



Review

The Mechanism and Role of N^6 -Methyladenosine (m^6A) Modification in Atherosclerosis and Atherosclerotic Diseases

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Abstract: N^6 -methyladenosine (m^6A) modification is a newly discovered regulatory mechanism in eukaryotes. As one of the most common epigenetic mechanisms, m^6A 's role in the development of atherosclerosis (AS) and atherosclerotic diseases (AD) has also received increasing attention. Herein, we elucidate the effect of m^6A on major risk factors for AS, including lipid metabolism disorders, hypertension, and hyperglycemia. We also describe how m^6A methylation contributes to endothelial cell injury, macrophage response, inflammation, and smooth muscle cell response in AS and AD. Subsequently, we illustrate the m^6A -mediated aberrant biological role in the pathogenesis of AS and AD, and analyze the levels of m^6A methylation in peripheral blood or local tissues of AS and AD, which helps to further discuss the diagnostic and therapeutic potential of m^6A regulation for AS and AD. In summary, studies on m^6A methylation provide new insights into the pathophysiologic mechanisms of AS and AD, and m^6A methylation could be a novel diagnostic biomarker and therapeutic target for AS and AD.

Keywords: N^6 -methyladenosine (m^6A); atherosclerosis; atherosclerotic diseases; diagnostic biomarkers; targeted therapeutics



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1. Introduction

Atherosclerosis (AS) is a chronic inflammatory disease with multiple pathological features, such as endothelial dysfunction, vascular inflammation, and cholesterol accumulation. AS can cause artery plaque and stenosis, leading to the occurrence of atherosclerotic diseases (AD), such as coronary artery disease, stroke, and other arterial diseases [1,2]. AD remain the leading causes of death worldwide, and have created a vital global burden, which is still increasing [3,4]. However, the pathogenesis of AS and AD is extremely complex and largely unclear. In a word, it is of great significance to investigate the new mechanism and potential therapeutic targets of AS and AD.

A growing number of studies [5,6] show that post-transcriptional epigenetic modifications are closely related to the processes of AS and AD. N^6 -methyladenosine (m^6A) modifications (one of the common post-transcriptional epigenetic modifications) are involved in the occurrence and development of AS and AD, and are novel and potential therapeutic targets and diagnostic biomarkers for AS and AD [7–9].

m^6A methylation is a post-transcriptional epigenetic modification at the RNA level, which is a process of methylation of adenine at the sixth nitrogen atom catalyzed by

RNA methyltransferases. m^6A methylation is the most prevalent and reversible type of modification in eukaryotic mRNA, and it also plays a role in noncoding RNAs such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) [10–13]. m^6A methylation can regulate RNA stability, positioning, transport, splicing, and translation [14,15], which will affect the structure and function of RNAs. It plays a crucial regulatory role in the pathogenesis of various diseases, such as tumors, cardiovascular, and cerebrovascular diseases, etc. [16,17]. Recent studies [7–9] have identified the significant role of m^6A methylation in the occurrence and development of AS and AD. In this review, we describe the relationship between m^6A and risk factors of AS, highlight its mechanism in the pathogenesis of AS, and elucidate the impact of m^6A methylation on the development of AS and AD. We also discuss the diagnostic and therapeutic potential of m^6A methylation regulators for AS and AD. Our review may provide novel insights into the pathophysiologic mechanisms, diagnostic biomarkers, and therapeutic targets for AS and AD.

2. Regulators of m^6A Methylation

Since its first discovery in the 1970s [18], m^6A has been identified as the most common mRNA internal modification in most eukaryotic species [18–23]. Similar to DNA methylation and histone modification, RNA methylation is a dynamic and reversible modification that regulates gene expression. m^6A modifications are mediated by three regulators: “writers” (methyltransferases), “erasers” (demethylases), and “readers” (m^6A -binding proteins) (Figure 1). The m^6A methylation site has a typical consensus sequence RRACH (R=G or A; H=A, C, or U), which is enriched in the coding sequence and 3′ untranslated region, particularly around stop codon regions [20,21]. Interactions among m^6A -modified writers, readers, and erasers are involved in the regulation of the RNA life cycle, thereby affecting many physiological and pathological processes, such as cell differentiation, self-renewal, and apoptosis, and the development of cancer, cardiovascular, and metabolic diseases.

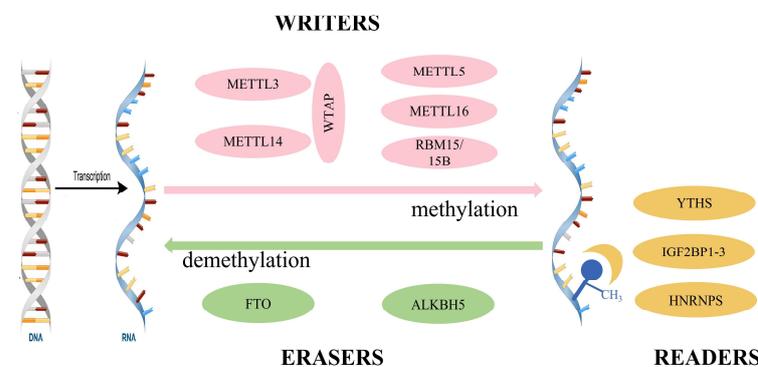


Figure 1. Regulators of m^6A methylation. METTL3, methyltransferase-like 3; WTAP, Wilms tumor 1-associated protein; RBM15/15B, RNA binding motif protein 15/15B; FTO, fat mass and obesity-related protein; ALKBH5, alkylation repair homologous protein 5; YTHS, YTHDF homeodomain family proteins; IGF2BP1-3, insulin-like growth factor 2 mRNA binding protein; HNRNPS, heterogeneous ribonucleoproteins.

2.1. Writers

The methyltransferases, also known as the codons or writers, are involved in the composition of the methyltransferase complex (MTC). MTC is composed of methyltransferase-like 3 (METTL3), METTL14, and other related regulators such as Wilms tumor 1-associated protein (WTAP), METTL5, METTL16, and RNA binding motif protein 15/15B (RBM15/15B) [24–28].

METTL3 was discovered in 1997 and it contains two S-adenosylmethionine binding sites called catalytically active methyltransferase domains [29]. METTL14, a homolog of METTL3, plays an important role in structurally supporting RNA binding by providing an RNA-binding scaffold [30,31]. WTAP can bind to the METTL3-METTL14 complex and

plays an important role in regulating the localization of the METTL3-METTL14 complex to nuclear foci [32]. In addition, METTL5, METTL16, RBM15/15B, and ZC3H13 play integral roles in m⁶A methylation [25–28].

2.2. Erasers

In contrast to MTC, demethylases are called erasers. Their role is to remove m⁶A methylation [33]. Demethylases include fat mass and obesity-related protein (FTO) and alkylation repair homologous protein 5 (ALKBH5) [22,34]. Although these two enzymes have similar functions, they play different roles in the process of demethylation.

In 2007, Frayling et al. [30] discovered a genetic variation in a gene associated with obesity risk, which was officially named FTO. FTO is abundant in the brain, especially in neurons. Hence, it may play an important role in the brain. FTO-dependent m⁶A demethylation contributes to human obesity and regulates energy balance, which is critical for its biological role in the cardiovascular system [35]. ALKBH5 is another nuclear-localized m⁶A demethylase. Zheng et al. [22] found that m⁶A total RNA levels were reduced in ALKBH5-overexpressing cells, which have been shown to regulate mRNA export, RNA metabolism, and mRNA assembly in nuclear speckles. In addition, ALKBH5 also plays a key role in biological processes such as cell cycle, stress response, and apoptosis [36].

2.3. Readers

Similar to DNA methylation, the biological function of m⁶A methylation is mediated by the recognition of m⁶A sites by m⁶A “readers”. m⁶A readers include YTDF homeodomain family proteins (YTDF1, YTDF2, YTDF3, YTDC1, and YTDC2), insulin-like growth factor 2 mRNA binding protein (IGF2BP1-3), and heterogeneous ribonucleoproteins (HNRNPA2B1, HNRNPC, and HNRNPG) [37].

Different readers have different biological functions. YTHDF1 promotes the translation of m⁶A methylated mRNAs, YTHDF2 accelerates the decay of m⁶A methylated mRNAs, and YTHDF3, together with YTHDF1 and YTHDF 2, significantly enhances the metabolism of m⁶A methylated mRNAs in the cytoplasm [38]. In addition, IGF2BP expressed in the cytoplasm not only enhances mRNA stability but also increases translation efficiency [39]. Moreover, HNRNPG is involved in mRNA splicing and regulates pre-mRNA processing [40].

3. The Effects of m⁶A Methylation in AS Major Risk Factors

Dyslipidemia, hypertension, and diabetes are the most common risk factors for AS. We reviewed the effects of m⁶A methylation on the development of AS major risk factors as follows (Figure 2).

3.1. Lipid Metabolism Disorder

Atherosclerotic lesions are based on lipid metabolism disorders [41]. Serum low-density lipoprotein levels are negatively correlated with m⁶A levels [42]. In addition, FTO catalyzes the demethylation of m⁶A methylation to alter mRNA processing, maturation, and translation of lipid-related genes [22,43,44].

Previous studies [45] have demonstrated that FTO inhibits the macrophage uptake of extracellular lipids, promotes intracellular lipid efflux, and inhibits macrophage lipid accumulation and foam cell formation. Scavenger receptor CD36, the primary transporter mediating extracellular lipid uptake by macrophages, is directly targeted by the oxisome proliferator-activated receptor γ (PPAR γ). Mo et al. [46] subsequently observed that FTO-dependent m⁶A demethylation reduced PPAR γ protein expression, resulting in downregulation of CD36 expression and decreased lipid uptake in RAW264.7 cells. Furthermore, Wu et al. showed that [47] FTO promotes AMPK phosphorylation and up-regulated ATP-binding cassette transporter A1 (ABCA1) in macrophages of mice. ABCA1 consumes ATP to mediate intracellular cholesterol efflux, which strongly prevents excessive lipid accumulation in macrophages. Reduced AMPK activity was shown to block FTO-induced

upregulation of ABCA1. Additionally, FTO increases ABCA1 expression in an AMPK activity-dependent manner [46,48].

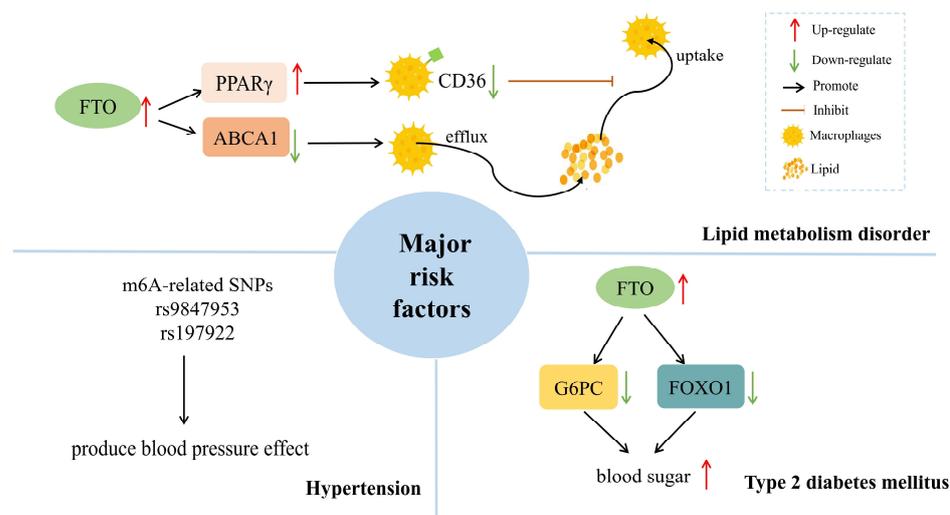


Figure 2. Effects of m⁶A methylation on the development of AS major risk factors. PPAR γ , proliferator-activated receptor γ ; SNPs, single nucleotide polymorphisms; G6PC, glucose-6-phosphatase catalytic subunit; FOXO1; forkhead box protein O1.

In conclusion, FTO is the key to regulating lipid homeostasis. m⁶A demethylation of FTO inhibits macrophage lipid influx by downregulating PPAR γ protein expression and accelerates cholesterol efflux by phosphorylating AMPK, thereby preventing foam cell formation and development of AS.

3.2. Hypertension

Hypertension is one of the main risk factors for AS, but the mechanism by which hypertension promotes the occurrence of AS is unclear. However, one study showed [49] that epigenetics could influence the pathogenesis of hypertension.

Wu et al. [50] demonstrated by m⁶A high-throughput sequencing analysis that the average abundance of m⁶A was reduced in microvascular pericytes of spontaneously hypertensive rats. This means that m⁶A methylation may regulate hypertension in mammals. Genetic variation affects m⁶A expression by altering the RNA sequence of the target site, which can be referred to as m⁶A-related single nucleotide polymorphisms (SNPs) [51]. The study by Mo et al. [52] showed that many m⁶A-related SNPs, such as rs9847953 and rs197922, affect the expression of related genes, such as C1orf167, DOT1L, and thus produce blood pressure effects. These findings may shed light on the underlying mechanism of hypertension from the perspective of m⁶A modification.

3.3. Type 2 Diabetes Mellitus (T2DM)

T2DM is a common risk factor for AS. A previous study [53] showed that specific variants in FTO could predispose individuals to T2DM. Among these variants, the FTO rs9939609 (T > A) polymorphism is the most studied; for example, in the Oulu Project Elucidation of Atherosclerosis Risk study [54], it was shown that the FTO rs9939609 minor allele individuals with genetic variants had significantly higher rates of cardiovascular disease events or deaths. Yang et al. [55] showed that FTO positively regulates gluconeogenesis-related genes, such as the glucose-6-phosphatase catalytic subunit (G6PC) and forkhead box protein O1 (FOXO1), in an m⁶A-dependent manner. In T2DM patients, decreased m⁶A promotes hepatic gluconeogenesis, which leads to increased blood glucose by reducing the expression of gluconeogenesis-related genes. Furthermore, in a study of pancreatic islet cells from T2DM patients [56], m⁶A methylation was significantly reduced in β cells, but

not in α cells, providing evidence that m^6A methylation controls cellular insulin secretion. This evidence suggests that m^6A methylation plays a vital role in T2DM.

4. The Mechanisms of m^6A Methylation in AS

Endothelial cells, macrophages, and smooth muscle cells are the most important initiating and developing cell types of AS. We summarized the mechanism by which m^6A regulates these cell types to induce AS as follows (Figure 3).

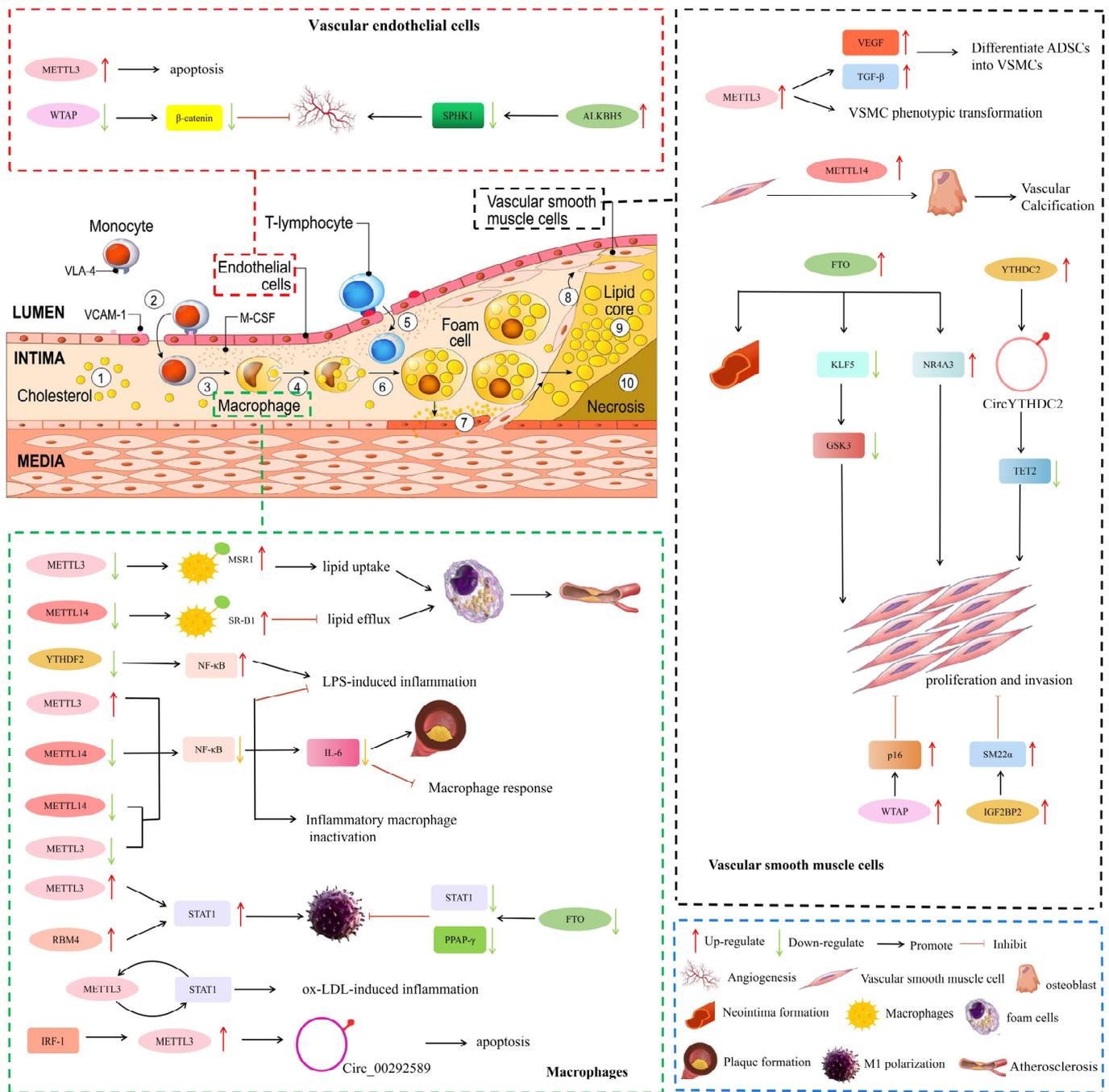


Figure 3. Potential mechanisms involved in m^6A methylation-mediated regulation of AS. NR4A3, nuclear receptor subfamily 4 group A member 3; GSK3, glycogen synthase kinase 3; TET2, ten-eleven translocation 2; SM22 α , smooth muscle 22 α ; ADSCs, adipose-derived stem cells; VSMCs, Vascular Smooth Muscle Cells; MSR1, macrophage scavenger receptor A; SR-B1, scavenger receptor B type 1; STAT1, signal transducer and activator of transcription 1; IRF-1, interferon regulatory factor-1.

4.1. Vascular Endothelial Cells

During the initial stages of AS, endothelial dysfunction and morphological damage occur, which lead to leukocyte adhesion, vasoconstriction, platelet aggregation, and thrombosis [57]. Vascular endothelial cell dysfunction is a key factor in the pathogenesis of AS.

m⁶A methylation plays a major role in post-transcriptional regulation in vascular endothelial cells. Zhu et al. [58] found that human cytomegalovirus (HCMV) infection could induce abnormally elevated m⁶A methylation, especially METTL3 and YTHDF3, leading to endothelial cell apoptosis. Wang et al. [59] used RNA transcriptome sequencing and found that in cerebral arteriovenous malformations, the expression levels of WTAP were significantly reduced but could inhibit endothelial cell angiogenesis.

m⁶A demethylation also plays important roles in endothelial cell angiogenesis. For example, Rajesh Kumari et al. [60] found that ALKBH5 levels were up-regulated after ischemia and correlated with the maintenance of ischemia-induced endothelial cell angiogenesis. ALKBH5 contributes to the maintenance of endothelial angiogenesis after acute ischemic stress by reducing SPM1 m⁶A methylation and downstream eNOS-AKT signaling.

4.2. Macrophages Response and Inflammation

m⁶A methylation can influence AS progression by affecting macrophage cholesterol efflux and cell death. Cholesterol accumulation in macrophages, foam cell formation, and atherosclerotic lesions are all affected by macrophage cholesterol efflux capacity [61]. Zhao et al. [62] showed that during AS, oxidized low-density lipoprotein (ox-LDL) induced the expression of dead box protein 5 (DDX5) in macrophages and restricted the METTL3 function. METTL3 can transfer methyl groups to macrophage scavenger receptor A (MSR1) mRNA. Eventually, MSR1 mRNA stabilizes, and more MSR1 is synthesized. The uptake of more lipids further promotes the formation of foam cells, leading to the progression of AS. However, the specific mechanism of METTL3 inhibition by DDX5 is unclear. Park et al. [63] showed that MELL14 knockout attenuated cholesterol efflux and promoted foam cell formation by affecting m⁶A levels of scavenger receptor B type 1 (SR-B1) mRNA.

Inflammation is one of the major and fundamental pathological processes for all stages of AS [64]. The transformation of macrophages into an inflammatory phenotype is closely related to the progression of AS. Signal transducer and activator of transcription 1 (STAT1) is a key transcription factor whose activation leads to signaling cascades activated by pro-inflammatory macrophages. Liu et al. [65] showed that METTL3 has been shown to directly methylate STAT1 mRNA to increase mRNA stability, thereby upregulating STAT1 expression and promoting the polarization of M1 macrophages. Huang et al. [66] demonstrated that RBM4 regulates M1 macrophage polarization by targeting STAT1-mediated glycolysis. This study shows that RBM4 may be a candidate for regulating M1 polarization and inflammatory responses in macrophages. In addition, Gu et al. [67] found that the FTO gene knockout of m⁶A demethylase inhibited the phosphorylation of key proteins in the NF- κ B signaling pathway, and was involved in reducing the mRNA stability of STAT1 and PPAR γ through YTHDF2, thereby hindering macrophages polarization of cells. Similarly, Li et al. [68] also showed that ox-LDL stimulation significantly increased m⁶A-modified mRNA levels in macrophages. METTL3 promotes ox-LDL-triggered inflammation by interacting with STAT1 protein and mRNA in macrophages. In summary, m⁶A via the STAT1 pathway plays an important role in macrophage inflammation in AS.

In addition, m⁶A via the NF/ κ B signaling pathway also plays a crucial role in macrophage inflammation in AS. Wang et al. [69] showed that METTL3 reduced lipopolysaccharide (LPS)-induced macrophage inflammatory response by inhibiting the NF- κ B pathway. However, Yu et al. [70] showed that downregulation of YTHDF2 significantly increased the LPS-induced expression of pro-inflammatory cytokines, such as IL-6 and TNF- α , and activated the MAPK and NF- κ B signaling pathways. In addition, Yu et al. [71] found that the inhibition of METTL14 and METTL3 expression in macrophages could abolish m⁶A methylation of NF- κ B mRNA, affect the stability of NF- κ B mRNA, and ultimately lead to the inactivation of inflammatory macrophages, thereby significantly alleviating

the progression of AS. Zheng et al. [72] found that Mettl14 knockout significantly reduced macrophage inflammatory response and atherosclerotic plaque formation through the NF- κ B/IL-6 signaling pathway.

Moreover, Zhang et al. [73] identified a role for METTL3 in promoting oxidized LDL-induced monocyte inflammation. Guo et al. [74] showed that overexpression of interferon regulatory factor-1 (IRF-1) promoted apoptosis and inflammatory responses in atherosclerotic macrophages by upregulating m⁶A methylation levels and METTL3 expression on circ_0029589.

4.3. Vascular Smooth Muscle Cell (VSMC)

During AS progression, contractile VSMCs undergo phenotypic transformation into proliferative synthetic cells that generate an extracellular matrix, form fibrous caps, and stabilize plaques [75]. Accumulating evidence suggests that m⁶A can affect the pathophysiological function of VSMCs.

The “writers” of m⁶A methylation are involved in VSMC proliferation and migration. Lin et al. [76] showed that hypoxia can affect METTL3 expression and further affect m⁶A modification of related factors such as VEGF and TGF- β , thereby inducing adipose-derived stem cells (ADSCs) to differentiate into VSMCs. Chen et al. [77] found that overexpressed METTL14 increased m⁶A methylation by promoting the transformation of VSMCs to osteoblasts, and played an important role in the pathological mechanism of vascular calcification. Furthermore, in the study by Zhu et al. [78], the expression of WTAP in VSMCs altered cell proliferation and migration. Total notoginseng saponins regulate p16 m⁶A methylation by promoting WTAP expression, thereby inhibiting intimal thickening.

The “erasers” of m⁶A demethylases have been reported to promote VSMC proliferation and migration. For example, Ma et al. [79] demonstrated that both FTO overexpression and Ang II-induced FTO expression promoted VSMC proliferation and migration. FTO promotes the expression of Kruppel-like factor 5 (KLF5) mRNA by reducing the m⁶A methylation of KLF5 mRNA, thereby upregulating the expression of downstream glycogen synthase kinase 3 (GSK3). Similarly, Huo et al. [80] also showed that FTO promoted Ang II-induced VSMC proliferation and inflammatory response by demethylating the m⁶A methylation of nuclear receptor subfamily 4 group A member 3 (NR4A3) mRNA. In addition, Deng et al. [81] established a rat carotid artery balloon injury model to confirm the role of the FTO in neointima formation.

Different m⁶A “readers” function differently in VSMC proliferation and migration. Yuan et al. [82] found that YTHDC2-mediated m⁶A modification stabilizes circYTHDC2, which promotes VSMC proliferation and migration by negatively regulating the expression of ten-eleven translocation 2 (TET2). However, Zhang et al. [83] showed that IGF2BP2 increased the stability of smooth muscle 22 α (SM22 α) mRNA by acting as a “reader” for m⁶A-modified SM22 α , inhibited the proliferation and migration of VSMC, and inhibited intimal hyperplasia.

5. The Role of m⁶A Methylation in AS and AD

m⁶A methylation not only causes the most common atherosclerotic diseases (such as coronary heart disease (CHD) and ischemic stroke (IS) through AS. Moreover, m⁶A also plays an important role in the injury and repair of CHD and IS. In Table 1, we reviewed the progress of m⁶A methylation regulator-guided epigenetic modification in AS and AD.

Table 1. m⁶A methylation regulator-guided epigenetic modification in AS and AD.

Atherosclerotic Process	m ⁶ A Regulators	Expression	Target Gene	Main Function	Reference
AS	METTL3	↑	LRP6 and DVL1	Enhances translation of LRP6 and DVL1, modulates Wnt signaling, and thus exerts angiogenic effects	[84]
	METTL3	↑	PGC-1α mRNA	Promotes mitochondrial dysfunction and ox-LDL-induced inflammation	[73]
	METTL3	↓	JAK2/STAT3	Alleviates ox-LDL-induced endothelial cell dysfunction, prevents in vivo angiogenesis of developing embryos, and hinders progression in AS mice models	[85]
	METTL3	↑	NLRP1 and KLF4	Up-regulates NLRP1, down-regulates KLF4, hypermethylates m ⁶ A, and triggers atherosclerotic response	[86]
	METTL3	↑	miR-375-3p/PDK1	Makes AS plaques more vulnerable	[87]
	METTL3	↑	EGFR	Promotes EGFR degradation and alleviates endothelial atherogenic progression	[88]
	METTL14	↑	FOXO1	Increases FOXO1 m ⁶ A methylation, aggravates endothelial inflammation and AS	[89]
	METTL14	↓	miR-19a	Inhibits the proliferation and invasion of ASVEC	[90]
	METTL14	↑	LncRNA ZFAS1	Plays a vital role in AS	[91]
	METTL14	↓	p65 mRNA	Relieves the development of AS	[92]
	METTL14	↓	NF-κB/IL-6	Reduces the inflammation response of macrophages and the development of AS plaques	[72]
	FTO	↑	Not known	Modulates neointima formation in vivo	[81]
	FTO	↓	NR4A3	Alleviates AngII-induced VSMC proliferation and inflammatory response	[80]
	ALKBH5	↓	HIF1α	Inhibits the expression of MIAT induced by ox-LDL	[42]
CHD	METTL3	↑	TFEB	Promotes cardiomyocyte apoptosis	[8]
	WTAP	↑	ATF4	Promotes endoplasmic reticulum stress and apoptosis, aggravates myocardial I/R injury	[93]
	FTO	↑	SERCA2A MYH6/7 RYR2	Reverses ischemic damage	[94]
	FTO	↑	MHRT	Inhibits cardiomyocyte apoptosis	[95]
	ALKBH5	↓	TFEB	Promotes cardiomyocyte apoptosis	[8]
	ALKBH5	↑	WNT5A	Regulates angiogenesis after ischemia	[96]

Table 1. Cont.

Atherosclerotic Process	m ⁶ A Regulators	Expression	Target Gene	Main Function	Reference
IS	METTL3	↑	miR-335	Promotes formation of SG and reduces damage of IS	[97]
	YTHDC1	↑	Not known	Protects rats from brain damage	[98]

↑, high expression; ↓, low expression; AS, atherosclerosis; METTL3, methyltransferase-like 3; LRP6, lipoprotein receptor-related protein 6; DVL1, dishevelled 1; ox-LDL, oxidized low-density lipoprotein; NLRP1, NOD-like receptor protein 1; KLF4, Kruppel-like factor 4; EGFR, epidermal growth factor receptor; FOXO1, forkhead box protein O1; ASVEC, atherosclerotic vascular endothelial cell; lncRNA, long non-coding RNA; ZFAS1, Zinc finger NFX type 1 antisense RNA 1; FTO, fat mass and obesity-related protein; NR4A3, nuclear receptor subfamily 4 group A member 3; ALKBH5, alkylation repair homologous protein 5; HIF1 α , hypoxia-inducible factor 1 α ; CHD, coronary artery heart disease; MIAT, myocardial infarction-associated transcript; TFEB, transcription factor EB; WTAP, Wilms tumor 1-associated protein; ATF4, activated transcription factor 4; SERCA2A, sarcoplasmic reticulum Ca²⁺-ATPase; MYH6/7, myosin heavy chain 6/7; RYR2, ryanodine receptor 2; MHRT, myosin heavy chain-related RNA transcript; WNT5A, WNT family member 5A; IS, ischemic stroke; SG, stress granule; YTHDC1, YTH Domain Containing 1.

5.1. AS

AS is the main cause of CHD and IS [99]. Quiles Jiménez et al. [6] used mass spectrometry to analyze m⁶A methylation levels in tissue from non-atherosclerotic arterial and carotid atherosclerotic patients, which showed the changes in the expression levels of m⁶A writers, erasers, and readers in atherosclerotic tissue. The findings of Wu et al. [42] showed that m⁶A methylation levels were significantly reduced in peripheral blood leukocytes of atherosclerotic patients and mice. The bioinformatic analysis indicated that differentially methylated genes were involved in the pathogenesis of AS. These findings suggest that m⁶A methylation is involved in the occurrence and progression of AS.

METTL3-dependent m⁶A methylation was recently shown to play an important role in AS. For example, Yao et al. [84] demonstrated that METTL3 promotes the translation of low-density lipoprotein receptor-related protein 6 (LRP6) and dishevelled 1 (DVL1) in human umbilical vein endothelial cells (HUVEC) under hypoxic stress in a YTHDF1-dependent manner, thereby exerting an angiogenesis effect. Zhang et al. [73] demonstrated that METTL3 plays a role in ox-LDL-induced monocyte inflammation, in which METTL3 and YTHDF2 synergistically modify PGC-1 α mRNA, mediate its degradation, and reduce PGC-1 α protein levels, thereby enhancing the inflammatory response. This study provides new insights into the role of METTL3-dependent m⁶A methylation of PGC-1 α mRNA in the inflammatory response of monocytes. In addition, Dong et al. [85] explored the role and molecular mechanism of m⁶A-METTL3 in AS progression from an in vivo perspective using an AS mouse model and an in vivo chick embryo chorioallantoic membrane assay. The results indicated that METTL3 knockout prevented AS progression through IGF2BP1 inhibition of the JAK2/STAT3 pathway. Furthermore, Chien et al. [86] showed that METTL3 up-regulated NOD-like receptor protein 1 (NLRP1) and down-regulated Kruppel-like factor 4 (KLF4) in an m⁶A-dependent manner. METTL3 exerts pro-inflammatory effects in HUVEC or mouse aortic endothelial cells exposed to pro-atherosclerotic oscillatory stress or TNF- α stimulation, thereby promoting inflammatory cell adhesion and AS pathogenesis. In a recent study, Chen et al. [87] found that silencing METTL3 alleviated AS progression in mice. Silencing METTL3 suppressed m⁶A levels and decreased the binding of DGCR8 to pri-miR-375, further limiting the expression of miR-375-3p. miR-375-3p targets PDK1 transcription. Ultimately silencing METTL3 plays a role in stabilizing AS plaques. However, Li et al. [88] reported a protective role of METTL3 in AS. The authors found that METTL3 promotes m⁶A-dependent degradation of epidermal growth factor receptor (EGFR) mRNA, a molecule associated with vascular endothelial cell (EC) dysfunction, thereby attenuating the progression of endothelial atherosclerosis.

Similarly, METTL14 also plays a pivotal role in the process of AS. Jian et al. [89] constructed a model of EC inflammation induced by TNF- α . With an increase in the expression of METTL14 in endothelial cells stimulated with TNF- α , METTL14 increases the m⁶A

methylation of FOXO1, promoting its expression, which triggers endothelial inflammatory responses and the development of AS. Subsequent *in vivo* experiments showed that METTL14 knockout could inhibit AS plaque development in an m⁶A-dependent manner in METTL14 knockout mice. Furthermore, Zhang et al. [90] pointed out that METTL14 promoted the production of mature miR-19a by increasing the expression of m⁶A in miR-19a, thereby accelerating the invasion and proliferation of cardiovascular ECs. Chen et al. [100] showed that the m⁶A methylation of Zinc finger NFX type 1 (ZNF1) antisense RNA 1 (ZFAS1) was significantly higher in AS patients than in controls, and that m⁶A methylation in ZFAS1 was regulated by METTL14. Tang et al. [91] found that METTL14 affects the expression of downstream ADAM10/RAB22A by affecting the m⁶A methylation of LncRNA ZFAS1, thereby participating in cholesterol metabolism and vascular inflammation, and ultimately regulating the occurrence and development of AS. Liu et al. [92] demonstrated that silencing METTL14 attenuates the development of AS through the m⁶A methylation of p65 mRNA by establishing an *in vitro* atherosclerotic cell model and an *in vivo* high-fat diet mouse model. Zheng et al. [72] showed that Mettl14 plays a crucial role in macrophage inflammation in AS through the NF- κ B/IL-6 signaling pathway. METTL14 knockout significantly reduced the macrophage inflammatory response and atherosclerotic plaque formation.

In addition, demethylases also play an important role in AS. For example, Deng et al. [81] established a rat carotid artery balloon injury model, which confirmed that FTO could induce neointima formation. Huo et al. [80] used Ang II to construct vascular smooth muscle cells (VSMC) and vascular inflammation models *in vitro* and *in vivo*, and confirmed that the FTO/NR4A3 axis plays a key role in Ang II-induced VSMC proliferation and inflammation. Wu et al. [42] found that ox-LDL-induced ALKBH1 promotes myocardial infarction-associated transcript (MIAT) transcription by promoting the binding of hypoxia-inducible factor 1 α (HIF1 α). In addition, ALKBH1 knockdown inhibited ox-LDL-induced MIAT expression. All in all, the present findings suggest that the ALKBH1-m⁶A axis may control atherosclerotic plaque progression by regulating MIAT expression.

5.2. AD

5.2.1. CHD

CHD, also known as ischemic cardiomyopathy, refers to the clinical syndrome of long-term myocardial ischemia caused by coronary atherosclerosis, resulting in diffuse myocardial fibrosis [101].

Mathiyalagan et al. [94] demonstrated for the first time that mRNA m⁶A methylation was significantly higher in ischemic myocardium than in non-ischemic regions. Song et al. [8] demonstrated that m⁶A RNA methylation is involved in the development of myocardial hypoxia/reperfusion injury by regulating autophagy. Deng et al. [81] identified differentially methylated m⁶A sites in mRNAs and lncRNAs between peripheral blood mononuclear cells of the CHD group and control group. These studies suggest that m⁶A RNA methylation plays a crucial role in CHD.

Song et al. [8] established a mice model of hypoxia-reperfusion and ischemia-reperfusion and found that the m⁶A methylation levels in mice cardiomyocytes increased, and METTL3 is the main cause of abnormal modification of m⁶A methylation. Silencing METTL3 enhances autophagic flux and inhibits cardiomyocyte apoptosis in hypoxic/reoxygenated cardiomyocytes. However, the overexpression of METTL3 or inhibition of m⁶A demethylase ALKBH5 promoted cardiomyocyte apoptosis. This suggests that METTL3 is a negative regulator of autophagy. Similarly, WTAP promotes endoplasmic reticulum (ER) stress and apoptosis by increasing mRNA m⁶A levels of activated transcription factor 4 (ATF4), a transcription factor that controls the expression of ER-related genes, and up-regulates its expression, thereby aggravating myocardial I/R injury [93].

FTO-mediated m⁶A demethylation is also associated with myocardial I/R injury. FTO can selectively demethylate sarcoplasmic reticulum Ca²⁺-ATPase (SERCA2A), myosin heavy chain 6/7 (MYH6/7), ryanodine receptor 2 (RYR2), and other mRNAs that affect

cardiac calcium homeostasis, myofibril synthesis, and contractile function. It increases the transcription and translation of the above genes through an m⁶A-dependent pathway, thereby reversing ischemic injury [94]. Myosin heavy chain-related RNA transcript (MHRT) is a heart-specific lncRNA derived from the antisense strand of the MYH7 gene. Shen et al. [95] demonstrated that overexpression of FTO inhibited apoptosis in I/R-treated cardiomyocytes by reducing the m⁶A modification of MHRT.

In addition, overexpression of ALKBH5 can reverse the damaging effects of METTL3 on cardiomyocytes [8]. Another study explored the effect and mechanism of ALKBH5 on angiogenesis after ischemia. Zhao et al. [96] demonstrated that ALKBH5 negatively regulates angiogenesis after ischemia by reducing the mA levels of WNT family member 5A (WNT5A) mRNA and by promoting its degradation in cardiac microvascular endothelial cells.

5.2.2. IS

The stenosis of the cerebral arterial lumen often occurs due to AS, resulting in ensuing thrombosis and IS. Emerging evidence [9,102] suggests that m⁶A methylation is involved in the injury and repair of IS.

Si et al. [97] established an oxygen–glucose deprivation/reperfusion model in primary cortical neurons and PC12 cells by using a middle cerebral artery occlusion model in rats to explore m⁶A methylation of potential mechanisms involved in stress granule (SG) formation in the early stages of acute ischemic stroke. Both in vitro and in vivo results showed that METTL3 protein, m⁶A levels, and miR-335 expression were significantly decreased with prolonged reperfusion time. The finding suggests that METTL3-mediated m⁶A methylation plays an important role in promoting SG formation and reducing IS damage in the early stages of disease.

Similar to METTL3, YTHDC1 also plays a protective role in the pathological process of IS. Zhang et al. [98] found that the knockout of YTHDC1 aggravated ischemic brain injury, while the overexpression of YTHDC1 protected rats from brain injury; mechanistically, YTHDC1 promotes PTEN mRNA degradation to increase Akt phosphorylation, thereby promoting neuronal survival, especially after ischemia.

6. Potential Diagnostic Biomarkers and Therapeutic Targets of m⁶A for AS and AD

The above findings provide new information for understanding the molecular pathogenesis of AS and exploring potential diagnostic biomarkers and therapeutic targets for AS and AD.

6.1. Potential Diagnostic Biomarkers of m⁶A for AS and AD

The levels of m⁶A methylation in the tissue of AS patients are significantly lower than that of non-AS patients and that of early AS patients. The expression levels of WTAP, METTL3, YTHDF2, and FTO are significantly lower than those of non-AS patients [6]. In addition, m⁶A levels in peripheral blood leukocytes are negatively correlated with carotid plaque size and thickness [42]. Thus, these biomarkers may potentially be used in the future for the early diagnosis of AS. In addition, the m⁶A levels in peripheral blood mononuclear cells of CHD patients are significantly lower than that of the control group, and the expression levels of FTO, METTL14, and ALKBH5 in the CHD patients are also lower than those of the control group [81]. Moreover, global m⁶A levels in ipsilateral cortical tissue around cerebral infarction are significantly elevated after transient focal ischemia, and FTO levels are significantly reduced after stroke [9]. Taken together, these findings indicate that m⁶A may be a potential biomarker for the diagnosis of AD. In summary, m⁶A levels in RNA may prove to be a valuable diagnostic biomarker for AS and AD. However, the relationship between m⁶A and AS or AD, and its diagnostic specificity and sensitivity, would need to be confirmed by clinical studies with easy access to specimens such as peripheral blood.

6.2. Potential Therapeutic Targets of m⁶A for AS and AD

Numerous studies have shown that methyltransferases are associated with aberrant m⁶A modification and lead to the development of AS and AD, which indicate that m⁶A methylation may be the potential therapeutic target. METTL3 promotes ox-LDL-triggered inflammation by interacting with STAT1 protein and mRNA in macrophages [68]. METTL14-mediated m⁶A modification of ZFAS1/RAB22A may play an important role in AS [100], and METTL14 plays a crucial role in macrophage inflammation in AS through the NF-κB/IL-6 signaling pathway [72]. In addition, experiments *in vivo* have shown that silencing METTL3 can stabilize atherosclerotic plaques [87]. Moreover, METTL14 knockout can inhibit the development of AS plaques [89], and silencing METTL14 can alleviate the development of AS [92]. These indicated that METTL3 and METTL14 may be promising therapeutic targets for the clinical treatment of AS. Likewise, ALKBH5 can negatively regulate angiogenesis after ischemia [96]. Thus, targeting ALKBH5 may be a potential therapeutic option for CHD. Additionally, a key link between METTL3-ALKBH5 and autophagy provides a new direction for m⁶A methylation therapy in CHD [8]. Moreover, in IS, METTL3-mediated m⁶A modification plays an important role in reducing damage in the early stages of stroke [97]. Furthermore, YTHDC1 is a novel regulator of neuronal survival [98]. However, further experimental and clinical evidence is needed to confirm these potential therapeutic targets.

Based on the above therapeutic targets, exploratory research on the treatment of AS with chemical drugs and botanical drugs are ongoing. In terms of chemical drugs, Zhu et al. [58] showed that vitamin D3 inhibited HCMV-induced vascular endothelial cell apoptosis by correcting m⁶A modification of mitochondrial calcium transporter mRNA, which was regulated by METTL3 and YTHDF3. This study highlighted the significance of vitamin D3 supplementation in HCMV-induced AS. For botanical drugs, several studies have also shown that Chinese herbal medicine could significantly delay the onset and progression of AS [71,103,104]. Hua Tuo Zai Zao Wan (HTZZW) was the most frequently studied traditional Chinese medicine. In the study by Yu et al. [71], positive effects were observed in AS mice treated with HTZZW. HTZZW exerts its effect through epigenetic regulation, which can regulate the expression of METTL14 and METTL3 in macrophages, thereby eliminating the m⁶A modification of NF-κB mRNA, and finally leading to the inactivation of macrophages, which has the effect of preventing AS.

In conclusion, m⁶A modifications are potential therapeutic targets for AS and AD, and drugs that affect m⁶A methylation are expected to be explored in AS and AD treatment in the future.

7. Discussion and Perspectives

This review expounds on the impact of m⁶A methylation on the main risk factors for AS, such as lipid metabolism disorders, hypertension, and hyperglycemia. We also describe the m⁶A methylation mechanisms that may contribute to the development of AS, including vascular endothelial cell injury, macrophage responses, inflammation, and the proliferation and migration of smooth muscle cells. We then summarized the pathophysiological role of m⁶A methylation in AS and AD, and discussed m⁶A methylation and its regulators as diagnostic biomarkers and treatment targets.

In terms of mechanism, the study of m⁶A revealed a potential link between this epigenetic modification and AS and AD. However, the mechanism of AS is very complex, and the specific association between m⁶A methylation and AS remains to be elucidated. Studies of m⁶A methylation in AS have mainly focused on METTL3 and METTL14 expression. Future studies should also explore how other m⁶A regulators, such as erasers and readers, regulate the expression of downstream proteins, and the interactions between m⁶A writers, erasers, and readers. In addition, it is unclear whether m⁶A methylation crosstalk with other epigenetics, such as non-coding RNA, DNA methylation, and histone modification, occurs in the development of AS.

In terms of clinical application, m⁶A methylation is dynamic and reversible, and has important implications for the diagnosis, prevention, and treatment of AS and AD. For diagnostic application, most studies on differential expression of m⁶A levels in AS and AD were performed in animal, and most of them are from local tissues (such as artery, heart, or brain), which is difficult to obtain clinically. In addition, a comprehensive study of the relationship between m⁶A methylation from peripheral blood and the disease in human is badly needed, which will help identify potential biomarkers for the diagnosis of AS and AD. All in all, it is a beautiful blueprint to use a simple detection method to determine the level of m⁶A or related proteins in peripheral blood to achieve the purpose of diagnosing AS and AD. For therapeutic application, m⁶A inhibitors or agonists for the treatment of AS are still at the stage of animal experiments, and more effective drugs and new therapeutic strategies related to m⁶A remain to be discovered.

8. Conclusions

Studies on m⁶A methylation provide new insights into the pathophysiologic mechanisms of AS and AD, and m⁶A methylation will be a novel diagnostic biomarker and therapeutic target for AS and AD in the near future.

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