of global morbidity and mortality [112]. Studies over the past decade have found that transcription regulates endothelial function and atherosclerosis.

In this review, we focus on the role of key transcription factors in regulating endothelial function, atherosclerosis and targeted drug therapy. In addition to the role of transcription factors, gene variations and differential expressions of genes may influence the ion channels, activity of transcription factors, development of myocardium fibrosis or cardiac conduct system, and have a key part in the

pathogenesis of MI and CAD. MI-related transcription factors regulate studies and assessment of targets, and CAD may facilitate the development of new treatments for MI and CAD.

## Abbreviations

TF, transcription factors; MI, myocardial infarction; CAD, coronary artery disease; LDL, low-density lipoprotein; EC, endothelial cells; GWAS, Genome-wide association studies; GATA2, GATA-binding protein 2; MEF2, myocyte enhancer factor 2; NF- $\kappa$ B, nuclear factor-kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PPAR $\beta/\delta$ , peroxisome proliferator-activated receptor- $\beta/\delta$ ; MEF2A, myocyte-specific enhancer factor subtype 2A; ATF3, activating transcription factor 3; STAT3, signal transducer and activator of transcription 3; eNOS, endothelial nitric oxide synthase; VCAM-1, vascular EC adhesion molecule 1; PECAM-1, platelet/EC adhesion molecule 1; KDR, kinase insert domain receptor; PCAF, p300/CBP-associated factor; RHD, Rel-homology domain; I $\kappa$ B, inhibitory kappa B; VEGF, vascular endothelial growth factor; CREB, cAMP-responsive element-binding; GEO, Gene Expression Omnibus; DEGs, different expression genes; JAKs, Janus-activated kinases.

## Author Contributions

CL—Formal analysis, Funding acquisition, Visualization, Writing - original draft, review & editing, Supervision. YR—Formal analysis, Writing - original draft. PS—Formal analysis, Writing - original draft. HW—Writing - review & editing. WY—Formal analysis, Writing - original draft. YG—Formal analysis. DW—Conceptualization, Funding acquisition, Writing - review & editing.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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