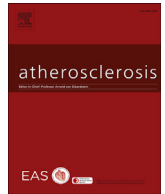




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Review article

The role of Krüppel-like factor 14 in the pathogenesis of atherosclerosis

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The Krüppel like factor (KLF) family, as the SP/KLF transcription factors, plays important roles in regulating the expression of genes required for the proper execution of important biological and pathological processes. Recent studies have demonstrated that KLF14, a member of the KLF family, participates in the initiation and progression of atherosclerotic cardiovascular disease (CVD). From the molecular function aspect, this review focuses on the impact of KLF14 mediated regulation in major atherosclerosis related diseases and pathological processes, such as insulin resistance, type 2 diabetes, dyslipidemia, inflammation, obesity, metabolic syndrome, cell proliferation and differentiation. This review was designed to help understand the roles of KLF14 in the pathogenesis of atherosclerosis and define KLF14 as a potential disease biomarker and a novel therapeutic target in CVD.

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1. Introduction

Atherosclerosis, the primary cause of cardiovascular disease (CVD), is one of the major causes of mortality and disability worldwide [1,2]. It has been demonstrated that many factors, such as disturbance in homeostatic regulation, inflammation [3], dyslipidemia [4,5], obesity [6,7], insulin resistance [8,9], diabetes [10] and other independent risk factors of native atherosclerosis, are closely associated with Krüppel like factor 14 (KLF14) gene expression [11]. Thus, further clarification of the relationship between KLF14 and atherosclerosis related risk factors may be the key to the treatment of CVD and subsequent clinical complications.

2. KLF14 has a novel role in etiology and pathophysiology of atherosclerosis

The KLF family, the evolutionarily conserved transcription factor, is composed of 17 members, which are characterized by the presence of their conserved DNA binding domain containing three Cys2/His2 zinc fingers that are similar to those at the carboxyl terminus of Sp1 [12,13]. Through those C terminal zinc fingers, critical for recognition and binding to the GT/GC rich cis regulatory sites present in gene promoters and enhancers, the KLFs regulate the expression of genes involved in many important biological and pathological processes of the organism, such as proliferation, differentiation, apoptosis, development and tumor growth, obesity, cardiovascular disease and inflammation [14,15]. Interestingly, a large number of members are known to play important roles in the initiation and progression of atherosclerosis through promoter activation of target genes associated with some key vascular events [16–18], although many studies have focused on tumorigenesis [19,20]. It is noteworthy that the abnormal expression of some KLF members, such as KLF14, has been identified with an implication in CVD [21]. Scohy et al. first identified a new member of zinc finger

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transpiration factor SP/XKLF family, named *KLF14*, which is localized in the human chromosome 7q32.2 and codes 323 amino acids [22]. In addition, recent genome wide association studies (GWAS) verified that *KLF14* variant was implicated in the etiology of atherosclerotic CVD, including ischaemic stroke (IS) and myocardial infarction (MI) [21]. It is worthy of further attention to exploring whether *KLF14* participates in myocardial apoptosis and death induced by reactive oxygen species (ROS) or calcium overload that mediates myocardial cell injury and vascular remodeling (VR) in IS and MI. The *in vivo* studies using *apoe*^{-/-} mice have shown that hepatic specific *kflf14* deletion markedly accelerated the development of atherosclerotic lesions due to the lack of *kflf14* mediated apoA I promoter activation and decreased HDL C levels and cholesterol efflux. On the other hand, activation of *kflf14* is known to reduce atherosclerosis, suggesting *kflf14* as a potential novel therapeutic target to reduce the risk of atherosclerotic CVD [11]. However, how *kflf14* expression is regulated in atherosclerotic plaque lesions remains poorly understood.

Aging is an important risk factor for atherosclerosis and type 2 diabetes (T2D) [23–25]. The previous report has demonstrated gene methylation of *ELOVL2*, *FHL2*, *PENK* and *KLF14* without any change in their gene expression in isolated peripheral blood mononucleated cells (PBMCs) may act as the age related epigenetic biomarkers [26]. More importantly, DNA methylation loci in *KLF14* have linearly correlated with human age, providing a very accurate final estimate of chronological age [27]. Subsequent studies by Kananen group reported that CpG sites located in the *KLF14* (cg08097417, cg09499629, and cg07955995) appeared aging associated alteration of hypermethylation in whole blood samples of middle aged individuals using 450BeadChip technology [28]. Meanwhile, age related DNA methylation level of *KLF14* has been considered as a biomarker of T2D diabetes risk [29]. Taken together, these findings suggest that DNA methylation level of *KLF14*, as a novel biomarker, may help with the clinical diagnosis of atherosclerosis.

There have been several lines of evidence showing that *KLF14* participates in the regulation of atherosclerosis related diseases and pathological processes, including diabetes [29,30], dyslipidemia [4,11], dysarteriotony [31], obesity [6], coronary heart disease [21], and metabolic syndrome [32]. To focus on the roles of *KLF14* in the risk factors associated with the progression of atherosclerosis will be helpful to understand and expand the insights about *KLF14* biology and its roles in etiology and pathophysiology of atherosclerosis.

3. *KLF14* regulates lipid metabolism through HDL biogenesis and triglycerides, cholesterol homeostasis

During past few years, more and more prospective studies have demonstrated that atherosclerosis is a chronic metabolism related pathological process characterized by lipid disorder, such as unusual increase in low density lipoprotein cholesterol (LDL C) and/or a significant decrease in high density lipoprotein cholesterol (HDL C) [33–37]. Recently, *KLF14* has been identified as a critical regulator in lipometabolism [4,9]. Genome wide association studies (GWAS) indicated that single nucleotide polymorphism (SNP) in the *KLF14* locus, as a candidate gene associated with CAD, decreased high density lipoprotein cholesterol (HDL C) and increased triglyceride (TG) in European populations [5]. In addition, the study performed independently by Huang P et al. tested the association of *KLF14* SNPs with serum lipid profile in prospective cohorts comprising 740 subjects of Han populations in China's Guangxi Zhuang Autonomous Region and found that the T allele carriers of *KLF14* gene had significantly lower levels of HDL cholesterol (HDL C) and the ratio of apoA I to apoB than the

noncarriers [38]. Similarly, recent studies by Nair et al. identified that rs4731702 SNP at *KLF14* locus is associated with HDL C levels in female participants of Pima Indians [39], besides rs1562398 and rs4731702 SNPs in the Tunisian populations and China's Guangxi Mulao candidates [32,38]. Those above studies suggested that *KLF14* may regulate atherosclerosis related serum lipid profile. It is likely that regulatory variants of *KLF14* may influence the expression of a network of *KLF14* target genes related lipid metabolism, including *TPMT*, *ARSD*, *SLC7A10*, *APH1B*, *NINJ2*, *KLF13*, *GNB1*, *MYL5* [9]. The potential mechanism underlying the function of *KLF14* as a novel regulator of lipid metabolism is associated with transcriptional activation of the hepatic *SK1* promoter with the consequent up regulation in sphingosine 1 phosphate (S1P) lipid signaling [4]. S1P, the product of SK1, is a critical determinant of HDL functionality. In fact, reduced levels of S1P in the HDL particles result in dysfunctional HDL, while S1P loading of the HDL particles improves their functionality [40]. On the one hand, *KLF14* regulates plasma HDL C levels and cholesterol efflux capacity via regulating hepatic apoA I production [11]. Given that HDL functionality is more important than HDL C concentrations as recently reported [41], *KLF14* has a beneficial effect on HDL functionality through activating SK1 [40,42]. On the other hand, *KLF14* affects the concentration or the size of plasma high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) particles [43]. Interestingly, genetic variants newly identified in the *KLF14* were implicated not only in the expression of genes related to lipid metabolism but also in the etiology of atherosclerosis [3,11] and the altered risk of CAD [21], which may be associated with S1P antagonistic effects on myocardial ischemia reperfusion injury, thus decreasing the extent of myocardial infarction [44], suggesting a potential role for *KLF14* in atherosclerotic diseases associated with maintaining body lipid homeostasis.

In the vertebrates, the metabolic processes of triglycerides (TG), usually present in the core of triglyceride rich lipoproteins (TRLs), are tightly controlled and dynamically balanced with energy consumption and also closely associated with atherosclerotic cardiovascular disease (ASCVD) as a risk biomarker and treatment strategy of the gene [45]. The study by Kong et al. revealed that the allele of rs972283 near *KLF14* was associated with a higher risk for elevated TG in 5169 T2D patients of Chinese participants [31]. In another study, rs1562398 in *KLF14* was observed an association between this locus and TG level in European women, but not in men [5]. The same gender disparity was observed in another study demonstrating an association between this locus and impaired fasting glucose only in men of Tunisian [32]. This phenomenon may be explained by the difference in the genetic background of the populations [32]. So, it is necessary to further study these differences between males and females in different populations. Moreover, it is even more noteworthy that *KLF14* influences the expression of obesity related gene profile, such as *TPMT*, *ARSD*, *SLC7A10*, *C8orf82*, *PRMT2*, *GNB1* and *MYL5*, to mediate the effects of *KLF14* on TG metabolism and body mass index (BMI) as described by Small et al. using large scale GWAS data [30], supporting a trans causal link between *KLF14* expression and fat metabolism through influencing multiple genes [9]. The expression of lipoprotein lipase (LPL), the rate limiting enzyme for the hydrolysis of the triglyceride (TG) core of circulating TRLs, influences the progress of atherosclerosis [46–49]. It will be critical to further determine the potential link between LPL and *KLF14* in the regulation of development of atherosclerosis.

Those previous studies focused on *KLF14* effects on hepatic lipometabolism, but whether it has any effect on macrophage mediated atherosclerosis is not yet clear. Therefore, to further elucidate the role of extrahepatic *KLF14* in the inflammatory

response and lipid metabolism may shed new light on the diagnosis and intervention treatment strategy of atherosclerosis.

4. KLF14 plays a key role in the regulation of adipogenesis and obesity

The ability for vertebrates to regulate fat metabolism and maintain energy homeostasis is essential for growth, development, reproduction, and dynamical balance with fat storage and utilization which disruption is closely associated with metabolic syndrome and atherosclerosis in humans [50–54]. In a recent study, a maternally expressed transcription factor *KLF14*, which is associated with lipid metabolism, lipid signaling and the *cis* acting expression quantitative trait locus of HDL [4,30], was shown to act as a master transregulator of adipose gene expression [9]. By examining expression QTL data in 23,720 transcripts for subcutaneous adipose tissue, Voight et al. discovered that *KLF14* SNPs at rs738134 and rs972283 are strongly associated with expression of *KLF14* in adipose tissue [55]. Subsequent analyses of global gene expression data revealed that *klf14* expression was significantly elevated in the inguinal fat tissue of male B6 mice with obesity by feeding an obesogenic diet compared with those with lean for 4 weeks [7]. In addition, in Anunciado Koza's study, the adipose mesoderm specific transcript (Mest) mRNA expression, which is susceptible to the development of obesity, was found with a very high correlation with *klf14* expression in both subcutaneous and visceral white adipose tissues (WAT) of C57BL/6J mice fed a high fat diet (HFD) for only 2 weeks, suggesting that *klf14* transcriptional activity may at least partially mediate strong expressions of WAT Mest with *Bmp3*, *Sfrp5*, *Nkd1*, and *Lep* to promote fat mass accumulation [6]. *KLF14* will be even more valuable due to its roles in physiological metabolisms, such as adipocyte differentiation and proliferation, cellular lipid uptake and fat catabolism.

5. KLF14 participates in inflammatory and immune responses

Atherosclerosis, a chronic inflammatory disease, is well characterized by the transformation of macrophages into foam cells through uptake of lipoprotein derived cholesterol and secretion of various inflammatory cytokines in the arterial intima [56–58]. Therefore, how to efficiently control activation and functions of inflammatory cells, such as differentiation, polarization, migration and infiltration of macrophage and T cell, and the secretion of inflammatory cytokines has become a key issue for developing therapeutic approaches for atherosclerosis [59,60]. As the novel role in lipid metabolic pathways, *KLF14* may have a profound impact on immune functions and on driving T cell differentiation especially. Interestingly, a recent study showed that *KLF14* is highly expressed within primary and secondary lymphatic organs, suggesting a novel role for *KLF14* in maintaining the differentiated state of T regulatory cells and a potential mechanism for repressing the expression of immune gene *FOXP3* that is critical to T cell fate through binding to the Treg specific demethylation region (TSDR) enhancer locus of *FOXP3* [61]. Wei etc. Recently found that *klf14* knockdown significantly decreased the circulating levels of inflammatory cytokines, such as TNF α , IL 6, and MCP 1, in *apoe*^{−/−} mice fed HFD. However, overexpression of *klf14* obviously suppressed the secretion of those cytokines in RAW264.7 cells. The p38 MAPK and ERK1/2 signal pathways may be, at least in part, involved in the effect of *klf14* on Ac LDL induced inflammatory cytokine secretion in macrophages [3].

6. The effects of KLF14 on T2D and insulin signaling

Many epidemiologic studies have revealed that patients with

T2D gain a higher risk of atherosclerosis and CAD complications [62–66]. Recently, the research into genetic factors that are correlated with T2D has increased [67–71]. The increased age related DNA methylation of *KLF14* in pancreatic islets, as a blood based epigenetic biomarker, has been identified to associate with the severity of T2D, suggesting that *KLF14* methylation level in the blood may be used as a biomarker of functional status in human islets [28,29]. Notably, SNPs at *KLF14* genetic locus have been identified to closely associate with both lipid disorder and T2D through GWAS large scale association analysis [30,39,55]. Further studies revealed that the SNPs of the risk allele, such as rs1562398, rs972283, rs4731702, rs738134, and rs13234269 in or near *KLF14*, participate in increasing the levels of fasting glucose and susceptibility to T2D worldwide [32,55,67,72–76]. Among the newly identified loci, the most compelling signal was at rs972283, which is strongly associated with the expression of *KLF14* in adipose tissue and at rs738134 with the strongest *KLF14* *cis* expression signal [34]. This suggests that the variation may result in a change of *KLF14* expression level which mirrors the parent of origin effects for T2D susceptibility at this locus [10]. On the one hand, a primary effect of *KLF14* variation in T2D risk allele loci on insulin action which is not driven by obesity may result in higher fasting insulin, on the other hand, is associated with reduced insulin sensitivity [55,77]. Meanwhile, *KLF14* increases the levels of HDL C [11], which is known to increase both pancreatic beta cell secretion and direct glucose uptake by the muscle via 5' AMP activated protein kinase or AMPK [78,79]. Therefore, the metabolic phenotype may be associated with an appreciated role of *KLF14*, which regulatory effect on HDL C is protective against T2D risk [80,81]. Recently, several studies have focused on the T2D pathogenesis and the effects of *KLF14* variants on insulin action [55,82]. The genetic variants or SNPs of *KLF14* had a close association with metabolic syndrome as the result of type 2 diabetes characterized by primary effects on insulin sensitivity [69,74,83,84]. Modulation of *KLF14* expression influenced the expression of a network of genes, such as *TPMT*, *APH1B*, *GNB1*, *ARSD* and *C8orf82*, which are associated with insulin sensitivity, insulin level and glycometabolism [9]. In addition, overexpression of *klf14* in Hepa1 6 cells reversed the inhibition of glucose uptake and Akt phosphorylation induced by T2D serum, suggesting that *KLF14* may improve glucose uptake and insulin sensitivity of the cells probably through PI3K/Akt signaling pathway mediated related genes activation [8]. And yet for all that, *KLF14* plays an essential role in maintaining glycometabolism homeostasis. At the same time, recent studies have shown that diabetes or insulin resistance selectively inhibits antiatherogenic actions of insulin via the IRS/PI3K/Akt pathway [85]. Therefore, we speculated that *KLF14* may influence atherosclerosis via the PI3K/Akt pathway. However, signaling profiles related to specific mechanisms for its effects on insulin action and insulin sensitivity remain incompletely understood and should be further investigated.

7. KLF14 in cell proliferation and differentiation

Transforming growth factor beta (TGF β) family is a group of pleiotropic cytokines, which have been described to participate in the modulation of cellular homeostases, such as cell differentiation, proliferation, apoptosis, and migration, as inhibitory or stimulatory properties in both physiological and pathological conditions [86]. Notably, TGF β is an antiatherosclerotic cytokine through reducing cell proliferation in the earliest stages of atherogenesis and creates a more stable plaque that is less prone to rupture [87,88]. Previous studies have shown that *KLF14* is an important non Smad protein up regulated upon TGF β treatment, which efficiently represses the TGF β receptor II (TGF β RII) via silencing the TGF β RII promoter

activity, and suggest that KLF14 may play an important role in the process of cell homeostasis related to atherosclerosis [89]. In addition, *tgf* β 1 mediated cell proliferation in Leydig cells may involve the *klf14* induced expression of *alk 1*, which subsequently leads to the signaling pathway of proliferation [90]. These results prompted us to speculate that the transcription factor KLF14 participates in the intracellular homeostasis events response to TGF β treatment. Moreover, KLF4, as another well known transcription factor, will reset the somatic cell epigenome during induced pluripotent stem cell generation [91]. Meanwhile, some reports have revealed that the *CPA4 KLF14* region on chromosome 7, which encodes both mRNAs and imprinted genes, may have some effects on the extent of cell pluripotency since it is similar to *Dlk1 Dio3* region which activation is related to cell pluripotency level [92,93]. It has demonstrated that a subset of SP/KLF proteins, including KLF11, KLF14, and KLF16, inhibited cellular growth transformation and increased cell apoptosis in these cells, at least in part, through binding to the *cyclin A* promoter and subsequent regulation of the promoter activity [94]. Interestingly, that KLF proteins function as epigenetic reprogramming factors during the differentiation of immune cells has especially received much attention [61], supporting a potential role for KLF14 in maintaining the differentiated state of immune cells, which is significantly associated with the occurrence and progression of atherosclerosis.

8. Future directions and challenges of KLF14 studies in atherosclerosis field

The KLF family would regulate the gene transcription required for the biological and pathological phenotypes by binding of those zinc finger regions to the gene promoters and enhancer *cis* regulatory sites [14,15]. KLF14, a new member of KLF gene family, plays a pivotal biological role through a similar way to other family members. Notably, the genetic variants, SNPs and DNA methylation that were newly identified in or near the *KLF14* gene were

implicated not only in the change of lipometabolism and glyco metabolism but also in the risk of atherosclerosis and CAD in the pathology (Table 1). For example, *KLF14* SNPs in rs738134, one of T2D risk allele loci, are associated with higher fasting insulin level, lower insulin sensitivity [77], and more adipogenesis in adipose tissue [41], suggesting that *KLF14* variants in certain loci will influence multiple related sensitive factors. For the first time, Chen et al. identified that SNPs near/in the *KLF14* gene (rs4731702/rs111400400) are closely related to the change of atherosclerosis related phenotype that had a significant decrease in the risk of CVD [21]. A large amount of evidence suggests that epigenetic change of *KLF14* may serve as a biomarker of age related atherosclerosis [26,27]. From this point, the efficient gain of function mutation or epigenetic modification to upregulate the activity of KLF14 at transcriptional and posttranscriptional levels might offer a theoretical appeal to KLF14 based gene therapy for atherosclerosis. In addition, it will be important to determine what and how to regulate KLF14 expression during biological processes that govern atherosclerosis (see Fig. 1). The detailed description about those points will be significantly worthy of therapeutic benefits due to the potential antiatherogenic capability of KLF14 to modulate a cohort of gene networks.

Participation of KLF14 has been verified in several pathophysiological events, such as lipid metabolism, inflammatory response, adipogenesis, insulin signaling and cell proliferation and differentiation which play the key roles in the onset and progress of atherosclerosis (Fig. 2). Thus, it is conceivable that KLF14 plays an important regulatory role in atherosclerosis. On the one hand, overexpression of hepatic *klf14* has markedly reduced atherosclerotic lesions through increasing circulatory apoA 1 and HDL that mediate reverse cholesterol transport (RCT) *in vivo*, suggesting that tissue specific upregulation of *klf14* expression may be a promising clinical approach for increasing HDL in the treatment of atherosclerotic CVD, such as Perhexiline [11]. The synthetic agonists or activators of specific KLF14 in atherosclerosis animal models have

Table 1

Experimentally verified a *KLF14*-associated *trans* regulatory network of genes associated with atherosclerosis-related diseases and pathological processes.

Gene	Gene name	Gene ID	Chr	<i>KLF14</i> SNPs	Trait	Reference
TPMT	Thiopurine S-methyltransferase	7172	6p22.3	rs4731702	HDL, TG, BMI, INS, HOMA	[9,29]
ARSD	Arylsulfatase D	414	Xp22.33	rs4731702	HDL, TG, BMI, INS, HOMA, GLU	[9,29]
SLC7A10	Solute carrier family 7 member 10	56,301	19q13.11	rs4731702	LDL, WHR, HDL, TG, BMI	[9,29]
C8orf82	Chromosome 8 open reading frame 82	414,919	8q24.3	rs4731702	T2D, BMI	[9,29]
APH1B	Aph-1 homolog B	83,464	15q22.2	rs4731702	HDL, INS, HOMA	[9,29]
PRMT2	Protein arginine methyltransferase 2	3275	21q22.3	rs4731702	BM1	[9,29]
NINJ2	Ninjurin 2	4815	12p13.33	rs4731702	LDL	[9,29]
KLF13	Krüppel-Like factor 13	51,621	15q13.3	rs4731702	LDL, WHR	[9,29]
GNB1	G protein subunit beta 1	2782	1p36.33	rs4731702	HDL, TG, BMI, INS	[9,29]
MYL5	Myosin light chain 5	4636	4p16.3	rs4731702	BMI	[9,29]
ApoA-1	Apolipoprotein A-I	335	11q23.3	rs4731702	HDL	[5,11,38,39]
SK1	Sphingosine kinase 1	8877	17q25.1		Lipid	[4]
FOXP3	Forkhead box P3	50,943	Xp11.23		Cell differentiation	[61]
ALK-1	Activin receptor-like kinase 1	94	12q13.13		Cell proliferation	[89]
CCNA	Cyclin A	890	4q27		Cell transformation, cell apoptosis	[84]
MAPK	Mitogen-activated protein kinase	5594	22q11.22		Inflammation, TC, CE	[3]
P13K	Phosphatidylinositol-4,5-bisphosphate 3-kinase	5290	3q26.32		GLU, HOMA	[8]
				rs4731702	IS, MI	[21]
				rs111400400	MI	[21]
				rs1562398	FPG, TG	[5,32]
				rs4731702	LDL, ApoB1	[8]
				rs972283	T2D, HOMA, TG	[55,31]
				rs738134	T2D	[72]
				rs13234269	T2D	[74]

Chr, chromosome; BMI, body mass index; GLU, glucose levels; HDL, high density lipoprotein levels; HOMA, index of insulin sensitivity; INS, insulin levels; LDL, low density lipoprotein levels; TG, triglyceride; T2D, type 2 diabetes; WHR, waist-hip ratio; IS, ischemic stroke; MI, myocardial infarction; FPG, fasting plasma glucose; ApoB1, apolipoprotein B1; TC, total cholesterol; CE, cholesteryl ester.

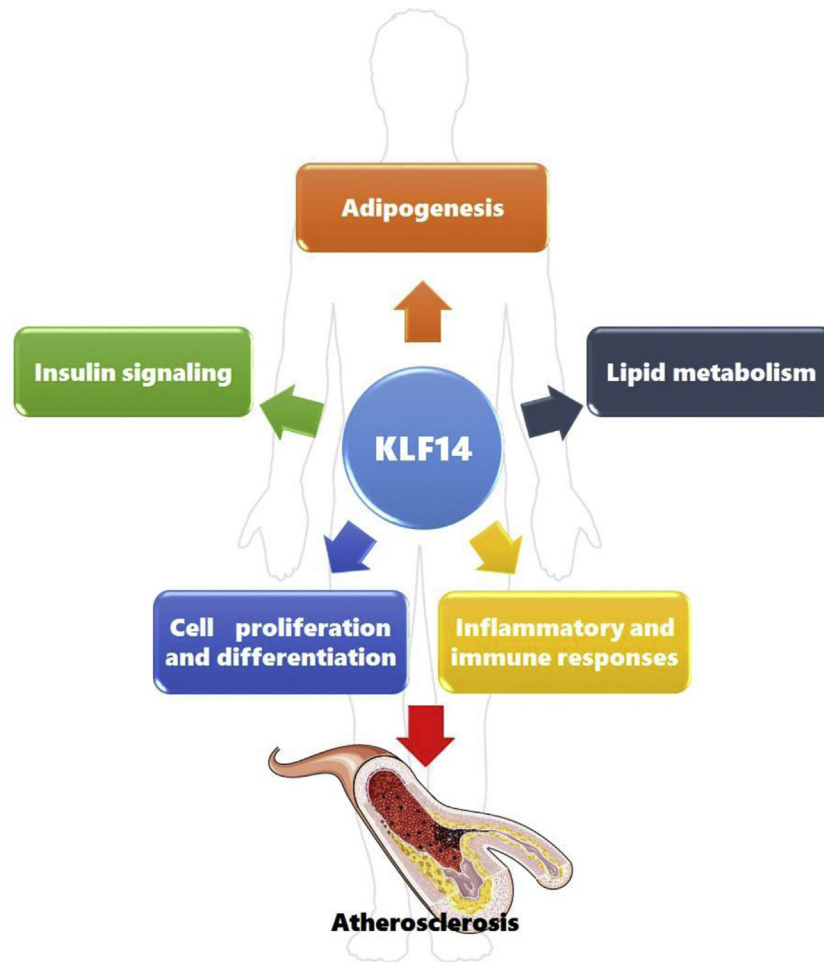


Fig. 1. KLF14-mediated regulation in the atherosclerosis-related risk factors.

not been available, but there will be an increased interest. Wei et al. have verified that *klf14* significantly altered the contents of cholesterol (TC and CE) and the ratio of CE to TC, and then changed atherosclerotic lesion formation [3]. It is well known that the cellular cholesterol efflux, through which cholesterol is transferred from nonhepatic peripheral tissues (macrophage and smooth muscle cell etc.) to HDL particles, also plays critical roles in the process of RCT. At the same time, cellular cholesterol biochemical metabolisms play an important role in lipid homeostasis. To assess KLF14 mediated atheroprotective effects, therefore, it is critical to further confirm whether KLF14 regulates the expression of the key genes and/or molecular factors involved in the cellular cholesterol efflux, influx and esterification/hydrolysis, such as ATP binding cassette transporter (ABCA1 and ABCG1), sterol regulatory element binding protein 1 (SREBP1), CD36, acyl coenzyme A cholesterol acyltransferase 1 (ACAT1) and lecithin cholesterol acyl transferase (LCAT). On the other hand, the effects of KLF14 on atherosclerotic lesion formation have been referred to not only the cholesterol metabolisms, but also inflammatory response [3]. Importantly, the changed expression of inflammatory factors, such as MCP 1, IL 6, and TNF α , was closely associated with *klf14* induced marked enhancement of phosphorylation levels of p38 MAPK and ERK1/2 [3]. Nevertheless, it is still unclear whether PPAR and NF κ B, two important transcription factors to regulate in inflammatory cytokines, participate in above mentioned pathway. Increasing evidence indicates that KLF14 modulates a well

circumscribed cohort of genes involved in atherosclerosis related diseases and pathological processes with a focus on diabetes, insulin signaling, adipogenesis, and obesity [13,40] (Fig. 2). It is also unknown how to specifically regulate atherosclerosis related gene profiles.

Although several interesting discoveries about KLF14 as a regulator participating in the regulation of atherosclerosis have attracted a lot of attention, the detailed roles and mechanisms underlying KLF14 effects in the initiation and progression of atherosclerosis are under intensive experimental investigation. These experimental results are expected to elaborate the exact functional roles and demonstrate target gene profile of KLF14 in atherosclerosis in the future. The combination of experimental techniques, such as bioinformatics analysis, the technology of genetic engineering, and gene knockout animal model will be needed for those studies. More importantly, our further understanding of mechanisms underlying KLF14 functions will help us treat atherosclerosis by targeting different signaling molecules in different cells, tissues, and species.

In summary, KLF14 studies in the field of atherosclerosis are still at very early stage. Many interesting and key issues about the exact roles of KLF14 in atherosclerosis will likely stimulate the researchers in the field to further elucidate its pathophysiological roles before the novel KLF14 based therapeutics can be considered for clinical applications. A better understanding of the mechanisms that underlie KLF14 mediated drug resistance/sensitivity of

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