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REVIEW

Recent Advances in the Mutual Regulation of m6A Modification and Non-Coding RNAs in Atherosclerosis

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Abstract: Atherosclerosis, a progressive inflammatory disease of the arteries, remains a leading cause of cardiovascular morbidity and mortality worldwide. Recent years have witnessed the pivotal role of N6-methyladenosine (m6A) RNA methylation in regulating various biological processes, including those implicated in atherosclerosis. Current evidence suggested that m6A regulators (writers, erasers, and readers) participated in the modification of multiple non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), thereby affecting their metabolism and functions. Meanwhile, ncRNAs have also emerged as key modulator of m6A regulators expression in turn. Therefore, understanding the mutual regulation between m6A modifications and ncRNAs is of great significance to identify novel therapeutic targets for atherosclerosis and has great clinical application prospects. This review aims to summarize the recent advances in the reciprocal regulation and provide insights into the interaction between m6A modification and ncRNAs in the context of atherosclerosis.

Keywords: N6-methyladenosine (m6A), non-coding RNAs (ncRNAs), mutual regulation, atherosclerosis, epigenetics

Introduction

Atherosclerosis, a chronic inflammatory disease characterized by the accumulation of lipids and fibrous elements within the arterial wall, is the leading cause of cardiovascular disease (CVD) globally.[1] Atherosclerosis is a complex process involving interactions between multiple cellular and molecular mechanisms, including endothelial dysfunction, inflammation, oxidative stress, and altered lipid metabolism.[2] Recent advances in epigenetic research have highlighted the critical role of RNA modifications in regulating gene expression and cellular functions, offering novel insights into the pathogenesis of atherosclerosis.[3]

Among these modifications, N6-methyladenosine (m6A) is the most abundant and dynamic internal modification in eukaryotic messenger RNAs (mRNAs) and non-coding RNAs (ncRNAs).[4] This modification can affect RNA stability, splicing, localization, and translation, thereby modulating cellular processes.[3] Emerging evidence suggests that m6A modifications may play a pivotal role in modulating the expression of genes involved in inflammation, lipid metabolism, and endothelial function—key processes underlying atherosclerosis.[5]

NcRNAs, such as microRNA (miRNA), long noncoding RNA (lncRNA), and circular RNA (circRNA), have emerged as critical regulators of atherosclerosis.[6] It is generally acknowledged that miRNAs negatively regulate gene expression by base-pairing with target mRNAs, and lncRNAs can function as scaffolds, decoys, guides, or enhancers to modulate gene expression, while circRNA is formed primarily through spliceosome-mediated reverse splicing of precursor mRNA (pre-mRNA) connecting the upstream 3′-splice site to the downstream 5′-splice site, resulting in a circular transcript.[7–9]

m6A modification is involved in cell differentiation and development processes. It regulates the expression of key genes related to development and differentiation, affecting the fate determination and functional specialization of cells.

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For example, during embryonic development, m6A modification participates in the regulation of cell lineage commitment and organogenesis. In response to various stress stimuli such as hypoxia and nutrient deficiency, the m6A modification level in cells changes. This modification can regulate the expression of stress response genes, enabling cells to quickly adjust their physiological states to adapt to the stress environment. For instance, under hypoxic conditions, the expression of certain m6A-related enzymes and binding proteins changes, which in turn affects the stability and translation of hypoxia-responsive gene mRNAs.

The role of m6A modification in atherosclerosis is a rapidly evolving field with many exciting avenues for future research. Studies are needed to further elucidate the mechanisms by which m6A regulates gene expression and cellular functions in the context of atherosclerosis. Additionally, identifying specific m6A-modified mRNAs and proteins that are critical for disease progression could lead to the development of new therapeutic targets for atherosclerosis. However, the role of reciprocal epigenetic regulation between m6A modification and ncRNAs in atherosclerosis remains relatively unexplored. For instance, by modulating the expression and function of atherosclerosis-related genes, this interaction can influence lipid metabolism, inflammation, and oxidative stress.[10–12] Understanding these mechanisms may lead to the identification of novel therapeutic targets for atherosclerosis.

In this review, we summarize the current understanding of the role of m6A modification and its interaction with ncRNAs in atherosclerosis, especially provide a comprehensive framework for exploring how m6A modification and ncRNAs in regulating gene expression and cellular functions, affecting RNA stability, splicing, localization, and translation, thereby modulating cellular processes critical to atherosclerosis. Understanding these mechanisms may pave the way for identifying novel therapeutic targets into the epigenetic regulation of atherosclerosis, with the ultimate goal of improving clinical outcomes for patients with this devastating disease.

The Pathogenesis of Atherosclerosis

The pathogenesis of atherosclerosis is a complex multifactorial process involving the interaction of multiple cellular and molecular mechanisms.[13] It begins with endothelial cell injury caused by various risk factors such as hypertension, hyperglycemia, smoking, and hyperlipidemia.[14] This damage increases vascular permeability, facilitating lipid infiltration and deposition, particularly of low-density lipoprotein (LDL) which oxidizes to form oxidized low-density lipoprotein (ox-LDL).[15] Monocytes are then recruited to the site, differentiating into macrophages that engulf ox-LDL and transform into foam cells.[16] Smooth muscle cells (SMCs) also proliferate and migrate to the intima, contributing to the formation of a fibrous cap over the growing lipid core.[17] Local inflammation persists, with inflammatory cells releasing cytokines that further promote lesion development.[18] Over time, this leads to the formation of an atherosclerotic plaque.[18] The following outlines the key mechanisms of atherosclerosis:

(1) Endothelial cell injury:[19] Endothelial cells, which form the inner lining of blood vessels, regulate vascular permeability, anticoagulation, anti-inflammation, and other vital functions. When exposed to harmful stimuli such as hypertension, hyperglycemia, hyperlipidemia, and smoking, these cells can become damaged, leading to endothelial dysfunction. This allows lipids and inflammatory cells from the blood to more easily penetrate the vessel wall, triggering atherosclerosis.[20,21]
(2) Lipid deposition:[22] Following endothelial cell injury, lipids such as LDL in the blood tend to accumulate at the site of injury. These lipids gradually build up within the vessel wall, forming lipid streaks that evolve into fibrous plaques and atherosclerotic plaques.[23]
(3) Inflammatory response:[22] Lipid deposition initiates a series of inflammatory reactions, including the infiltration and activation of white blood cells (such as monocytes and macrophages).[24] These inflammatory cells release various inflammatory mediators, including cytokines, chemokines, and proteases, which further exacerbate endothelial cell damage and lipid deposition, creating a vicious cycle.[25]
(4) Smooth muscle cell proliferation and migration:[26] Vascular smooth muscle cells play a crucial role in the atherosclerotic process.[26] Stimulated by inflammation, these cells migrate from the tunica media to the tunica intima of the blood vessel and proliferate.[26,27] Macrophages also release growth factors that stimulate smooth

muscle cell proliferation.[24] These smooth muscle cells can synthesize and secrete extracellular matrix components like collagen fibers and proteoglycans, altering the structure and stability of plaques.[26,27]

(5) Calcification:[28] In the later stages of atherosclerosis, calcification may occur within the plaque. This calcification makes the plaque harder and more fragile, increasing the risk of cardiovascular events.[29]

Clinically, atherosclerosis can lead to inadequate tissue perfusion due to vessel narrowing or obstruction, resulting in various symptoms and signs.[2] Initial partial vessel occlusion may cause transient ischemic events, manifesting as temporary functional loss in affected areas like dizziness, weakness, or numbness.[26] As the disease progresses, worsening obstruction and potential thrombosis can lead to severe ischemia and tissue infarction, presenting as myocardial infarction or stroke depending on the location.[30] Peripheral artery disease can cause pain, especially during physical activity, limiting mobility and potentially leading to disability or gangrene.[31] Stroke occurs when brain-supplying vessels are obstructed, causing neurological deficits.[32] Simultaneous involvement of multiple vascular beds can result in a combination of ischemic symptoms across different organ systems, indicating an increased risk of ischemic complications elsewhere.[33]

In summary, the pathogenesis of atherosclerosis involves endothelial cell injury, lipid deposition, inflammatory response, smooth muscle cell proliferation and migration, and calcification (Figure 1). These interconnected and interacting processes contribute to the development and progression of atherosclerosis.

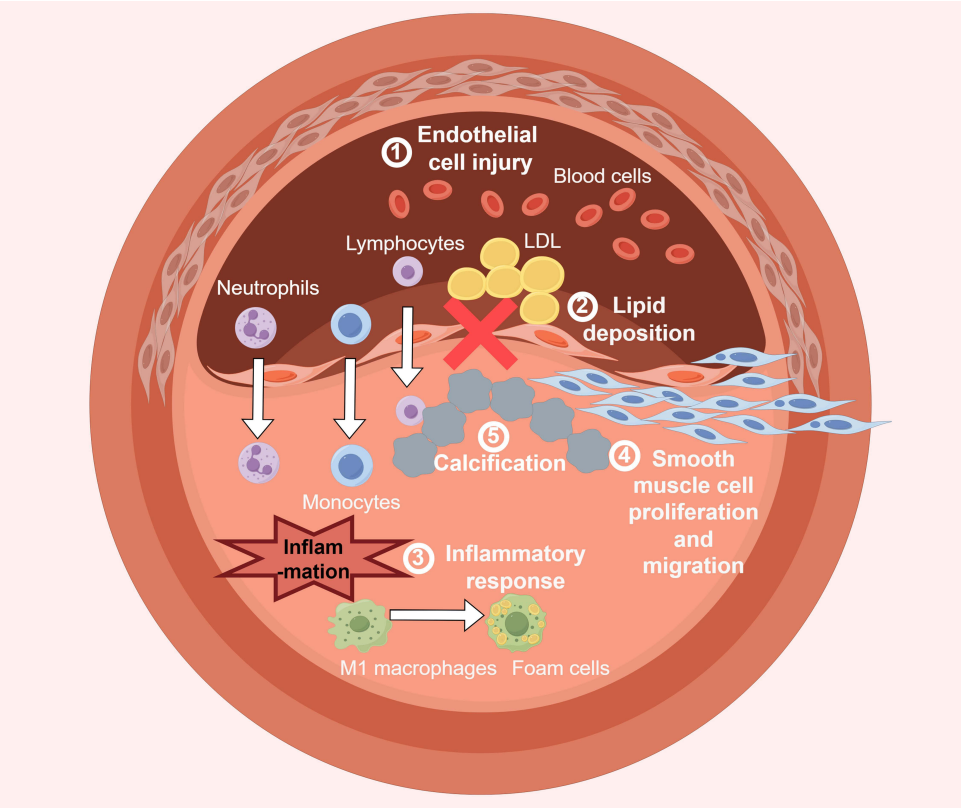

Figure 1 Schematic diagram of atherosclerosis pathogenesis. The pathogenesis of atherosclerosis is initiated by endothelial cell injury, which enables lipid deposition. Subsequently, an inflammatory reaction occurs, which promotes the proliferation and migration of smooth muscle cells. Calcification also occurs during this process. These processes - ①endothelial cell injury, ②lipid deposition, ③inflammatory response, ④smooth muscle cell proliferation and migration, and ⑤calcification - are intertwined and interact with one another, jointly promoting the development and progression of atherosclerosis.

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The Machinery of m6A Modification on ncRNAs

Among various RNA modifications, m6A has emerged as the most prevalent internal modification in eukaryotic messenger RNAs (mRNAs) and non-coding RNAs (ncRNAs).[34] The dynamic and reversible nature of m6A modifications is orchestrated by "writers" (m6A methyltransferases), "erasers" (m6A demethylases), and "readers" (binding proteins that recognize m6A modifications and regulate RNA fate).[35] The Writers, including enzymes like methyltransferase-like 3 (METTL3) and METTL14, are responsible for adding m6A marks to RNA. The Erasers, such as fat mass and obesity (FTO)-associated protein and alkB homolog 5 (ALKBH5), remove these marks, fine-tuning RNA's fate and function. The Readers, like the YT521-B homology domain (YTHD)-containing protein family, recognize and bind to m6A-modified RNA, regulating its various functions.[36,37]

This modification occurs in different RNA types, including mRNAs, rRNAs, and snRNAs, and is catalyzed by specific enzymes.[37] m6A modification plays a crucial role in regulating RNA functions like translation, degradation, stability, splicing, and nuclear export.[38] For instance, it can enhance translation by binding to initiation factors or induce protein synthesis. It can also promote RNA degradation or stability, depending on the reader protein involved.[39] In summary, m6A modification, through the coordinated action of its writers, erasers, and readers, significantly impacts RNA functions and fate, thereby influencing gene expression and multiple cellular processes.[39,40]

This intricate m6A machinery also regulates gene expression at the post-transcriptional level by interacting with ncRNAs (such as miRNAs, lncRNAs and circRNAs) in diverse cellular processes, including RNA processing, stability, translation, and subcellular localization, thereby modulating cellular responses to environmental stimuli and disease states.[40,41]

The Interaction Between m6A-Modified Proteins and miRNAs

miRNAs are a class of short non-coding RNA made up of 22–25 nucleotides in length that mainly regulate gene expression by binding to the 3'UTR region of target mRNAs and inhibiting translation or promoting degradation.[7] m6A-modified proteins indirectly regulate target gene expression by affecting the maturation, stability, and function of miRNAs.[42]

m6A writers: Some m6A methyltransferases may participate in the processing of miRNA precursors and affect their stability and processing efficiency through m6A modification.[43] For example, the METTL3 and METTL14 complex may methylate specific miRNA precursors with m6A to promote their recognition and cutting by Drosha enzyme into pre-miRNA.[44]

m6A erasers: As demethylating enzymes, FTO and ALKBH5 affect the stability and function of miRNAs by removing m6A modification from them.[45] Studies have shown that FTO can demethylate specific miRNAs, enhance their stability, and promote their binding to target mRNAs, thereby enhancing the inhibitory effect of miRNAs.[41]

m6A readers: As m6A-binding proteins, YTHDF family proteins affect the regulation of downstream target genes by recognizing and binding to m6A modification on miRNAs.[41] For example, YTHDF2 may promote the recruitment of the CCR4-NOT complex by recognizing and binding to miRNAs with m6A modification, accelerating the degradation of target mRNAs.[46]

The Interaction Between m6A-Modified Proteins and lncRNAs

lncRNAs are a class of non-coding RNAs that are longer than 200 nucleotides and are widely involved in the regulation of gene expression.[47] m6A-modified proteins regulate the stability, localization, and function of lncRNAs, thereby influencing their biological roles in cells.[47]

m6A writers: METTL3 and other methyltransferases modify lncRNAs with m6A, affecting their secondary structure and stability, and subsequently regulating their interactions with other molecules.[48] For example, m6A modification may promote the binding of lncRNA to specific proteins, forming RNA-protein complexes, and participating in the regulation of gene expression.[49]

m6A erasers: FTO and ALKBH5, among other demethylases, remove m6A modification from lncRNAs, affecting their stability and function.[50] Demethylated lncRNAs may be more easily degraded or lose their original biological activity.[51]

m6A readers: YTHDF family proteins and other m6A-binding proteins, regulate the cellular localization and biological function of lncRNAs by recognizing and binding to m6A modification on lncRNAs.[36] For example, YTHDF1 may promote the entry of lncRNAs containing m6A modification into ribosomes, enhancing the translation efficiency of RNA.[52]

The Interaction Between m6A-Modified Proteins and circRNA

circRNA is a class of non-coding Rnas that exist in a covalent closed loop form with high stability and tissue specificity.[53] The m6A modified protein affects the biological function of circRNA by regulating the m6A modified level of circRNA.[54]

m6A writers: Methyltransferases such as METTL3 modify circRNA through m6A, affecting its stability and interaction with other molecules.[55] m6A modification may promote circRNA to bind to specific proteins or RNAs to form functional complexes.[54]

m6A erasers: Demethylases such as FTO and ALKBH5 regulate circRNA stability and function by removing m6A modifications on CircrNA.[55] After demethylation, circRNA may be more easily degraded or lose its original biological activity.[56]

m6A readers: m6A binding proteins such as YTHDF and HNRNP family proteins regulate cell localization and biological function by recognizing and binding m6A modifications on circRNA.[55] For example, YTHDF2 may accelerate the degradation of circRNA by recognizing and binding to circRNA containing m6A modifications and promoting its recruitment of degradation complexes.[57]

To sum up, m6A-modified proteins are involved in a variety of biological processes through their interactions with ncRNAs (miRNAs, lncRNAs, and circRNAs) to finely regulate gene expression at the post-transcriptional level (Figure 2). In the future, with the deepening of the research, we are expected to reveal more about the molecular mechanism of the interaction between m6A-modified proteins and ncRNAs, and provide new ideas and methods for the treatment and diagnosis of diseases.

Roles of m6A Modification on ncRNAs in Atherosclerosis

In atherosclerosis, m6A-modified proteins can modulae gene expression patterns critical for lipid metabolism, inflammation, and endothelial function.[41,58] For instance, m6A writer METTL3 promotes atherosclerosis by increasing NLRP1 expression and reducing Kruppel-like factor 4 (KLF4) levels in endothelial cells.[59] Conversely, m6A eraser FTO alleviates atherosclerosis by reducing fat accumulation and enhancing cholesterol efflux.[60]

The Regulation of m6A Modification on miRNAs in Atherosclerosis

Accumulating evidence has revealed that m6A writers (METTL3 and METTL14) can modulate m6A modification of miRNAs, affecting the development of atherosclerosis.[61] For instance, silencing METTL3 inhibited the expression of miR-375-3p targeting PDK1 transcription, which limited the phenotypic transformation of vascular smooth muscle cells (VSMCs) and made atherosclerosis plaques more stable.[62] METTL3 also promoted pri-miR-221/222 maturation in an m6A-dependent manner, enhancing VSMCs proliferation and neointimal hyperplasia.[63,64] In addition, METTL3 enhanced m6A modification of miR-29a-3p and increased miR-29a-3p expression resulting in reducing alveolar epithelial cell PANoptosis.[65] Similarly, Shao et al showed that METTL3-dependent modificated miRNA-29a inhibits atherosclerotic plaque formation by mediating macrophage autophagy through the PI3K/AKT/mTOR pathway.[66] Together, these studies highlight the therapeutic potential of METTL3 on miRNAs in treating atherosclerosis.

METTL14 is known to be a component of the m6A methyltransferase complex that mediates m6A modifications in mRNAs, and miRNAs have also been shown to be subject to such modifications.[67] METTL14 regulated m6A methylation-modified primary miR-19a, thereby promoting cardiovascular endothelial cell proliferation and invasion involved in angiogenesis.[67] Meanwhile, Wang et al explored that miR-99a-5p could target mTOR and subsequently

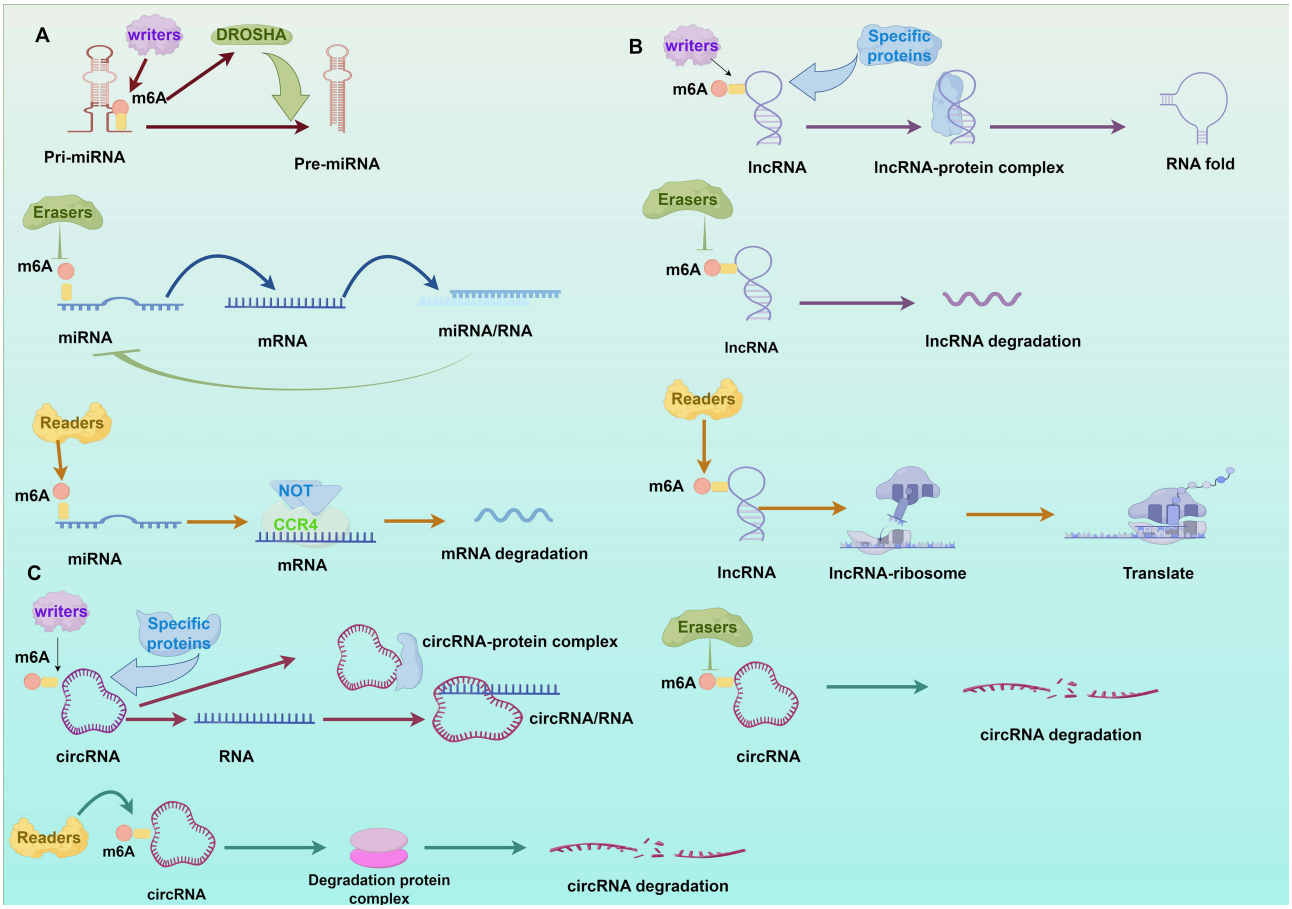

Figure 2 Overview of the interaction between m6A modification and ncRNAs in the context of atherosclerosis. This figure provides an illustrative overview of how m6A modification interacts with ncRNAs, including (**A**) miRNAs, (**B**) lncRNAs, and (**C**) circRNAs, to regulate gene expression and cellular functions in the context of atherosclerosis. The m6A modification machinery, comprising writers (enzymes that add m6A marks), erasers (enzymes that remove m6A marks), and readers (proteins that recognize m6A marks and regulate RNA fate), plays a crucial role in modulating the stability, localization, and function of ncRNAs. These interactions influence various biological processes implicated in the pathogenesis of atherosclerosis, such as lipid metabolism, inflammation, and endothelial function.

inhibiting NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome activation and promoting macrophage autophagy in atherosclerosis, resulting from the upregulation of METTL14 modulating m6A-mediated processing.[68,69]

As m6A eraser, FTO interacted with DGCR8 and modulated the processing of miR-515-5p in an m6A-dependent manner, resulting in reduced apoptosis and inhibited inflammation, which improves vascular endothelial cell injury in atherosclerosis.[70,71]

The m6A readers consist of the YTHD-containing protein family, which includes YTHDC1 in nucleus and YTHDC2, YTHDF1, YTHDF2, and YTHDF3 in the cytoplasm, and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs including IGF2BP1, IGF2BP2, and IGF2BP3).[72] The cytoplasmic m6A reader YTHDC2 interacted with PBRM1 can bind to HIF-1α mRNA for its translation, which upregulates miR-210 and downregulates miR-383 levels in lesional macrophages and inflammatory bone marrow-derived macrophages.[73,74] miR-210 enhances mitochondrial reactive oxygen species production, while miR-383 inhibits necroptosis by targeting genes involved in the DNA damage repair pathway.[74] The study suggests a new mechanism by which HIF-1α increases necroptosis through miRNA-mediated ATP depletion, thus potentially contributing to the development of atherosclerosis by necrotic core formation.[74] Another m6A readers, IGF2BP3 can stabilize lncRNA AGAP2-AS1 and promotes macrophage M2 polarization through the regulation of the miRNA-9-5p, which sponged with circ_0090231 in the injury of endothelial cells caused by ox-LDL.[75,76]

In summary, accumulating evidence suggests that m6A writers, specifically METTL3 and METTL14, play a crucial role in modulating m6A modification of miRNAs, thereby influencing the progression of atherosclerosis. METTL3, for

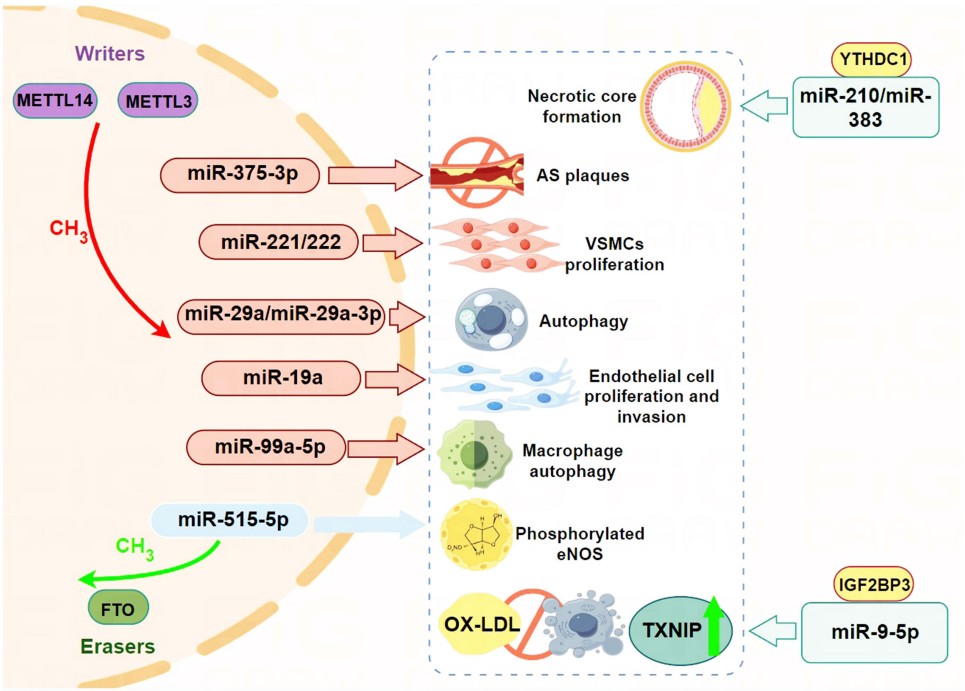

Figure 3 Mechanisms of m6A modification on miRNAs in atherosclerosis. m6A writers METTL3 regulates specific miRNAs to affect VSMCs transformation and plaque stability, while METTL14 mediates m6A modifications in miRNAs, impacting endothelial cell proliferation and invasion. Additionally, the m6A eraser FTO and readers like YTHDC2 and IGF2BP3 also regulate miRNA processing and expression, contributing to various cellular processes in atherosclerosis.

instance, regulates the expression of certain miRNAs, affecting vascular smooth muscle cell transformation and plaque stability in atherosclerosis. Similarly, METTL14 mediates m6A modifications in miRNAs, influencing cardiovascular endothelial cell proliferation and invasion. Additionally, the m6A eraser FTO interacts with DGCR8 to modulate miR-515-5p processing, reducing apoptosis and inflammation in atherosclerosis. Furthermore, m6A readers such as YTHDC2 and IGF2BP3 regulate miRNA expression and macrophage polarization, respectively (Figure 3 and Table 1). These findings highlight the therapeutic potential of targeting m6A modifications in treating atherosclerosis.

The Regulation of m6A Modification on lncRNAs in Atherosclerosis

m6A modifications facilitated by m6A writers have the ability to regulate the generation of lncRNAs, subsequently influencing their biological functions. Typically, METTL3 adjusts the stability of lncRNAs, which can contribute to the development of atherosclerosis. Firstly, The interaction between METTL3 and lncRNA H19 appears to be a key mechanism in hypoxic preconditioning, while the overexpression of lncRNA H19 and its regulation of signaling pathways are implicated in the development of atherosclerosis.[77,78] Secondly, METTL3 enhances the methylation of lncRNA GAS5, which promotes mitochondrial fission and upregulates the splicing factor SRSF10, impairing cardiac fibrosis and endothelial autophagy leading to atherogenesis for maintaining endothelial cell health and function.[79,80] Thirdly, METTL3 is found to methylate lncRNA MALAT1 through enhancing its stability and function, which leads to the upregulation of PTBP1/USP8/TAK1 involved in inflammatory signaling, ultimately triggers pyroptosis in endothelial cells and promotes the M1 polarization of macrophages.[81,82] Final, METTL3 modification mediates the alternative splicing of lncRNA ANRIL, whose stability and function can inhibit VSMCs phenotypic switching to prevent atherosclerotic plaque development.[83,84]

Research has demonstrated that METTL14, another m6A writer, has the capability to adjust the stability of lncRNAs through m6A-dependent mechanisms interacted with m6A readers, thereby impacting the biological role of lncRNAs in the context of atherosclerosis. For example, METTL14-enhanced m6A modifications downregulating lncRNA NEAT1 and then recognized by YTHDC1 induces endothelial pyroptosis by binding KLF4 to promote the transcriptional activation of the key pyroptotic protein NLRP3 in atherosclerosis.[85] METTL14 can also modulate m6A modification of lncRNA XIST and

Table 1 Roles of m6A Modification on miRNAs in Atherosclerosis

m6A Regulators	miRNAs	Mechanisms of m6A Modification	Functions in Atherosclerosis	Refs.
METTL3	miR-375-3p	METTL3-mediated m6A modification in promoting VSMCs phenotype transformation via the miR-375-3p/PDK1 axis.	This process makes AS plaques more vulnerable.	[62]
METTL3	miR-221/222	METTL3 promotes pri-miR-221/222 maturation in an m6A-dependent manner.	This process enhances VSMCs proliferation and neointimal hyperplasia.	[63,64]
METTL3	miR-29a/miR-29a-3p	METTL3-mediated modification of m6A increased the expression of miR-29a-3p and elevated miR-29a.	This process induces increased autophagy in atherosclerosis progression by down-regulating the PI3K/AKT/mTOR pathway.	[65,66]
METTL14	miR-19a	METTL14 regulates m6A methylation-modified primary miR-19a.	This process promotes cardiovascular endothelial cell proliferation and invasion.	[67]
METTL14	miR-99a-5p	METTL14 upregulates miR-99a-5p by modulating m6A-mediated processing, which targets mTOR, subsequently inhibiting NLRP3 inflammasome activation.	This process promotes macrophage autophagy in atherosclerosis.	[68,69]
FTO	miR-515-5p	Overexpression of FTO decreased the methylation level of m6A, and Silencing of FTO inhibited the expression of mir-515-5p leading to overexpression of ROCK1.	This process inhibits the expression of phosphorylated eNOS to antagonize ox-LDL-induced Human Umbilical Vein Endothelial Cells (HUVECs) injury.	[70,71]
YTHDF2	miR-210/miR-383	The cooperation between PBRM1 and YTHDF2 in controlling HIF-1α protein translation, which promotes inflammatory macrophage necroptosis through the regulation of miR-210 and miR-383.	This process increases necroptosis through miRNA-mediated ATP depletion, increasing atherosclerosis by necrotic core formation.	[73,74]
IGF2BP3	miR-9-5p	IIGF2BP3 stabilizes AGAP2-AS1 binding to miR-9-5p through m6a modification, activating PI3K/AKT signaling pathway and inducing macrophage M2 polarization.	This process increases TXNIP expression and inhibits apoptosis to alleviate ox-LDL-induced HUVECs injury.	[75,76]

promotes the degradation of lncRNA XIST by recognizing the m6A reader YTHDF2, inhibiting the proliferation and migration of VSMCs and protecting endothelial cells from ox-LDL in the development of atherosclerosis.[86–88]

Wilm's tumor-associated protein (WTAP), an adaptor protein of the m6A methyltransferase complex, can also participate in the m6A modification of lncRNAs.

WTAP-mediated m6A modification of lncRNA NORAD is recognized by YTHDF2 and induces the degradation of NORAD transcripts, which enhances the expression of inflammatory cytokines, adhesion molecules, and apoptosis-related proteins in vascular endothelial cells treated with ox-LDL.[89,90]

Recent studies have indicated that m6A erasers hold significant importance in facilitating the m6A modification of lncRNAs, thereby controlling their biological activities. ALKBH5, an m6A demethylase, interacts with lncRNA PVT1 and mediates its demethylation, thereby promoting atherosclerosis progression via the miR-106b-5p/ACSL4 axis along with increasing lipid deposition and atherosclerotic plaque number.[91,92]

Another demethylase of m6A, ALKBH1, is also involved in regulating the ox-LDL-increased level of hypoxia-response gene lncRNA MIAT controlling advanced atherosclerotic lesion formation and plaque destabilization in the pathogenesis of atherosclerosis.[93,94]

Here, we delved into the significant role of m6A modifications in regulating the stability and functions of lncRNAs, particularly in relation to atherosclerosis. It highlights how m6A writer METTL3, adjusts the stability of lncRNAs like H19, GAS5, and MALAT1, affecting biological processes such as blood cholesterol synthesis, cardiac fibrosis, and inflammation, all of which contribute to atherogenesis. Furthermore, we discussed the regulatory roles of other m6A writers, METTL14 and WTAP, and m6A erasers, ALKBH5 and ALKBH1, in modulating lncRNAs and their impact on

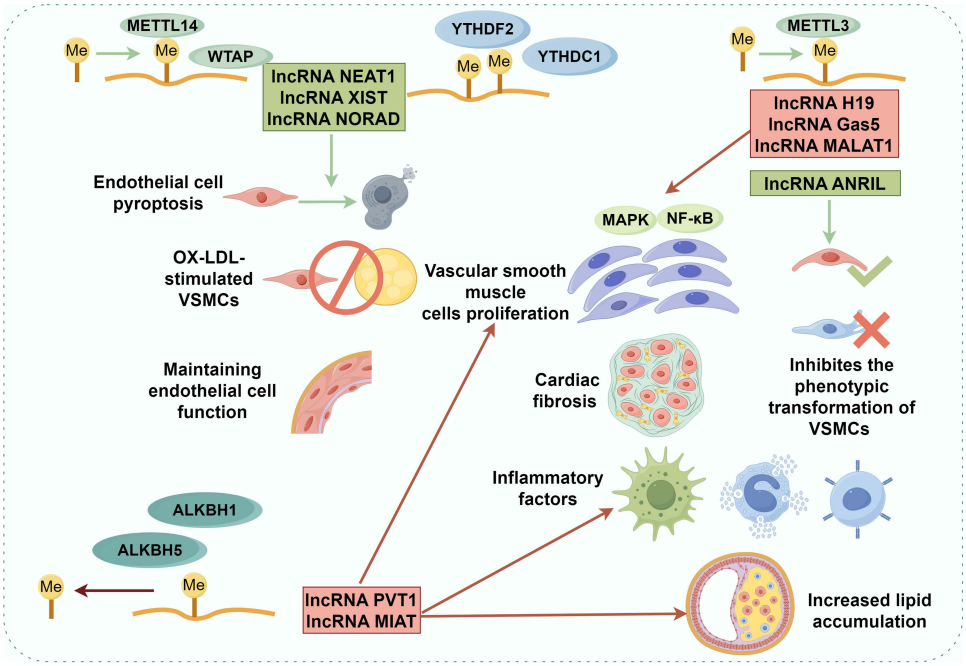

Figure 4 Mechanisms of m6A modification on lncRNAs in atherosclerosis. m6A writers, such as METTL3 and METTL14, along with the adaptor protein WTAP, can adjust the stability of lncRNAs through m6A-dependent mechanisms, impacting various biological processes that contribute to atherogenesis. Additionally, m6A erasers like ALKBH5 and ALKBH1 play significant roles in facilitating m6A modification of lncRNAs, thereby controlling their biological activities and influencing atherosclerosis development.

atherosclerosis development (Figure 4 and Table 2). The intricate interplay between these factors sheds light on the complex molecular mechanisms underlying the disease.

The Regulation of m6A Modification on circRNAs in Atherosclerosis

circRNAs, characterized by their covalently closed single-stranded structures, typically originate from the exons of protein-coding genes, although they can also emerge from intronic, intergenic, untranslated, and non-coding regions. The formation of CircRNA primarily occurs through spliceosome-mediated reverse splicing of precursor mRNA (pre-mRNA) , linking the upstream 3 significant importance in regulating the biosynthesis and function of circRNAs, thereby

Table 2 Roles of m6A Modification on lncRNAs in Atherosclerosis

m6A Regulators	lncRNAs	Mechanisms of m6A Modification	Functions in Atherosclerosis	Refs.
METTL3	lncRNA H19	METTL3 can directly bind to lncRNA H19 and up-regulate its expression, which leads to the increase of p38 and p65, thereby activating the MAPK and NF-κB signaling pathways in HUVECs and VSMCs, respectively.	This process promotes the proliferation of vascular smooth muscle cells and suppresses apoptosis by regulating the MAPK and NF-κB signaling pathways.	[77,78]
METTL3	lncRNA Gas5	METTL3 enhances the methylation of lncRNA GAS5 leading to mitochondrial fission, and lncRNA GAS5 upregulates SRSF10 impairing endothelial autophagy for maintaining endothelial cell health and function.	This process is associated with cardiac fibrosis, characterized by the accumulation of fibrous tissue in the cardiovascular system, affecting endothelial autophagy and atherogenesis.	[79,80]

(*Continued*)

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Table 2 (Continued).

m6A Regulators	lncRNAs	Mechanisms of m6A Modification	Functions in Atherosclerosis	Refs.
METTL3	lncRNA MALAT1	METTL3 increases the level of lnc MALAT1 through m6a modification, and initiates pyroptosis and inflammation of macrophages and endothelial cells via PTBP1/USP8/TAK1 pathway and miR-30c-5p/Cx43 axis, respectively.	This process penetrates the integrity of the endothelial barrier, increases vascular permeability, and releases a large number of inflammatory factors, which further promoting the formation and development of atherosclerosis.	[81,82]
METTL3	lncRNA ANRIL	METTL3 promotes the increase of m6A modification level in lncRNA ANRIL, in favour of its stability and function.	This process inhibites the phenotypic transformation of VSMCs to prevent atherosclerosis development.	[83,84]
METTL14/ YTHDC1	lncRNA NEAT1	METTL14 modified lncRNA NEAT1 m6A site, and was recognized by YTHDC1 to promote lncRNA NEAT1 expression, and then regulated NLRP3 transcription by binding with KLF4.	This process increase the pyroptosis level of endothelial cells in atherosclerosis.	[85]
METTL14/ YTHDF2	lncRNA XIST	METTL14 enhanced the m6A level of lncRNA XIST and induced a significant decrease in its expression level. Meanwhile, m6A methylated lncRNA XIST was recognized by m6A reader YTHDF2 and mediated its degradation.	This process inhibits the proliferation, migration, and invasion of OX-LDL-stimulated VSMCs, as well as the apoptosis, inflammatory response, and oxidative stimulation of OX-LDL-induced HUVECs, thereby slowing the progression of atherosclerosis.	[86–88]
WTAP/ YTHDF2	lncRNA NORAD	Increased WTAP promotes interactions between lncRNA NORAD and methyltransferase complexes, including METTL3 and METTL14, and thenincreased m6a modification levels down-regulates the stability of NORAD transcripts.	This process plays a protective role in maintaining endothelial cell function and inhibiting atherosclerosis progression.	[89,90]
ALKBH5	lncRNA PVT1	lncRNA PVT1 promotes atherosclerosis progression via the miR-106b-5p/ACSL4 axis through its interaction with ALKBH5 and m6A demethylation.	This process results in increased lipid accumulation, more atherosclerotic plaques, and larger plaque size in animal models, suggesting a pivotal role in the development of atherosclerosis.	[91,92]
ALKBH1	lncRNA MIAT	ALKBH1-mediated m6a demethylation promotes HIF1α binding to MIAT and transcriptional up-regulation of its expression.	This process in advanced atherosclerosis, controls the proliferation, apoptosis and phenotype transformation of smooth muscle cells, as well as proinflammatory properties of macrophages.	[93,94]

augmenting biological processes associated with atherosclerosis. Guo et al demonstrated that Interferon Regulatory Factor-1 (IRF-1) effectively macrophage pyroptosis by modulating the METTL3-regulated m6A modification of circ_0029589 involved in the development and progression of acute coronary syndrome (ACS) and atherosclerosis.[95] Furthermore, DEAD-box helicase 5 (DDX5) recruits METTL3 to promote the m6A modification of circHIPK3 leading to the inactivation of the Wnt signaling pathway significantly contributes to the promotion of aortic valve calcification.[96]

YTH domain-containing proteins may play a critical role in mediating m6A modification of circRNAs and the progression of atherosclerosis. YTHDF2 promotes the degradation of circSQSTM1 upon recognizing its m6A modification sites, indirectly regulating various biological functions downstream of circSQSTM1, such as Sirt1 and FOXO1 signaling pathways.[97] By influencing the levels of circSQSTM1, YTHDF2 can modulate endothelial cell functions, including inflammation, oxidative stress, and autophagy in atherosclerosis.[97] In addition, YTHDF2 promotes the

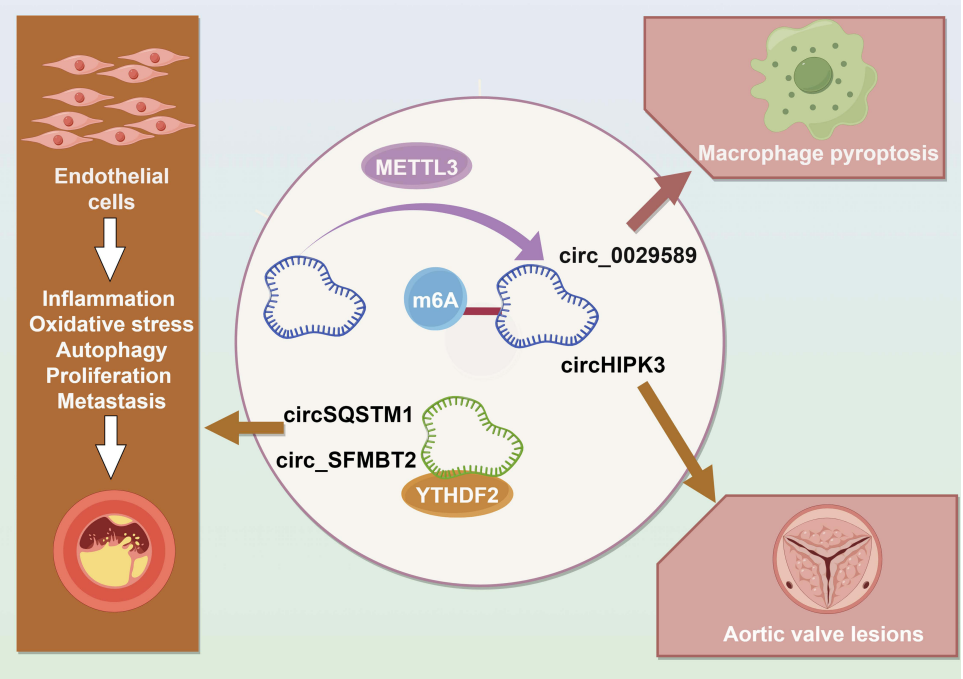

Figure 5 Mechanisms of m6A modification on circRNAs in atherosclerosis. m6A modifications, facilitated by m6A writers such as IRF-1 and DDX5, regulate the biosynthesis and function of circRNAs, thereby influencing biological processes associated with atherosclerosis. Specifically, IRF-1 regulates the m6A modification of circ_0029589 involved in acute coronary syndrome and atherosclerosis, while DDX5 affects the Wnt signaling pathway and aortic valve calcification through the m6A modification of circHIPK3. Additionally, the m6A eraser YTHDF2 mediates the m6A modification of circRNAs, regulating their stability and downstream biological functions, such as inflammation, oxidative stress, autophagy, cell proliferation, and metastasis.

degradation of circ_SFMBT2 in an m6A-dependent manner, thereby regulating its stability.[98] By mediating the degradation of circRNAs such as circ_SFMBT2, YTHDF2 also plays a pivotal role in regulating downstream signaling pathways and biological processes, including cell proliferation, metastasis, and inflammation, highlighting the importance of circRNAs in atherosclerosis and their potential as biomarkers and therapeutic targets.[99,100]

In summary, circRNAs with their unique covalently closed single-stranded structures, originate primarily from exons of protein-coding genes but can also emerge from other regions. Their formation relies on spliceosome-mediated reverse splicing of pre-mRNA (Figure 5 and Table 3). m6A modifications, facilitated by m6A writers, play a crucial role in

Table 3 Roles of m6A Modification on circRNAs in Atherosclerosis

m6A Regulators	circRNAs	Mechanisms of m6A Modification	Functions in Atherosclerosis	Refs.
METTL3	circ_0029589	The overexpression of IRF-1 was found to suppress the RNA expression of circ_0029589 via by modulating the m6A modification of METTL3 in human macrophages.	This process induces macrophage pyroptosis in the development of ACS and atherosclerosis.	[95]
METTL3	circHIPK3	circHIPK3 binds to DDX5 to drive target m6A modification by recruiting METTL3, modulating Wnt/β-catenin pathway to synergistically.	This process significantly contributes to the promotion aortic valve lesions in the progression of cardiovascular diseases.	[96]
YTHDF2	circSQSTM1	YTHDF2 enhances the degradation of circSQSTM1 in an m6A-dependent manner.	This process regulates multiple biological functions in endothelial cells, including inflammation, oxidative stress, and autophagy.	[97]
YTHDF2	Circ_SFMBT2	YTHDF2 promotes the degradation of circ_SFMBT2 in an m6A-dependent manner, thereby regulating its stability.	This process regulates circRNAs regulate downstream signaling pathways and biological processes in atherosclerosis, including cell proliferation, metastasis, and inflammation.	[98–100]

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regulating circRNA biosynthesis and function, thereby influencing biological processes linked to atherosclerosis. Specifically, IRF-1 regulates the m6A modification of circ_0029589 involved in acute coronary syndrome and atherosclerosis, while DDX5 promotes the m6A modification of circHIPK3, affecting the Wnt signaling pathway and aortic valve calcification. As m6A eraser, YTHDF2 mediates m6A modification of circRNAs, regulating their stability and downstream biological functions. For instance, YTHDF2 promotes the degradation of circSQSTM1 and circ_SFMBT2, modulating various signaling pathways and biological processes including inflammation, oxidative stress, autophagy, cell proliferation, and metastasis. This highlights the significance of circRNAs in atherosclerosis and their potential as biomarkers and therapeutic targets.

As discussed above, modulating the m6A modification machinery represents a novel therapeutic approach for atherosclerosis, by targeting specific miRNAs, lncRNAs, and circRNAs to stabilize plaques, minimize inflammation, and enhance endothelial function. Firstly, targeting METTL3 and METTL14 through miRNAs modulation could potentially stabilize plaques, alleviate inflammation, and enhance endothelial cell health, presenting novel therapeutic approaches for atherosclerosis. Secondly, adjusting lncRNAs through m6A writers and erasers could target specific molecular pathways involved in atherosclerosis, offering new treatment options. Thirdly, circRNAs, as potential biomarkers and therapeutic targets, can be modulated through m6A modifications to influence signaling pathways involved in atherosclerosis, presenting new diagnostic and treatment options. In short, this understanding facilitates the development of personalized therapies tailored to individual patients' molecular profiles, offering more targeted and effective treatment strategies for atherosclerosis.

Roles of ncRNA in Regulation of m6A Modification in Atherosclerosis

As mentioned above, m6A regulators, including m6A writers, erasers, and readers, have the ability to adjust the m6A modification of ncRNAs biogenesis, stability, and translational efficiency, thereby significantly influencing atherosclerosis development. By targeting or influencing these m6A regulators conversely, ncRNAs exert a crucial role in controlling the advancement and progression of atherosclerosis. Namely, ncRNAs can also regulate m6A modification by targeting m6A modification enzymes. For instance, miR-33a-5p inhibits ox-LDL-stimulated vascular smooth muscle cells (VSMCs) calcification by targeting METTL3.[101] Furthermore, miR-145-5p downregulates YTHDF2, an m6A reader, leading to decreased degradation of SIRT3 mRNA and improved endothelial cell survival.[102] In contrast, miR-192-5p aggravates atherosclerosis by inhibiting FTO, an m6A eraser.[103]

Regulatory Effects of miRNAs on m6A Modification in Atherosclerosis

miRNAs are small ncRNAs that post-transcriptionally regulate gene expression. Several miRNAs have been implicated in atherosclerosis by targeting genes involved in inflammation, lipid metabolism, and endothelial dysfunction. Simultaneously, miRNAs have the capability to specifically bind to m6A writers, erasers and readers, resulting in decreased mRNA and protein expression levels that contribute to atherosclerosis development.

Multiple studies have shown that various miRNAs can directly target the m6A writer METTL3 and reduce its mRNA and protein expression levels, thereby modulating its expression and activity. For instance, Zhang M et al showed that miR-186-5p sponged by SNHG3, a long non-coding RNA, upregulated METTL3 leading to increased m6A levels.[104] Similarly, Wu H et al reported that miR-338-5p could directly target METTL3, thus suppressing the m6A/c-Myc pathway.[105] Other studies revealed that miR-30c-5p, miR-33a-3p and miR-33a directly targeted METTL3 mRNA in regulating KRAS or AREG-mediated biological processes, respectively.[106–108] Furthermore, several papers investigated that miR-212-5p, miR-373 and miR-1269b inhibited cells growth and metastasis by downregulating METTL3 expression.[109–111] Additionally, Wang A et al showed that MEG3 induces microRNA-493-5p expression by downregulating the METTL3/MYC axis, highlighting the importance of this regulatory network in METTL3-mediated biological processes.[112] Taken together, these studies underscore the complex regulatory network between miRNAs and METTL3, and METTL3 triggers atherosclerotic reactions by elevating NLRP1 levels and reducing KLF4 levels, leads to an increase in the expression of autophagy-related proteins ATG5 and ATG7, which subsequently enhances the formation of autophagosomes.[59,113] Lastly, The downregulation of METTL3 accelerates the degradation of phosphatidylinositol 3-kinase (PI3K) mRNA, effectively shutting down the PI3K/AKT signaling pathway and thus suppressing the phenotypic transformation of VSMC.[114] Future research may focus on further elucidating the molecular

mechanisms underlying these interactions and exploring the potential of targeting specific miRNA/METTL3 axes for atherosclerosis therapy.

miRNAs can also modulate other types of m6A writer regulating atherosclerosis progression. Recent studies have illuminated that miR-4729 targeted METTL14, affecting its expression and consequently, the m6A modification of TIE1 mRNA.[115] Meanwhile, miR-26a-5p targeted METTL14, which in turn regulates NLRP3, a key component of the inflammasome pathway involved in pyroptosis, a form of programmed cell death.[116] Noteworthily, METTL14 exhibits marked upregulation in atherosclerosis models, both in vivo and in vitro, as well as in clinical atherosclerosis cases. This upregulation plays a pivotal role in promoting vascular endothelial cell proliferation and inflammatory responses, while also facilitating smooth muscle cell calcification, proliferation, and migration.[117–121] Furthermore, miR-144-3p, miR-139-5p, miR-455-3p, miR-29a and miR-501-3p can also directly target another type of m6A writer, WTAP, modulating its expression at mRNA level and consequently affecting Cellular replication, movement, infiltration, and colony establishment.[121–125] Through m6A modification, WTAP enhances p16 expression, thereby suppressing the activity, proliferative capacity, and migratory potential of VSMCs.[126] The increased expression of WTAP primarily relies on the activation of NF-κB p65, and WTAP positively modulates the inflammatory response.[127]

miRNAs play important roles in multiple biological processes by targeting and regulating m6A erasers. Firstly, Yang W et al found that miR-155 can regulate m6A levels and cellular processes by targeting FTO, significantly impacting on cell proliferation and migration.[128] Secondly, the research by Du P et al focused on the interaction between miR-27a-3p and FTO, especially under hypoxic conditions.[129] Thirdly, Zhang C et al explored the role of miRNA-192-5p in downregulating the expression of FTO, thereby aggravating kidney damage.[103] In addition, the research by Zhang X et al has shown that miR-22-3p from extracellular vesicles of bone marrow mesenchymal stem cells can promote osteogenic differentiation by inhibiting FTO.[130] Apart from the above studies, several other papers have explored the regulatory effects of other miRNAs on FTO. For example, Gu C et al found that miR-192 can attenuate high glucose-induced pyroptosis in retinal pigment epithelial cells.[131] Meanwhile, Shao F et al discovered the targeting effect of miR-33 expressed from an SREBF2 intron, interacted directly with predicted target sites in the FTO 3 'UTR.[132] Furthermore, studies by Hu F and Li Y et al revealed the important roles of miR-495 and miR-149-3p in regulating FTO and related biological processes, respectively.[133,134] In summary, these research findings collectively uncover the diverse regulatory mechanisms of different miRNAs on FTO, which could slow down lipid influx in macrophages by suppressing PPARγ and facilitate cholesterol efflux via AMPK phosphorylation, thus impeding the formation of foam cells and atherosclerosis.[60] Relying on AMPK activity, FTO boosts ABCA1 expression, which blocks lipid uptake, promotes cholesterol efflux, discourages foam cell creation, and halts the advancement of atherosclerosis.[60] Meanwhile, FTO notably decreased the concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDLC) and adipocyte apoptosis by activating the JAK2/STAT3 signaling pathway, while enhancing the development of atherosclerotic plaque.[135,136]

Increasing evidence has revealed that miRNAs can also directly target m6A readers, such as the YTH domain family of proteins. For instance, PLAGL2 promotes the expression of Snail, a key regulator of epithelial-mesenchymal transition (EMT), via the upregulation of lncRNA UCA1, in turn sponging miR-145-5p and then leading to the derepression of YTHDF1, which can bind to m6A methylated BRAF mRNA and promote its translation in macrophages increases with the progression of atherosclerosis.[137,138] At the same time, miR-3436 and miR-376c as the negative regulator of YTHDF1, demonstrated their direct binding to the 3'UTR of YTHDF1 mRNA.[139,140] Furthermore, Several studies have demonstrated the diverse ways in miR-495, miR-6125, miR-493-3p, miR-145 by modulating the expression or activity of YTHDF2, a key player in m6A-dependent mRNA degradation, respectively.[102,141–143] The downregulation of YTHDF2 prevents the degradation of SIRT3 mRNA, ultimately inhibiting endothelial cell apoptosis and mitigating the rapid progression of atherosclerosis associated with diabetes.[144] Similarly, miR-448 is found to directly target YTHDF3, inducing apoptosis of vascular endothelial cells through METTL3.[145,146] By binding to the 3'-UTR of YTHDF3 mRNA, miR-448 suppresses its expression, thereby modulating its downstream effects.[145]

miRNAs can also target other m6A readers by interacting with respective binding site at 3′-UTR. For example, several studies demonstrated that the diverse regulatory roles of miRNAs in modulating IGF2BP1 expression and function, such as miR-193b-3p, miR-4500, miR-670-3p, miR-29, miR-196b, miR-98-5p and miR-140-5p.[147–153] By mediating the JAK2/STAT3 pathway, IGF2BP1 plays a critical role in the progression of atherosclerosis, which can be inhibited by knocking down METTL3.[154,155] Meanwhile, IGF2BP1 silencing prevents ox-LDL-induced lipid accumulation and

inflammation by reducing RUNX1 expression and promoting macrophage autophagy.[155] In other studies, miR-555 and miR-34a inhibits the expression of heterogeneous nuclear ribonucleoprotein C1/C2 (hnRNP-C) and leucine-rich PPR-motif containing (LRPPRC), as novel m6A readers.[156,157] Wherein the depletion of LRPPRC can enhance macrophage autophagy, thereby suppressing the development of foam cells.[157] In atherosclerotic arteries, hnRNP-C exhibits pronounced expression not just in intimal cells but also in the medial layer's smooth muscle cells, indicating its potential as an indicator of vascular cell activation.[158]

In brief, miRNAs have the ability to impact the m6A modification of various RNAs by interacting with m6A writers, erasers, and readers, subsequently altering gene expression or protein functionality (Table 4). By adjusting the regulatory proteins involved in m6A modification, miRNAs can influence this process and engage in multiple physiological and pathological events. miRNAs can bind to the 3′-UTR of the downstream target mRNA of m6A regulators through complementary base pairing, resulting in the breakdown of the target mRNA or hindrance of protein translation. Conversely, miRNAs can adjust m6A levels within their intended transcripts. Given the significant role of miRNAs in

Table 4 Roles of miRNAs in Regulation of m6A Modification in Atherosclerosis

miRNAs	m6A Regulators	Mechanisms of nc RNAs Regulation	Functions in Atherosclerosis	Refs.
miR-33a-5p	METTL3	Overexpression of miR-33a-5p can downregulate METTTL3.	Inhibition of ox-LDL-stimulated VSMCs calcification.	[101]
miR-186-5p	METTL3	miR-186-5p binds to the 3'UTR of METTL3 to inhibit its expression.		[104–112]
miR-338-5p	METTL3	miR-338-5p binding to METTL3 inhibited the expression of METTL3.	(1) METTL3 causes atherosclerotic responses by increasing NLRP1 and decreasing KLF4, and Mettl3 knockout inhibits the formation of atherosclerotic lesions in mouse models.[59]	
miR-30c-5p	METTL3	miR-30c-5p can target and bind METTL3 to inhibit its expression.		
miR-33a-3p	METTL3	miR-33a-3p can target METTL3 and inhibit its expression.		
miR-33a	METTL3	miR-33a can directly target the 3 'UTR of METTL3 mRNA to inhibit the expression of METTL3.	(2) Overexpression of METTL3 promotes the expression of autophagy associated 5 (ATG5) and ATG7 proteins, thereby promoting the formation of autophagosomes, thereby inhibiting the proliferation, migration and transition from systolic phenotype to synthetic phenotype of VSMC.[113]	
miR-212-5p	METTL3	A binding site has been identified between miR-212-5p and the 3'-UTR of METTL3 mRNA, whereby miR-212-5p specifically inhibits the expression of METTL3.		
miR-373	METTL3	METTL3 is a direct target of miR-373, whose upregulation leading to a substantial decrease in both METTL3 mRNA and protein levels.	(3) METTL3 knockdown promotes phosphatidylinositol 3-kinase (Pi3k) mRNA decay, thereby inactivating PI3K/AKT signaling to inhibit phenotypic transformation of VSMC.[114]	
miR-1269b	METTL3	miR-1269b can target METTL3 mRNA 3′-UTR and negatively regulate the expression of METTL3.		
miR-493-5p	METTL3	miR-493-5p targets METTL3 and inhibits METTL3 expression.		
miR-4729	METTL14	Overexpression of miR-4729 can significantly inhibit the expression of METTL14 in vascular endothelial cells.	METTL14 is significantly upregulated in both in vivo and in vitro models and clinical cases of atherosclerosis and contributes to vascular endothelial cell proliferation and inflammatory response as well as smooth muscle cell calcification, proliferation, and migration.[117–121]	[115,116]
miR-26a-5p	METTL14	miR-26a-5p weakened the expression of mRNA methyltransferase METTL14.		

(*Continued*)

Table 4 (Continued).

miRNAs	m6A Regulators	Mechanisms of nc RNAs Regulation	Functions in Atherosclerosis	Refs.
miR-144-3p	WTAP	Following the overexpression of miR-144-3p, there was a noticeable reduction in both the mRNA and protein levels of WTAP.	(1)WTAP positively regulates p16 expression through m6a modification to inhibit the activity, proliferation and migration potential of VSMCS.[126]	[121–125]
miR-139-5p	WTAP	miR-139-5p regulates WTAP expression by targeting the negative 3 '-UTR direction of WTAP.		
miR-455-3p	WTAP	WTAP is the target of miR-455-3p, and overexpression of miR-455-3p leads to decreased WTAP level.	(2) The upregulation of WTAP expression is mainly dependent on the activation of NF-κB p65, and WTAP positively regulates the pro-inflammatory response.[127]	
miR-29a	WTAP	Overexpression of miR-29a inhibits WTAP expression by down-regulating QKI-6.		
miR-501-3p	WTAP	miR-501-3p directly binds to the predicted WTAP2 binding site and negatively regulates its expression.		
miR-155	FTO	miR-155 directly targets FTO to negatively regulate its expression.	(1) FTO reduces adipocyte apoptosis by activating the JAK2/STAT3 signaling pathway.[135]	[103,128–134]
miR-27a-3p	FTO	miR-27a-3p suppresses FTO expression by directly binding to it.	(2) FTO significantly reduced the levels of TC [cholesterol (CHOL)] and low density lipoprotein cholesterol (LDLC), and FTO improved the formation of atherosclerotic lesions.[136]	
miR-192-5p	FTO	miR-192-5p directly targets FTO and inhibits its expression.		
miR-22-3p	FTO	miR-22-3p targets FTO and negatively regulates its expression.		
miR-192	FTO	miR-192 negatively regulates FTO expression.	(3) FTO elevates ABCA1 expression in a manner reliant on AMPK activity, thereby inhibiting lipid intake, augmenting cholesterol efflux, suppressing foam cell formation, and hindering the progression of atherosclerosis.[60]	
miR-33	FTO	miR-33 can inhibit FTO expression by interacting directly with predicted target sites in the FTO 3 'UTR.		
miR-495	FTO	miR-495 can promote the transformation of macrophages into M1-type proinflammatory macrophages by inhibiting the expression of its target gene, FTO.	(4) FTO inhibits macrophage lipid influx by downregulating PPARγ and accelerates cholesterol efflux through AMPK phosphorylation, thereby impeding the formation of foam cells and atherosclerosis.[60]	
miR-149-3p	FTO	Overexpression of miR-149-3p inhibits the expression of the FTOby binding to the 3'UTR of its mRNA.		
miR-448	YTHDF3	miR-448 targets YTHDF3 and inhibits its mRNA levels.	HCMV promotes increased MCU translation and induces apoptosis of vascular endothelial cells through METTL3 and YTHDF3-dependent m6A methylation mechanism.[146]	[145,146]
miR-495	YTHDF2	miR-495 can target YTHDF2 and inhibit its expression.	Downregulating YTHDF2 inhibits the degradation of SIRT3 mRNA, thereby suppressing endothelial cell apoptosis and improving the accelerated development of atherosclerosis in diabetes.[144]	[102,141–143]
miR-6125	YTHDF2	MiR-6125 targets the 3'-UTR of YTHDF2 and downregulates its expression.		
miR-493-3p	YTHDF2	Overexpression of miR-493-3p down-regulates the expression of YTHDF2.		
miR-145	YTHDF2	miR-145 directly targets the 3′-UTR of YTHDF2 mRNA, enabling downregulation of YTHDF2 expression at both the mRNA and protein levels.		

(*Continued*)

Table 4 (Continued).

miRNAs	m6A Regulators	Mechanisms of nc RNAs Regulation	Functions in Atherosclerosis	Refs.
miR-145-5p	YTHDF1	Overexpression of miR-145-5p significantly decreased the expression of YTHDF1 gene and protein.	YTHDF1 can bind to m6A methylated BRAF mRNA and promote its translation in macrophages increases with the progression of atherosclerosis.[138]	[137–140]
miR-346	YTHDF1	YTHDF1 is negatively regulated by miR-346.		
miR-376c	YTHDF1	miR-376c negatively regulates YTHDF1 expression.		
miR-193b-3p	IGF2BP1	miR-193b-3p targets and induces IGF2BP1 expression.	(1) METTL3 knockdown inhibits the JAK2/STAT3 pathway via IGF2BP1, preventing the progression of atherosclerosis.[154]	[147–153]
miR-4500	IGF2BP1	Inhibition of miR-4500 increased IGF2BP1 expression.		
miR-670-3p	IGF2BP1	miR-670-3p regulates the expression of IGF2BP1 and influences the expression level of m6A.		
miR-29	IGF2BP1	IGF2BP1 is negatively regulated by miR-29 at the post-transcriptional level.	(2) Silencing IGF2BP1 inhibits ox-LDL-induced lipid accumulation and inflammation by reducing RUNX1 expression and promoting macrophage autophagy.[155]	
miR-196b	IGF2BP1	miR-196b directly targets the 3 'UTR of IGF2BP1 mRNA, causing its downregulated expression.		
miR-98-5p	IGF2BP1	The expression of IGF2BP1 protein is negatively regulated by miR-98-5p.		
miR-140-5p	IGF2BP1	miR-140-5p directly targets and down-regulates IGF2BP1.		
miR-555	hnRNP-C	hnRNP-C expression is negatively regulated by miR-555	In arteries with atherosclerotic lesions, hnRNP-C is strongly expressed not only in intimal cells but also in medial smooth muscle cells, suggesting that hnRNP-C may serve as a marker of vascular cell activation.[158]	[156]
miR-34a	LRPPRC	miR-34a inhibits the expression of LRPPRC by directly binding to its 3'-UTR.	LRPPRC knockdown can improve macrophage autophagy to inhibit the formation of foam cells.[157]	[157]

managing m6A modifications in atherosclerosis, further investigation into miRNA-regulated m6A modifications is necessary.

Regulatory Effects of lncRNAs on m6A Modification in Atherosclerosis

lncRNAs are longer than 200 nucleotides and regulate gene expression at multiple levels. Several lncRNAs have been shown to modulate atherosclerosis by interacting with m6A-modified transcripts. For instance, lncRNA H19 promotes atherosclerosis by regulating MAPK and NF-κB signaling pathways, which are partially mediated by m6A modifications.[78] Similarly, MALAT1, an m6A-modified lncRNA, contributes to macrophage pyroptosis and atherosclerosis through the METTL3/MALAT1/PTBP1 axis.[82]

Accumulating evidence has revealed that lncRNAs participate in m6A modification related biological processes by regulating m6A writers METTL3, METTL14 and WTAP. For instance, lncRNA BLACAT2 could increase the expression of METTL3 by sponging miR-193b-5p, which consequently stimulates cell growth, motility and infiltration.[159] lncRNA RASAL2-AS1 selectively interacts with the METTL14 protein, thereby enhancing the methylation status and stability of m6A.[160] By sponging miR-299-3p and miR-433-3p respectively, the lncRNA DLGAP1-AS1 and PCGEM1 stabilizes WTAP leading to increased m6A methylation levels.[161,162] Furthermore, an m6A-modified lncRNA, LINC00667, interacts with KIAA1429, an m6A methyltransferase complex subunit, and forms a positive feedback loop.[163]

Increasing evidence suggests that lncRNAs play critical roles in modulating m6A erasers and readers. The lncRNA MIAT and JPX modulate the function of YTHDF2, either by altering its binding to m6A-modified RNAs or by affecting its stability.[164,165] These interactions have significant impacts on gene expression patterns and cellular phenotypes, including cardiac hypertrophy. These findings suggest that targeting lncRNA-YTHDF2 interactions could provide novel therapeutic strategies for treating various diseases. Similarly, lncRNA AC105942.1 downregulates the expression of m6A reader hnRNPA2/B1 in VSMCs.[166] This downregulation is achieved through a direct interaction between AC105942.1 and hnRNPA2/B1, which disrupts the normal function of hnRNPA2/B1 in promoting cell proliferation. As a result, the proliferative capacity of VSMCs is attenuated, suggesting a potential role for AC105942.1 in regulating vascular homeostasis and preventing excessive cell growth.[166]

In brief, lncRNAs play a crucial role in regulating m6A modifications and their associated biological functions by specifically targeting m6A writers, erasers, and readers (Table 5). These lncRNAs have the capability to control m6A regulatory proteins and their corresponding target mRNAs by recruiting m6A writers and readers. Conversely, lncRNAs can also exert an indirect regulatory effect on m6A modifications, thereby influencing the stability of downstream genes.

Regulatory Effects of circRNAs on m6A Modification in Atherosclerosis

circRNAs are covalently closed continuous RNA molecules generated by back-splicing. They exhibit high stability and tissue-specific expression patterns. circRNAs have emerged as regulators of atherosclerosis through their interactions with m6A modification enzymes and ncRNAs. For instance, circSQSTM1 protects endothelial function in atherosclerosis by inhibiting inflammation and oxidative stress.[97] circRNA_0029589 modulates macrophage pyroptosis in acute coronary syndrome patients through m6A modifications.[95] Similarly, circPTPRA, a circRNA, blocks IGF2BP1-mediated recognition of m6A-modified mRNAs.[167]

Table 5 Roles of lncRNAs in Regulation of m6A Modification in Atherosclerosis

lncRAs	m6A Regulators	Mechanisms of nc RNAs Regulation	Functions in Atherosclerosis	Refs.
lncRNA BLACAT2	METTL3	BLACAT2 sponges miR-193b-5p and positively regulates METTL3.	Cell growth, motility and infiltration	[159]
lncRNA RASAL2-AS1	METTL14	lncRNA RASAL2-AS1 specifically binds to METTL14 protein and promotes the methylation level and stability of m6A.	Enhancement of the methylation status and stability of m6A	[160]
lncRNA DLGAP1-AS1	WTAP	DLGAP1-AS1 acts as a sponge to bind miR-299-3p through 3′-UTR, thereby alleviating the inhibition of WTAP expression and up-regulating the expression of WTAP.	Increased m6A methylation levels	[161,162]
lncRNA PCGEM1	WTAP	PCGEM1 acts as a miR-433-3p sponge to positively regulate WTAP.		
LINC00667	KIAA1429	LINC00667 positively regulates KIAA1429 by sponging miR-556-5p.	Overexpression of KIAA1429 inhibited the proliferation/migration of OX-LDL-treated HUVECs, while knockdown of KIAA1429 up-regulated the proliferation and migration of HUVECs[184].	[163]
lncRNA MIAT	YTHDF2	lncRNA MIAT interacts with YTHDF2, increasing its expression.	Impacts on gene expression patterns and cellular phenotypes, including cardiac hypertrophy	[164,165]
lncRNA JPX	YTHDF2	The interaction between lncRNA JPX and YTHDF2 leads to the destabilization of YTHDF2, through involved in mRNA stability and translation.		
lncRNA AC105942.1	hnRNPA2/B1	lncRNA AC105942.1 can down-regulate the expression of hnRNPA2/B1, thereby regulating the levels of CDK4 and p27.	lncRNA AC105942.1 down-regulates hnRNPA2B1 to prevent atherosclerosis by inhibiting VSMCs proliferation.[166]	[166]

Some circRNAs target m6A writers and regulate the expression of their downstream target genes via m6A modification. By sponging miR-590-5p, circPUM1 indirectly stabilizes METTL3, leading to increased m6A methylation and subsequent changes in gene expression that favor cell growth and glycolysis.[168] Induced by EIF4A3, circ_0001187 promotes the ubiquitin-proteasomal degradation of METTL3.[169] circVMP1 targets the miR-524-5p-METTL3/SOX2 axis, upregulating METTL3 and SOX2 expression by sponging miR-524-5p.[170] circ_0000523 sponges miR-let-7b, leading to the upregulation of METTL3 and subsequent changes in cell proliferation, apoptosis, and metastasis.[171] circ0008399 interacts with another m6A methyltransferase WTAP, leading to an increase in m6A methylation levels, which subsequently enhances the stability and translation efficiency of mRNAs.[172]

For m6A erasers, the regulatory roles of circRNAs in various biological processes, focus on their interactions with miRNAs and the FTO protein. For instance, circGPR137B acts as a sponge for miR-4739, thereby modulating the expression of FTO and other target genes.[173] circMAPK9 promotes adipogenesis through the modulation of the hsa-miR-1322/FTO axis.[174] circ_0072309 interacts with miR-607 through its miRNA response element, resulting in the upregulation of FTO expression.[175] circ-ZNF609 ameliorates cardiotoxicity by upregulating FTO, suggesting a protective role for certain circRNAs in the context of drug-induced toxicity.[176]

cicrRNAs can play an important role in m6A modification by targeting m6A readers, such as YTHDF1/2 and IGF2BP1-3. Generally, circMAP2K4 acts as a sponge for miR-139-5p, thereby regulating the expression of YTHDF1, an m6A reader protein.[140] YTHDF1 is known to bind m6A-modified RNAs and affect their translation and decay.[138] By sponging miR-766, circ_0001105 prevents this miRNA from binding to and repressing the expression of its target genes, including YTHDF2.[177] YTHDF2, in turn, is known to affect the stability and translation of m6A-modified RNAs, which are important for various cellular processes including gene expression regulation.[144] Furthermore, circPTPRA interacts with IGF2BP1, disrupting its ability to recognize RNA m6A modifications for the function and activity of IGF2BP1 in post-transcriptional gene regulation.[167] circFAM13B induced by HNRNPL, inhibits glycolysis through the IGF2BP1/PKM2 pathway, as well as IGF2BP1 upregulates the level of circRRM2 through its interaction with MYC, resulting in increased IGF2BP1 levels.[178,179] circEZH2 may directly interact with IGF2BP2, enhancing its stability by blocking the ubiquitination-dependent degradation of the IGF2BP2 protein, which enhances M1-like macrophage polarization, while STAT6 binds to the HMGA2 promoter and promotes IGF2BP2 expression to regulate IL-4-induced M2 macrophage activation.[180,181] In addition, circNEIL3 enhances the stability of IGF2BP3 protein by inhibiting ubiquitin/proteasome-dependent degradation.[182] It is worth noting that IGF2BP3 stabilizes SESN1 mRNA and mitigates oxidative DNA damage and endothelial dysfunction in HUVECs caused by ox-LDL by activating Nrf2 signaling.[183]

In brief, circRNAs have an impact on m6A modification by adjusting m6A regulators. Initially, circRNAs control the m6A modifications of their downstream target mRNAs (Table 6). Additionally, they indirectly regulate m6A

Table 6 Roles of circiRNAs in Regulation of m6A Modification in Atherosclerosis

circRNAs	m6A Regulators	Mechanisms of nc RNAs Regulation	Functions in Atherosclerosis	Refs.
circPUM1	METTL3	circPUM1 can sponge miR-590-5p positively regulating METTL3	Increased m6A methylation and subsequent changes in gene expression that favor cell growth and glycolysis	[168–171]
circ_0001187	METTL3	circ_0001187 enhanced the degradation of METTL3 protein through ubiquitin/proteasomal dependent degradation pathway		
circVMP1	METTL3	circVMP1 acts as a miR-524-5p sponge to up-regulate METTL3.		
circ_0000523	METTL3	circ_0000523 downregulates METTL3 expression by inhibiting the transcription of miR-let-7b.		

(*Continued*)

Table 6 (Continued).

circRNAs	m6A Regulators	Mechanisms of nc RNAs Regulation	Functions in Atherosclerosis	Refs.
cicr_0008399	WTAP	circ_0008399 binds to WTAP to promote the formation of the WTAP/METTL3/METTL14 m6A methyltransferase complex.	Enhancing the stability and translation efficiency of mRNAs	[172]
circGPR137B	FTO	circGPR137B co-located with miR-4739 in the cytoplasm, acting as a sponge of miR-4739, upregulates the demethylation of circGPR137B mediating m6a and promotes its expression, positively regulating FTO.	FTO activates the JAK2/STAT3 signaling pathway to reduce adipocyte apoptosis, decreases levels of TC and LDLC while improving atherosclerotic lesion formation, enhances ABCA1 expression via AMPK activity to inhibit lipid intake and foam cell formation, and downregulates PPARγ while phosphorylating AMPK to impede foam cell formation and atherosclerosis progression	[173–176]
circMAPK9	FTO	circMAPK9 promotes adipogenesis by alleviating the inhibitory effect of miR-1322 on fat mass and obesity-related proteins.		
circ_0072309	FTO	circ_0072309 interacts with miR-607 through its miRNA response element, resulting in the upregulation of FTO expression.		
CircZNF609	FTO	circZNF609 degrades FTO to inhibit its expression.		
circ_0001105	YTHDF2	circ_0001105 may function as a competing endogenous RNA (ceRNA) for miR-766, alleviating the inhibitory effect of miR-766 on its target, YTHDF2.	Affecting the stability and translation of m6A-modified RNAs	[140,177]
circMAP2K4	YTHDF1	circMAP2K4 acts as a miR-139-5p sponge to upregulate YTHDF1 expression.		
circPTPRA	IGF2BP1	circPTPRA binds to IGF2BP1 and blocks its recognition of downstream m6A-modified mRNA.	Enhancing M1-like macrophage polarization and mitigating oxidative DNA damage and endothelial dysfunction	[167,178,179]
circFAM13B	IGF2BP1	circFAM13B competitively blocks the recognition and binding of IGF2BP1 to the 3' UTR of PKM2, inhibiting the stability of PKM2 mRNA.		
circRRM2	IGF2BP1	IGF2BP1 upregulates the level of circRRM2 through its interaction with MYC, resulting in increased IGF2BP1 levels.		
circEZH2	IGF2BP2	circEZH2 may directly interact with IGF2BP2, enhancing its stability by blocking the ubiquitination-dependent degradation of the IGF2BP2 protein.	IGF2BP2 deficiency enhances M1-like macrophage polarization, while STAT6 binds to the HMGA2 promoter and promotes IGF2BP2 expression to regulate IL-4-induced M2 macrophage activation.[181]	[180,181]
circNEIL3	IGF2BP3	circNEIL3 enhances the stability of IGF2BP3 protein by inhibiting ubiquitin/proteasome-dependent degradation.	IGF2BP3 stabilizes SESN1 mRNA and alleviates ox-LDL-triggered oxidative DNA damage and endothelial dysfunction in HUVECs by activating Nrf2 signaling.[183]	[182,183]

modifications through sponging miRNAs. Gaining a deeper comprehension of the biological functions of circRNAs in m6A modifications will offer novel perspectives for atherosclerosis diagnosis and treatment.

Conclusions

In this review, we explored the potential interplay between m6A modifications and ncRNAs representing a novel layer of gene expression regulation in the context of atherosclerosis development. Firstly, we delved into the regulatory functions

of m6A modification on ncRNAs, influencing their maturation, stability, translation, and degradation, as a complex multifactorial process involving the interaction of multiple cellular and molecular mechanisms. Secondly, we elaborated on the capacity of ncRNAs to modulate m6A regulators. ncRNAs can target these regulators and adjust the stability of downstream genes through m6A modifications, thereby influencing atherosclerosis progression. Furthermore, we outlined the mutual relationship between m6A methylation and ncRNAs offers a fresh perspective for unraveling the regulatory mechanisms that underlie atherosclerosis progression and aids in developing targeted atherosclerosis therapies.

The mutual regulation between m6A modifications and ncRNAs in atherosclerosis holds significant implications for understanding the disease's pathophysiology and developing novel therapeutics. m6A modifications play a crucial role in fine-tuning the expression and function of ncRNAs such as miRNAs, lncRNAs, and circRNAs. This, in turn, impacts key processes in atherosclerosis, including lipid metabolism, inflammation, and endothelial function. For example, METTL3, a key m6A writer, can promote atherosclerosis by increasing NLRP1 expression and reducing Kruppel-like factor 4 (KLF4) levels in endothelial cells. On the other hand, m6A erasers like FTO can alleviate atherosclerosis by reducing fat accumulation and enhancing cholesterol efflux. By targeting specific components of this regulatory network, it may be possible to develop targeted therapies to modulate the progression of atherosclerosis.

ncRNAs also exert a reciprocal influence on m6A modification machinery. They can bind to m6A writers, erasers, and readers, thereby altering the m6A modification status of target RNAs and ultimately affecting gene expression. This complex interplay provides a rich landscape of potential targets for therapeutic intervention. For instance, miRNAs can directly target m6A writers such as METTL3 and METTL14, modulating their activity and influencing downstream gene expression related to atherosclerosis. Additionally, circRNAs can act as sponges for miRNAs or interact with m6A modification enzymes to regulate the stability and function of target mRNAs. Understanding these detailed mechanisms offers the potential to design drugs that can precisely modulate the m6A - ncRNA regulatory axis, providing new hope for the treatment of atherosclerosis.

Despite the significant progress made in understanding the relationship between m6A modifications and ncRNAs in atherosclerosis, several limitations exist. Current research is mainly based on in vitro and animal models, and the translation of these findings to human clinical applications requires further investigation. The complexity of the m6A - ncRNA regulatory network also poses a challenge. There are multiple m6A regulators and a vast array of ncRNAs, and their interactions are highly context-dependent. Disentangling these intricate relationships to identify the most critical nodes for therapeutic intervention is a daunting task.

Future studies should focus on several aspects. Firstly, more in-depth research is needed to elucidate the detailed molecular mechanisms underlying the m6A - ncRNA interaction in atherosclerosis. This includes understanding how different cell types in the atherosclerotic plaque respond to m6A modifications and ncRNA regulation. Secondly, the development of specific and potent inhibitors or activators targeting m6A regulators and ncRNAs is crucial. These tools can help to further validate the functional significance of the identified targets and potentially be developed into therapeutic agents. Thirdly, longitudinal clinical studies are required to assess the potential of m6A - related ncRNAs as biomarkers for atherosclerosis diagnosis, prognosis, and treatment response. By addressing these limitations and focusing on these future directions, we can hope to fully exploit the potential of the m6A - ncRNA axis in the management of atherosclerosis.

Informed Consent

Prior to completing the survey, each participant signed an informed consent form after fully understanding the study objectives.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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