m^{6}A in adipose tissue inflammation: A novel regulator of obesity and metabolic diseases (Review)

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Abstract. Adipose tissue hypertrophy, the local infiltration of immune cells, the increased production of proinflammatory cytokines, the whitening of brown adipose tissue, local hypoxia and angiogenesis disorders occur in obese individuals, which in turn lead to adipose tissue inflammation and promote the occurrence and development of metabolic diseases such as type 2 diabetes (T2DM), atherosclerosis and metabolic dysfunction-associated steatotic liver disease (MASLD). In recent years, N6-methyladenine (m^{6}A), the most representative epigenetic modification, has been shown to be significantly altered in individuals with obesity and to participate in the regulation of various metabolic diseases. In the present review, the links between m^{6}A modification and obesity-related metabolic diseases, such as MASLD and T2DM, from the perspective of adipose tissue inflammation are examined. Additionally, the challenges and prospects associated with targeting m^{6}A in adipose tissue inflammation and metabolic diseases are discussed to provide new ideas for the treatment of these conditions.

Contents

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1. Introduction

Obesity is generally defined as excessive body fat that impairs health. The primary measure of obesity is the ratio of weight to height squared (kg/m^2), known as body mass index (BMI) (1). The body weight classification criteria issued by the World Health Organization define a BMI >30 kg/m^2 as obesity and a BMI >40 kg/m^2 as severe obesity, wherein both being overweight or obese are associated with increased mortality (2,3). A number of studies have confirmed that obesity can trigger chronic low-grade inflammation and metabolic dysfunction in multiple organs (such as adipose tissue, skeletal muscle and the liver), significantly increasing the risk of type 2 diabetes (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) (4-6). Although research has demonstrated the participation of immune cells, hepatocytes and myocytes as well as inflammatory factors, adipokines and epigenetic regulation in obesity-related metabolic disorders, the precise molecular mechanisms and regulatory networks involved remain to be fully elucidated (7-11).

Adipose tissue is a crucial metabolic and endocrine organ whose functions extend far beyond simple energy storage. Owing to differences in structure and function, adipose tissue can be divided into white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is composed mainly of white adipocytes, which store excess energy in the form of triglycerides (TGs) (12). BAT is composed mainly of brown adipocytes, which are rich in mitochondria and uncoupling protein (UCP)1 and can actively generate heat (13). Additionally, beige adipose tissue and pink adipose tissue exist. Beige adipose tissue originates through the transformation of WAT, a process termed 'adipose browning'. Like brown fat, beige adipocytes exhibit high mitochondrial density and express thermogenesis-related genes, enabling energy dissipation by non-shivering thermogenesis (14). Moreover, pink adipose tissue has the ability to synthesize and secrete milk (15). Adipose tissue functions as

an active endocrine organ and regulates the metabolic-inflammatory balance through the secretion of adipokines (such as leptin and adiponectin) and inflammatory cytokines [such as IL-8, tumour necrosis factor-α (TNF-α) and monocyte chemoattractant protein-1 (MCP-1). These bioactive molecules can be autonomously secreted by adipocytes or produced by infiltrating immune cells within the tissue (16). However, in the context of obesity, adipocyte hypertrophy occurs, accompanied by impaired tissue angiogenesis and the extensive infiltration of immune cells (such as T cells and macrophages) into adipose tissue; these cells exhibit polarization towards proinflammatory phenotypes and increased secretion of proinflammatory cytokines (17,18). Moreover, enlarged fat cells also exhibit insulin resistance and increased production of proinflammatory cytokines and adipokines (19,20). These phenomena affect the limited healthy expansion of adipose tissue and increase various adverse metabolic consequences. Thus, the induction of adipose tissue establishes a long-term low-grade inflammatory state and has been shown to have a significant effect on obesity-induced metabolic diseases such as T2DM, MASLD and atherosclerosis (21-24).

N6-methyladenine (m^{6}A) modification is a reversible epigenetic change that occurs on the sixth nitrogen of adenine in RNA; it is regulated by three types of proteins: Writers, readers and erasers. This modification plays a crucial role in RNA processing. The term 'writer' refers to a methyltransferase, specifically a methyltransferase complex, involved in m^{6}A modification. This complex consists of two methyltransferase-like enzymes: Methyltransferase-like (METTL)3 and METTL14. METTL3 serves as the catalytic subunit, whereas METTL14 is an essential component that enhances RNA binding (25). Moreover, several coregulatory factors play roles in the m^{6}A methylation process, one of which is Wilms tumour 1-associated protein (WTAP). WTAP binds to a METTL3 and METTL14 dimer, forming a complex that accelerates and dynamically regulates m^{6}A modification (26). m^{6}A modifications can also be dynamically removed by specific demethylases known as 'erasers', which include fat mass and obesity-associated protein (FTO), alkB homologue (ALKBH)5, ALKBH1 and ALKBH3 (27,28). To exert its function, an m^{6}A modification needs to be recognized by the 'reader' binding protein. Mammalian binding proteins that function in m^{6}A modification include YTH domain-containing (YTHDC) proteins, heterogeneous nuclear ribonucleoproteins (hnRNPs), insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) and eukaryotic initiation factor 3 (29).

A growing body of evidence has demonstrated that m^{6}A modification plays crucial roles in various pathophysiological processes, including obesity, inflammation and tumour progression, and is represented by alterations in the expression levels of METTL3/14, WTAP, Vir-like m^{6}A methyltransferase associated, YTHDC1 and ALKBH5 regulators (10,30,31). To date, great progress has been made in understanding the role of various m^{6}A modifications in the regulation of adipose tissue function, which can be broadly divided into four major components. First, m^{6}A can affect the function of adipose tissue by regulating the number of adipocytes, such as via adipocyte generation (32-36). Second, m^{6}A can critically regulate the morphology and function of adipocytes, such as via hypertrophy and browning (37,38). Third, a number of studies have confirmed that m^{6}A can significantly regulate the activation, infiltration and phenotypic transformation of immune cells (39,40). Fourth, m^{6}A has been shown to promote angiogenesis (41,42). These processes can effectively regulate the occurrence and development of inflammation in adipose tissue.

Clarifying the intrinsic relationship between m^{6}A and adipose tissue inflammation is highly important for basic research and the clinical treatment of patients with obesity and related metabolic diseases. To the best of our knowledge, the present review is the first to explore the role of m^{6}A in adipose tissue hypertrophy, adipogenesis, brown-white adipocyte conversion and adipose tissue angiogenesis and to systematically elucidate the role of m^{6}A modification in the occurrence and development of inflammation in adipose tissue. Additionally, from the perspective of adipose tissue inflammation, the relationships between m^{6}A and obesity-related metabolic diseases, such as T2DM, MASLD and cardiovascular disease, are discussed. Finally, the potential challenges and future research trends of m^{6}A modification, adipose tissue inflammation and obesity-related metabolic diseases are discussed, with the hope of identifying a bridge between m^{6}A modification, adipose tissue inflammation and obesity-related metabolic diseases (Fig. S1).

2. m^{6}A in adipose tissue inflammation

Numerous studies have confirmed that m^{6}A can regulate major pathogenic changes, such as fat cell hypertrophy, macrophage activation, phenotypic and metabolic transformation, white fat cell growth, angiogenesis and dysfunction, in fat tissues (discussed below). Therefore, we propose that m^{6}A may be involved in inflammatory processes in adipose tissue through its influence on the aforementioned processes. Targeted m^{6}A modifications may play important roles in reducing the degree of adipose tissue inflammation and improving the progression of obesity-related metabolic diseases.

m^{6}A in adipose tissue hypertrophy. Obesity is the ultimate result of an imbalance between energy intake and energy expenditure. Excess lipids accumulate mainly in adipose tissue, leading to increased adipocyte size, which is known as hypertrophy. This is an important pathological mechanism of adipocyte expansion and occurs mainly in post-development (adult) WAT (43). Compared with smaller adipocytes, larger hypertrophic adipocytes exhibit increased secretion of interleukin (IL)-6, IL-8, MCP-1 and other inflammatory cytokines and decreased secretion of IL-10, an anti-inflammatory cytokine (19). In addition, a study has shown that in individuals with obesity, the capillaries between hypertrophic fat cells become thinner (44). Limited by the sparse organization of and mechanical stress on the capillaries, fat tissue does not expand as fat cells hypertrophy. Therefore, hypertrophic fat cells experience continuous hypoxia, some of which die, which causes macrophages to accumulate in the adipose tissue, especially near dead fat cells, thereby further increasing adipose tissue inflammation (45). If the hypertrophy of fat cells can be inhibited or the production of hypertrophic fat cells can be reduced, a direct therapeutic effect on adipose tissue inflammation can be achieved.

Studies have confirmed that m^{6}A, as an important mechanism that regulates lipid metabolism *in vivo*, can critically regulate adipose tissue hypertrophy. Specifically, an *in vivo* study has demonstrated that FTO deficiency leads to significant obesity and white adipocyte hypertrophy in high-fat diet (HFD)-fed mice through the downregulation of angiopoietin-like protein 4 transcription and inhibition of lipolysis (37). An *in vivo* and *in vitro* study has shown that, FTO overexpression upregulates perilipin 5 protein expression through an m^{6}A-dependent mechanism, reducing lipid droplet size in porcine adipocytes (46). While prevailing evidence supports a role for FTO in promoting fat breakdown, its function can be reversed in specific tissues or under certain conditions. For instance, in a mouse model of obesity caused by diet, targeted degradation of the FTO can alleviate liver steatosis in mice and reduce their body weight, providing evidence that inhibiting FTO can improve metabolic health (47). This highlights the complexity of the FTO regulatory network and its dependence on tissue type and microenvironment for its metabolic effects. Furthermore, in a study on human adipose tissue and *in vivo* research using chronic intermittent hypoxia rats, under conditions of intermittent hypoxia in adipose tissue, the downregulation of METTL3 expression decreases m^{6}A levels in monoglyceride lipase mRNA, promoting lipolysis and free fatty acid release and thereby ameliorating obstructive sleep apnoea syndrome-associated insulin resistance (48) (Fig. 1).

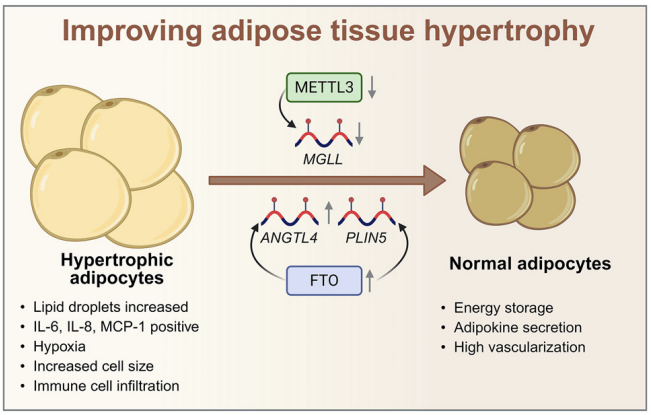

Figure 1. Role of m^{6}A in adipose tissue hypertrophy. Adipocyte hypertrophy is a prerequisite for obesity and the onset of adipose tissue inflammation. m^{6}A modification plays crucial roles in regulating lipid metabolism and adipose tissue hypertrophy. FTO and METTL3 influence the expression of ANGPTL4, PLIN5 and MGLL, thereby contributing to triglyceride clearance, promoting lipolysis and releasing free fatty acids, all of which are involved in adipose tissue hypertrophy. m^{6}A, N6-methyladenine; FTO, Fat mass and obesity-associated protein; METTL3, methyltransferase-like 3; ANGPTL4, angiopoietin-like protein 4; PLIN5, perilipin 5; MGLL, monoglyceride lipase; IL, interleukin; MCP-1, monocyte chemoattractant protein-1.

Previous studies on m^{6}A in adipose tissue hypertrophy have focused mainly on its effect on lipid catabolism in adipocytes, but there are numerous ways to improve adipocyte hypertrophy in individuals with obesity (46,49,50). For example, m^{6}A modification regulates fat accumulation by modulating the expression of lipid metabolism-related genes. Notably, in human oesophageal tissues and cell lines, low expression of hnRNPA2B1 downregulates ATP citrate lyase and acetyl-CoA carboxylase 1(ACC1), suppressing lipid synthesis in oesophageal cancer cells (51). FTO and YTH domain family 2 (YTHDF2) have been shown to promote long-chain fatty acid uptake in intestinal epithelial cells by regulating the m^{6}A modification of AMP-activated protein kinase (AMPK) and Parkin, thereby influencing TG and phospholipid synthesis in an *in vivo* study using obese mouse models (52). Additionally, in an *in vivo* study using leptin-deficient (ob/ob and db/db) obese mice, dysfunctional hypertrophic adipocytes are associated with NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation-induced pyroptosis (20). Moreover, in studies utilizing human tissue samples, as well as *in vivo* and *in vitro* research employing mouse models and relevant cell lines, m^{6}A modification mediated by WTAP, METTL3 and METTL14 plays a key regulatory role in the activation of the NLRP3 inflammasome (53-55). Therefore, examining whether m^{6}A can regulate the pyroptosis of hypertrophic fat cells through the NLRP3 inflammasome to alleviate inflammation in adipose tissue is highly valuable.

m^{6}A in adipogenesis. Adipogenesis is a complex process in which stem cells differentiate into adipocytes and form adipose tissue. The whole process consists of two steps: The commitment stage and the terminal differentiation stage (56). Lipogenesis occurs mainly during body development (that is, in adolescents and children), and the number of fat cells in adults is strictly regulated, even in individuals with obesity (57). However, a study has demonstrated that, during adipose tissue expansion in obese adult animals, adipose tissue dysplasia caused by adipocyte proliferation can also be alleviated by promoting *de novo* adipocyte differentiation to ensure safe energy storage in WAT (58). Insufficient adipogenesis in adipose tissue leads to persistent, chronic inflammation in adipose tissue, which further inhibits the differentiation of adipogenic precursors, creating a vicious cycle (56,59). Angiogenesis occurs prior to hyperplastic expansion to provide sufficient blood to the developing tissue. Therefore, ensuring adequate angiogenesis during adipogenesis plays a crucial role in the composition and function of adipose tissue. As such, obesity can promote the formation of new fat cells (lipogenesis) to distribute excess fat and replace hypertrophic adipocytes, which may have a positive effect on obesity and adipose tissue inflammation. Studies have confirmed that m^{6}A and its related factors play important roles in these two main pathways of adipogenesis and in angiogenesis, with the specific regulatory mechanisms described below.

Commitment. Adipogenesis commitment is a phase in which mesenchymal precursor cells are induced to form precursor adipocytes under the influence of signals from bone morphogenetic protein (BMP), hormones and insulin, during which time the cells do not undergo morphological changes (56). In an *in vivo* study using obese mouse models, METTL3 knockdown promoted the differentiation of bone marrow mesenchymal stem cells (BMSCs) into adipocytes by decreasing the translation efficiency of the parathyroid hormone 1 receptor (60). Moreover, an *in vitro* study using BMSCs obtained from porcine bone marrow revealed that METTL3 depletion in pig BMSCs reduces the m^{6}A levels of Janus kinase (JAK)1 and increases its expression, resulting in an increase in signal transducer and activator of transcription (STAT)5 expression, which significantly regulates the protein

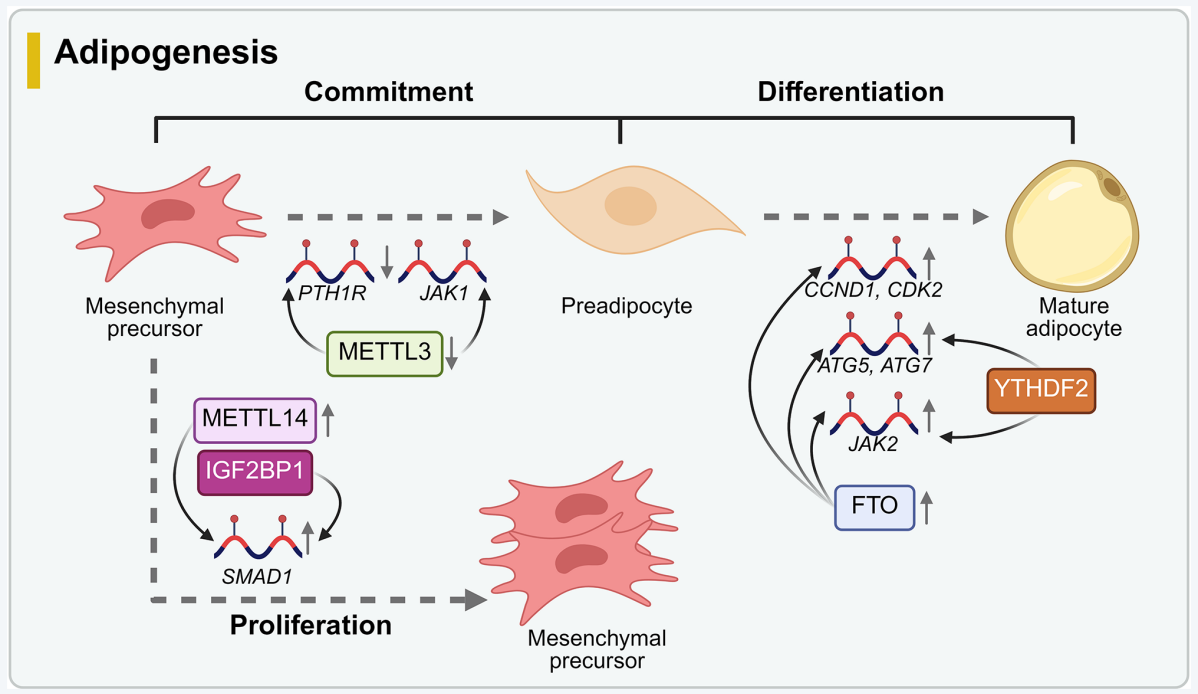

Figure 2. Role of m^{6}A in adipogenesis. Insufficient adipogenesis in adipose tissue leads to persistent, chronic inflammation. m^{6}A modification plays a crucial role in all stages of adipogenesis, from commitment to terminal differentiation. During commitment, METTL3 promotes lipogenic differentiation in BMSCs by regulating the m^{6}A levels of PTH1R and JAK1, whereas silencing METTL14 reduces the expression of SMAD1, inhibiting BMSC proliferation. During terminal differentiation, m^{6}A regulates MCE and the transition to mature adipocytes. FTO influences key genes such as ATG5, ATG7 and JAK2, affecting autophagy, STAT3 phosphorylation and adipogenesis. FTO knockout increases the m^{6}A levels of CCND1 and CDK2, blocking MCE. m^{6}A, N6-methyladenine; METTL, methyltransferase-like; PTH1R, parathyroid hormone 1 receptor; JAK, Janus kinase; BMSC, bone marrow mesenchymal stem cell; MCE, mitotic clone amplification; FTO, Fat mass and obesity-associated protein; ATG, autophagy-related; STAT3, signal transducer and activator of transcription 3; CCND1, cyclin D1; CDK2, cyclin-dependent kinase 2; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; YTHDF2, YTH domain family 2.

levels of CCAAT/enhancer binding protein bate (C/EBPβ) and stimulates the lipogenic differentiation of BMSCs (61). Furthermore, in a study involving *in vivo* and *in vitro* experiments using the ovariectomized mouse model and human BMSCs, as well as research on human skeletal tissue samples, METTL14 silencing was shown to downregulate SMAD1 expression through an IGF2BP1-dependent m^{6}A mechanism, which inhibits BMSC proliferation and osteogenic differentiation (62). It is therefore reasonable to speculate that m^{6}A may affect adipogenesis by modulating BMSC proliferation.

Studies on the differentiation of BMSCs into adipocyte precursors have focused on METTL3, but whether other m^{6}A-related proteins are involved in the regulation of this process remains to be confirmed. The process of adipogenic commitment is regulated mainly by factors related to those that promote adipogenesis, such as BMP2/4 (63). Thus, investigating whether such regulatory factors can have a more efficient effect on adipocyte production under the influence of m^{6}A is valuable. In addition, research has focused mainly on the regulation of m^{6}A-mediated commitment to adipogenesis in BMSCs, and research on whether adipose-derived stem cells (ADSCs), another major source of adipocytes, are regulated by m^{6}A during the process of adipocyte differentiation is insufficient.

Terminal differentiation. In the terminal differentiation stage of adipogenesis, the precursor adipocytes formed during the commitment stage first undergo expansion through mitotic cloning, in which stagnant preadipocytes undergo several rounds of mitosis (64). After undergoing mitotic clone expansion, preadipocytes become mature adipocytes wherein they lose their fibroblast form and accumulate cytoplasmic TGs (56). Studies have shown that m^{6}A also plays a regulatory role at this stage. For example, transcriptome analysis of mouse fat cell m^{6}A-sequencing data showed that FTO can target thousands of m^{6}A-modified genes that are closely related to obesity and adipogenesis (35). Furthermore, an *in vitro* study on mouse 3T3-L1 preadipocytes confirmed that after FTO knockout, YTHDF2 targets autophagy-related (ATG)5 and ATG7 transcripts, reducing the expression of ATG5 and ATG7 and resulting in reduced expression of C/EBPβ and autophagy inhibition, thus decreasing autophagy and adipogenesis. The overexpression of FTO promotes autophagy, which promotes adipogenesis (32). Moreover, an *in vitro* study using mouse 3T3-L1 preadipocytes demonstrated that a lack of FTO also inhibits the expression of JAK2, resulting in the phosphorylation-mediated inactivation of STAT3, thus inhibiting the transcription and expression of C/EBPβ and inhibiting adipogenesis (33). In addition, for mitotic clone amplification (MCE) in the early stage of terminal differentiation, the inhibition of FTO expression in 3T3-L1 cells leads to increased m^{6}A methylation levels of cyclin D1 (CCND1) and cyclin-dependent kinase 2, the protein expression of which is reduced after recognition by YTHDF2, resulting in blockade of the MCE process and in turn the inhibition of lipogenesis (65) (Fig. 2).

The regulatory effect of m^{6}A on the terminal differentiation phase of adipogenesis mainly involves FTO; however, whether other m^{6}A-related regulatory factors are involved in

this process needs to be investigated. For example, in an *in vivo* study using pigs, reducing the m^{6}A level of UCP2 mRNA in 3T3-L1 cells through a synonymous mutation inhibited the differentiation of 3T3-L1 cells into adipocytes (66). However, the regulation of m^{6}A-related proteins is still unknown, thus identifying the specific regulation of m^{6}A-related proteins is valuable. Furthermore, lipid accumulation is an important process in the terminal differentiation phase of lipogenesis. In *in vivo* and *in vitro* studies using mouse models and relevant cell lines, METTL3 was shown to be involved in the regulation of lipid accumulation and TG deposition in hepatocytes and cardiomyocytes (67,68). These findings suggest that m^{6}A modification may act on adipose tissue locally or in other organs through various interactions between the other organs and fat and may mediate adipose tissue morphological and functional remodelling via similar extracellular vesicles.

Adipose tissue angiogenesis. Angiogenesis is the process through which new capillaries are formed. Healthy adipose tissue is surrounded by a dense network of capillaries that supply the nutrients and oxygen necessary for the normal growth of adipocytes. This vascular network also facilitates the transport of lipids, such as fatty acids, into and out of adipocytes, serving as a crucial barrier that helps maintain tissue homeostasis and enables crosstalk with other organs. In the context of obesity, the expansion of adipose tissue requires marked angiogenesis to establish a vast vascular network that can provide ample oxygen and nutrients. During this process, adipocytes typically secrete a variety of mitogens specific to endothelial cells and other angiogenic growth factors to stimulate angiogenesis (69). However, when influenced by certain pathological factors, the rate of angiogenesis may match the rapid expansion of adipose tissue. If the formation of new blood vessels cannot adequately support the needs of excessive adipose tissue enlargement, local hypoxia may occur, exacerbating the inflammatory response. Angiogenesis is regulated primarily by various factors, including proangiogenic factors such as VEGF, basic fibroblast growth factor and apoptosis antigen 1 (70,71), and antiangiogenic factors, such as total suspended particulates, VEGF-A165b and platelet factor 4 (72-74), and the functions of endothelial cells (75). Endothelial cells are primarily located in the innermost layer of blood vessels, where they are responsible for regulating local vascular tone and permeability; they also coordinate with neighbouring cells to modulate immune/inflammatory responses and blood supply. The mutual balance of these factors maintains angiogenesis within the normal physiological range. Angiogenesis is a complex process that involves a variety of factors. It is essential to explore new molecular regulatory networks that can restore or enhance capillary formation in adipose tissue affected by obesity. Improving the function of endothelial cells is particularly important, as this can help alleviate hypoxia in hypertrophic adipocytes and reduce the local inflammatory microenvironment. Research in this area is important for understanding and addressing the complications associated with obesity.

Although there have been no studies that specifically address the role of m^{6}A in the regulation of angiogenesis in adipose tissue, numerous studies have confirmed that m^{6}A participates in the angiogenesis process during the pathogenesis of various diseases, including atherosclerosis, ischemia, tissue repair and tumours, by regulating angiogenic factors, anti-angiogenic factors and endothelial cell functions. For example, to promote angiogenesis, regulators such as ALKBH5, METTL3 and IGF2BP2/3 modulate the expression of proangiogenic factors, such as VEGF and VEGFA, through different pathways, thereby influencing angiogenesis in various tissues (41,42,76-79). These factors can also target angiogenesis in cancerous tumours and other sites through factors such as wingless type mouse mammary tumour virus integration site family member 5A, hepatoma-derived growth factor, hepatocyte growth factor, thymidine kinase 1, zinc ribbon domain containing 1 antisense RNA 1 and hypoxia inducible factor 1 α (HIF1A) (29,39,42,79-81). Moreover, changes in endothelial cell function are important for angiogenesis (82). Research has shown that the actions of m^{6}A regulatory factors, including METTL3, IGF2BP1 and WTAP, influence the proliferation, migration and angiogenesis of endothelial cells in conditions such as atherosclerosis and cerebral arteriovenous malformations (83-85). In summary, various m^{6}A effector proteins (such as METTL3, WTAP and ALKBH5) exert bidirectional regulatory effects (either inhibitory or promotional) on angiogenesis across different human disease models (such as arteriovenous malformations, lung cancer and colorectal cancer) by modulating key signalling pathways, with a detailed summary provided in Table I.

Researchers have developed a model of endothelial cell proliferation by specifically knocking out the phosphatase and tensin homologue gene in endothelial cells, to examine the mechanisms underlying the interaction between endothelial cells and adipose tissue. Their findings revealed that endothelial cells communicate with adipocytes by secreting polyamines, which promote angiogenesis in adipose tissue and help alleviate obesity (86). Therefore, m^{6}A may play a role in the communication between the endothelium and adipocytes, thereby influencing angiogenesis in adipose tissue. In addition to angiogenesis, the structural changes and permeability of blood vessels also significantly regulate inflammation in adipose tissue. Research has shown that long non-coding-small nucleolar RNA host gene 5 can interact with IGF2BP2 in breast cancer-associated fibroblasts, increasing the stability of zinc finger protein 281 mRNA in an m^{6}A-dependent manner. This interaction subsequently stimulates both angiogenesis and vascular permeability (87). However, relatively few studies on adipose tissue exist in this context, and systematic conclusions are lacking. Moreover, tumour blood vessels and adipose tissue blood vessels have different structures and functions. Therefore, elucidating the role of m^{6}A in the tumour vascular system may not be directly applicable to the adipose tissue vascular system, which indicates some limitations of current research. Therefore, there is great potential for future research in this direction. In addition, considering that the functional regulation and angiogenesis of endothelial cells depend on changes in the local microenvironment, it is difficult to form new capillaries in adipose tissue in individuals with obesity. Therefore, investigating whether m^{6}A, as the main modification that is regulated by the local microenvironment, mediates angiogenesis by sensing changes in the local microenvironment may become a new potential research direction with the aim of regulating adipose tissue angiogenesis and relieving inflammation in adipose tissue.

Table I. Role of m^{6}A in adipose tissue angiogenesis.

Authors, year	m^{6}A effector protein	Disease	Human/animal/cell model	Signalling pathways	Biological outcome(s)	(Refs.)
Wang *et al*, 2020	METTL3 deficiency	AVM	Pathological AVM cerebral tissues and HUVECs.	Reduced the level of heterodimeric notch e3 ubiquitin ligase formed by deltex-1 and deltex e3 ubiquitin ligase 3L, activating the notch signalling pathway.	Inhibited angiogenesis in endothelial cells.	(85)
Wang *et al*, 2020	Wilms tumour 1-associated protein deficiency	AVM	Brain with or without AVM, intracranial vascular tissue samples and HUVECs.	Decreased desmoplakin levels through IGF2BP1 and IGF2BP3 and promoted WNT signalling.	Inhibited angiogenesis in endothelial cells.	(84)
Shen *et al*, 2022	AlkB homologue 5 deficiency	LC	LC xenografts in zebrafish and A549, H1975 and 16HBE cells.	Reduced stability of plasmacytoma variant translocation 1, resulting in decreased expression of VEGFA.	Inhibited angiogenesis in LC cells.	(76)
Wang *et al*, 2022	YTH domain-containing protein 2 upregulation	LC	LC xenografts in nude mice, BEAS-2B cells and HUVECs.	Increased the stability of ZNRD1-AS1 and regulated the ZNRD1-AS1/micro RNA-942/tensin 1 pathway.	Inhibited the proliferation, migration and angiogenesis of LC cells *in vitro* and *in vivo*.	(81)
Ma *et al*, 2021	IGF2BP2 deficiency	LC	LC tissues and adjacent non-cancerous tissues, LC xenografts in nude mice and A549, H460, H1299 and NHBE cells.	Increased the expression of thymidine kinase 1.	Regulated cancer cell invasion, angiogenesis and tumour growth *in vivo* in LC cells.	(80)
Zhang *et al*, 2022	METTL3 upregulation	CRC	CRC tissues, HCT116 cells, HT29 cells and HUVECs.	Improved stability of LINC00662 RNA and VEGFA RNA.	Promoted the proliferation, migration and angiogenesis of CRC cells.	(78)
Yang *et al*, 2020	IGF2BP3 deficiency	CC	CC samples and paired non-tumour bowel tissues, CC xenografts in mice and HCT116 and RKO cells.	Decreased the mRNA expression and stability of cyclin D1 and VEGF.	Inhibited CC cell proliferation and angiogenesis.	(41)
Jiang *et al*, 2021	IGF2BP3 deficiency	SC	SC tissues and adjacent normal tissues, MKN-45 cells and HUVECs.	Inhibited hypoxia-induced cell migration and angiogenesis.	Reduced the mRNA expression of hypoxia inducible factor 1α.	(79)
Wang *et al*, 2020	METTL3 upregulation	GC	Human GC tissues, GC xenografts in nude mice and BGC823 and AGS cells.	Increased the mRNA stability of hepatoma-derived growth factor via IGF2BP3.	Promoted tumour angiogenesis and glycolysis in GC cells.	(29)

m^{6}A, N6-methyladenine; METTL, methyltransferase-like; AVM, Arteriovenous malformations; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; LC, lung cancer; VEGFA, vascular endothelial growth factor A; ZNRD1-AS1, zinc ribbon domain containing 1 antisense RNA 1; CRC, colorectal cancer; CC, colon cancer; SC, stomach cancer; GC, gastric cancer; HUVECs, human umbilical vein endothelial cells.

m^{6}A in the browning and development of adipose tissue. In mammals, WAT, which stores energy primarily in the form of triacylglycerol, mobilizes when needed in the form of fatty acids (lipolysis). The main function of BAT is to utilize glucose and lipids to maintain body temperature (thermogenesis) owing to the specific expression of UCP1, which uncouples the electron transport chain to produce heat instead of ATP (88). An *in vivo* study using mouse models has shown that, on the basis of the plasticity of WAT and in the context of obesity or high ambient temperature, there is a lack of leptin receptors, β-adrenergic conduction dysfunction in brown fat cells and lipase deficiency in the body, resulting in the gradual transformation of brown fat cells into white unilocular cells in individuals with obesity (89,90). The proportion of BAT in total body adipose tissue and activity of BAT decrease, whereas macrophage infiltration, brown fat cell death and crowd-like structure (CLS) formation increase, aggravating the inflammatory response in adipose tissue (89). However, under cold stimulation, increased body movement and the use of adrenergic receptor β receptor agonists, AMPK modulators (cordycepin or liraglutide), sirtuin activators and sodium-glucose cotransporter 2 inhibitors (empagliflozin) increase the content of BAT or transform some white adipose cells into beige adipose cells with similar characteristics and functions; that is, after WAT browning/beiging, the inflammatory response of adipose tissue and the body is significantly reduced (91-93). Therefore, the targeted inhibition of BAT whitening or the promotion of brown adipose cell generation or WAT browning are highly important for the treatment of adipose tissue inflammation and related metabolic diseases.

m^{6}A in the development of BAT. m^{6}A mainly regulates the development of BAT after birth and increases the number of brown adipose cells. For example, in an *in vivo* study using mouse models, METTL3 was shown to promote BAT development by upregulating the expression of PR-domain containing 16, peroxisome proliferator-activated receptor γ (PPARγ) and UCP1 through m^{6}A modification. Knockout of METTL3 downregulates thermogenesis- and lipid metabolism-related genes, impairing BAT function and leading to obesity and insulin resistance (94). Furthermore, in an *in vivo* study using mouse models, the prostaglandin E2/E-prostaglandin receptor 3 (EP3) signalling axis was shown to stabilize zinc finger protein 410 mRNA through WTAP-mediated m^{6}A modification, which promotes the differentiation of pre-brown adipocytes into brown adipocytes (95). The results of these studies are expected to provide new ideas for combating inflammation in adipose tissue caused by the whitening of brown fat cells.

m^{6}A in WAT browning. The browning of WAT enhances its thermogenic capacity by increasing UCP1 mRNA expression in white adipocytes. This mechanism not only synergizes with non-pharmacological interventions such as cold exposure, dietary modulation and physical exercise but also has significant therapeutic potential for ameliorating metabolic disorders and combating obesity (96,97). Studies have confirmed that m^{6}A can effectively regulate the browning of WAT in adults. For example, in an *in vivo* study using mouse models, FTO deletion in white adipose cells increased the m^{6}A level of HIF1A mRNA, which is recognized by YTHDC2 and increases the protein expression of HIF1A. This approach also activated the transcription of PPARγ coactivator-1α (PGC-1α) and other thermogenesis-related genes and promoted the expression of UCP1 in and the browning of white fat cells (38).

Additionally, as mitochondria are among the main components of WAT and BAT, changes in mitochondrial content and function are crucial for WAT browning. A number of studies have established that m^{6}A modulates mitochondrial function by regulating mitochondrial activity, dysfunction and biogenesis. For example, an *in vitro* study using the THP-1 cell model has discovered that, during inflammation, METTL3 increases the m^{6}A methylation of PGC-1α mRNA and promotes reactive oxygen species accumulation in monocytes, thereby exacerbating mitochondrial dysfunction (98). Moreover, an *in vitro* and *in vivo* study using mouse models has demonstrated that the knockdown of IGF2BP2 increases mitochondrial activity in haematopoietic stem cells (HSCs) by promoting the attenuation of B lymphoma Mo-MLV insertion region 1 mRNA, leading to the reactivation of mitochondria-related genes (99). Evidence from *in vivo* and *in vitro* studies using mouse models and relevant cell lines demonstrates that exosomes derived from ADSCs promote the differentiation of beige adipocytes and the browning of WAT, thereby ameliorating metabolic disorders in mice with diet-induced obesity (100,101). However, the exact exosomal components that mediate WAT browning and thermogenesis remain unknown and require further study. Therefore, whether m^{6}A affects WAT browning by regulating the crosstalk between adipocytes and other cells remains to be further confirmed. In summary, m^{6}A influences the browning of WAT, the development of BAT and the associated metabolic homeostasis by modifying key genes and regulating intercellular communication; its multiple roles in adipose tissue development and functional regulation are summarized in Fig. 3.

m^{6}A in adipose tissue macrophages: Key mediators of inflammatory amplification. Classical tissue-resident macrophages originate mainly from the yolk sac or foetal liver during the embryonic period, are maintained in adulthood through self-proliferation, and are independent of monocytes. However, under inflammatory conditions, the primary tissue-resident macrophages that infiltrate adipose tissue differentiated from monocytes (102). The main function of these phagocytic cells is to engulf cell debris and pathogens and activate lymphocytes or other immune cells. Additionally, they are essential for innate immunity and play notable roles in inflammatory responses. There are two main types of macrophages: M1 and M2. M1 macrophages are typically activated by interferon-γ and lipopolysaccharide and release proinflammatory factors. M2 macrophages are activated by type 2 helper T cell-derived cytokines such as IL-4 and immune complexes, which help suppress inflammatory factors. This activity contributes to the inhibition of inflammatory responses and the promotion of tissue repair (103,104). In the context of obesity, overnutrition leads to adipocyte dysfunction, the induction of local hypoxia and endoplasmic reticulum stress, the secretion of numerous chemokines and inflammatory signals, the recruitment of bone marrow-derived mononuclear macrophages and adipose tissue macrophage (ATM) infiltration. As an inflammatory microenvironment forms, the number of macrophages increases, as does the M1/M2 macrophage ratio (9). M1 macrophages are a

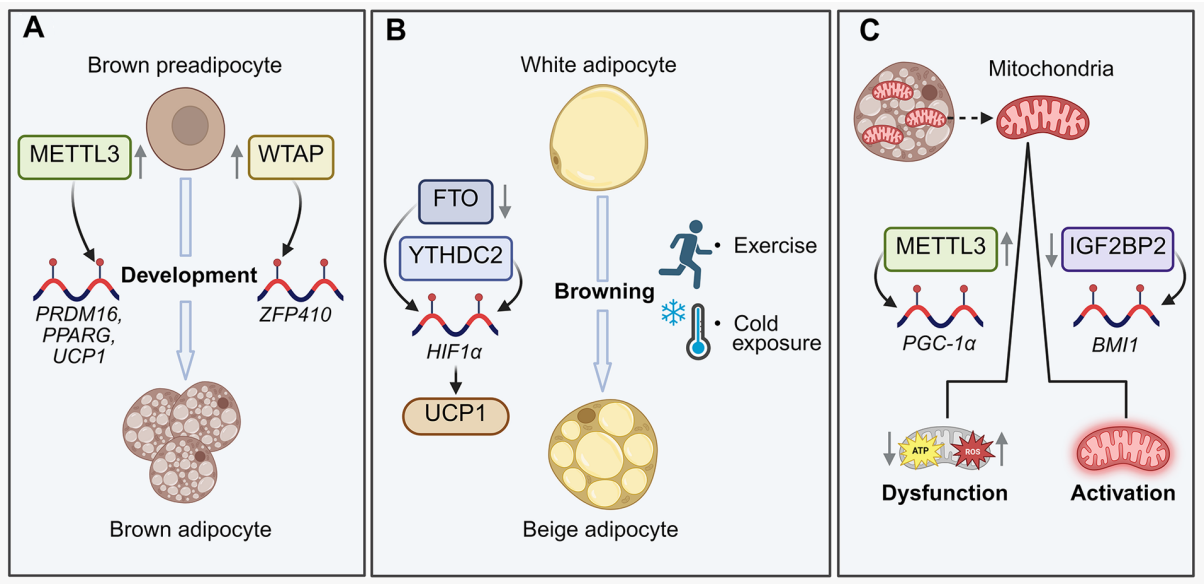

Figure 3. Roles of m^{6}A in the browning/whitening and development of adipose tissue. Promoting the generation of brown adipocytes and WAT browning are highly important for treating adipose tissue inflammation. m^{6}A plays critical roles in regulating the development of BAT and the browning of WAT. (A) METTL3 promotes BAT maturation and thermogenesis by increasing the expression of PRDM16, PPARG and UCP1. WTAP, which is activated via the PGE2/EP3 signalling axis, stabilizes ZFP410 mRNA, facilitating brown adipocyte differentiation. (B) FTO deletion increases the expression of thermogenesis-related genes through HIF1A, promoting UCP1-mediated browning. (C) METTL3 and IGF2BP2, which are essential for WAT browning, regulate mitochondrial function by modulating mitochondrial activity and biogenesis via PGC-1α and BMI1. m^{6}A, N6-methyladenine; WAT, white adipose tissue; BAT, brown adipose tissue; METTL, methyltransferase-like; PRDM16, PR-domain containing 16; PPARG, peroxisome proliferator-activated receptor γ; UCP1, uncoupling protein-1; WTAP, Wilms tumour 1-associated protein; PGE2, prostaglandin E2; EP3, E-prostaglandin receptor 3; ZFP410, zinc finger protein 410; FTO, Fat mass and obesity-associated protein; HIF1A, hypoxia inducible factor 1α; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; PGC-1α, PPARG coactivator 1-α; BMI1, B lymphoma Mo-MLV insertion region 1; ROS, reactive oxygen species.

subpopulation of cells with a predominantly proinflammatory phenotype; they accumulate around dead adipocytes to form a CLS and secrete various proinflammatory cytokines (17,18). Additionally, in a high-fat-diet-induced animal model of obesity, ATMs in the adipose tissue of obese mice exhibit increased accumulation of intracellular lipid droplets (LDs) (105). Based on analysis of tissue samples from obese patients, compared with normal ATMs, ATMs in obese individuals have a unique gene expression profile, which is significantly correlated to insulin resistance (106). Ultimately, the combination of these factors results in ATMs being closely involved in increasing the inflammatory response of local adipose tissue and further increasing the inflammatory response throughout the body.

m^{6}A plays a notable role in regulating various aspects of macrophage biology. First, it is involved in the development of macrophages. Specifically, *in vitro* studies in mice have found, m^{6}A modification, which is mediated by proteins such as YTHDF3, ALKBH5 and METTL3, regulates macrophage development by targeting genes such as CCND1, Fanconi anaemia-associated protein and α-thalassemia X-linked intellectual disability syndrome. Such regulation affects HSC recombination, the genomic stability of haematopoietic stem and progenitor cells (HSPCs) and the differentiation of HSPCs into monocytes (107-109). Second, m^{6}A plays a role in regulating the activation and polarization of macrophages. In *in vivo* and *in vitro* studies using mouse models and relevant cell lines, m^{6}A modification mediated by METTL3, METTL14, YTHDF1/2 and IGF2BP2 influences the expression of sprouty-related EVH1 domain-2, myeloid differentiation primary response 88, STAT1, suppressor of cytokine signalling 2 and tuberous sclerosis complex 1. These processes, in turn, directly or indirectly affect the expression of nuclear factor-κB, STAT3 and PPARγ, thereby controlling macrophage activation and polarization (110-115). Third, m^{6}A affects macrophage pyroptosis. A study demonstrated that in human peripheral blood mononuclear cells derived from patients with coronary artery disease, METTL3-induced m^{6}A can influence macrophage pyroptosis by regulating the protein levels of cysteinyl aspartate specific proteinase-1, IL-1β, IL-18 and gasdermin D N-terminal domain via circular RNA_0029589 (116). Additionally, an *in vivo* and *in vitro* study using mouse models and the mouse macrophage cell line RAW264.7 have found that m^{6}A modification also affects recombinant polypyrimidine tract-binding protein 1/ubiquitin-specific peptidase 8/TGFβ-activated kinase 1 signalling pathways by targeting long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (117). Fourth, m^{6}A influences lipid metabolism in macrophages. In *in vitro* experiments using human peripheral blood mononuclear cells (PBMCs) and the murine macrophage cell line RAW 264.7, it was shown that m^{6}A induced by METTL3 and METTL14 can alter lipid uptake by targeting macrophage scavenger receptor 1 (118) and regulating scavenger receptor type B1 in the cholesterol efflux pathway (119), reshaping the metabolic microenvironment of macrophages. The multilayered regulatory network by which m^{6}A modulates macrophage development, activation/polarization, pyroptosis and lipid metabolism is shown in Fig. 4.

Research on how m^{6}A influences macrophage development, polarization, pyroptosis and lipid metabolism and its role in inflammation has been somewhat comprehensive. However, few targeted studies have explored the effective regulation of ATMs. Using proteomics and transcriptomics, researchers have discovered that ATMs in individuals with obesity exhibit

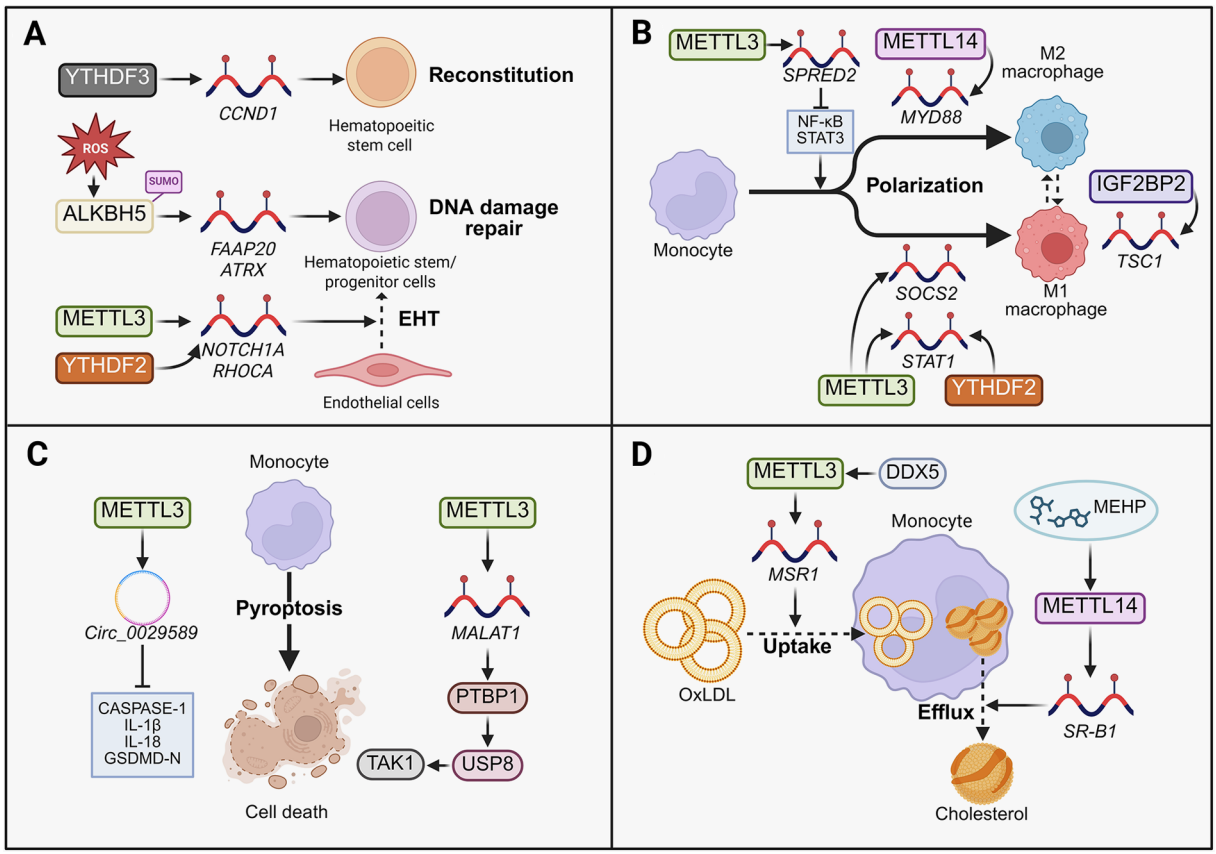

Figure 4. Role of m^{6}A in ATMs. ATMs are deeply involved in adipose tissue inflammation, and m^{6}A plays critical roles in macrophage biology, including their development, activation, pyroptosis and metabolism of lipids. (A) m^{6}A regulates macrophage development by targeting genes such as CCND1 and ATRX via YTHDF3, ALKBH5 and METTL3, affecting haematopoietic stem and progenitor cell differentiation. (B) m^{6}A modification mediated by METTL3, METTL14 and IGF2BP2 controls macrophage activation and polarization by influencing key genes such as SPRED2, MYD88 and STAT1, which impact the NF-κB and PPAR-γ pathways. (C) m^{6}A regulates macrophage pyroptosis by targeting CASPASE-1, IL-1β and MALAT1 and modulating pathways such as the PTBP1/USP8/TAK1 pathway. (D) Additionally, m^{6}A affects macrophage lipid metabolism by regulating lipid uptake and cholesterol efflux through MSR1 and SR-B1. m^{6}A, N6-methyladenine; ATMs, adipose tissue macrophages; CCND1, cyclin D1; ATRX, α-thalassemia X-linked intellectual disability syndrome; YTHDF3, YTH domain family 3; ALKBH5, alkB homologue 5; METTL, methyltransferase-like; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; SPRED2, sprouty-related EVH1 domain-2; MYD88, myeloid differentiation primary response 88; STAT1, signal transducer and activator of transcription 1; NF-κB, nuclear factor-κB; PPAR-γ, peroxisome proliferator-activated receptor γ; CASPASE-1, cysteinyl aspartate specific proteinase-1; IL, interleukin; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PTBP1, polypyrimidine tract-binding protein 1; USP8, ubiquitin-specific peptidase 8; TAK1, TGFβ-activated kinase 1; MSR1, macrophage scavenger receptor 1; SR-B1, scavenger receptor type B1; ROS, reactive oxygen species; TSC1, tuberous sclerosis complex 1; SOCS2, suppressor of cytokine signalling 2; GSDMD-N, gasdermin D N-terminal domain; OxLDL, oxidized low-density lipoprotein; MSR1, macrophage scavenger receptor 1; DDX5, DEAD-box helicase 5; MEHP, mono(2-ethylhexyl) phthalate.

a proinflammatory phenotype characterized by 'metabolic activation'. Notably, this phenotype operates independently of the 'classical activation' pathway, which is typically driven by proinflammatory and anti-inflammatory signals (120). Future studies should further investigate whether m^{6}A is involved in regulating the proinflammatory phenotype of ATMs mediated by metabolic activation. Other studies have demonstrated that exosomes derived from adipocytes mediate communication between adipocytes and macrophages, thereby influencing ATM polarization in the context of obesity (121). For example, in *in vivo* experiments using obese mouse models and studies employing adipose tissue samples from obese patients, it was found that microRNA (miR)-34a can signal to ATMs through exosomes, resulting in significant increases in M1 and M2 ATMs. This process exacerbates systemic inflammation and metabolic disorders associated with obesity (122). Similarly, an *in vivo* study using obese mouse models, miR-155 found in microvesicles derived from adipocytes was shown to influence the polarization of macrophages (123).

Few studies have investigated the role of m^{6}A in regulating the interactions among exosomes, extracellular vesicles and substances associated with ATMs. A verifiable hypothesis is that m^{6}A modification selectively packages ATM pathway-related mRNAs into exosomes through its recognition of proteins such as YTHDF2. Functional verification will require comparative analysis of exosomal RNA from normal and m^{6}A-deficient cells and combined analyses to clarify how these exosomes regulate DNA repair signals in recipient cells. In addition to adipocytes, interactions also occur between the intestinal microbiota and myostatin, which is secreted by skeletal muscle and influences ATMs (124,125). Furthermore, a study utilizing both PBMCs from patients with systemic lupus erythematosus and the MRL-lpr mouse model of spontaneous lymphocyte proliferation have shown that METTL3 upregulation promotes interferon regulatory factor 4 expression in an m^{6}A-dependent manner, thereby exacerbating plasma cell (another type of immune cell) infiltration in tissues (126). Whether m^{6}A can regulate macrophages by affecting the

signal transduction pathways involved in these interactions remains to be studied.

3. m^{6}A and adipose tissue inflammation are associated with metabolic diseases

As aforementioned, obesity-induced inflammation of adipose tissue is a primary contributor to various metabolic diseases, including T2DM and MASLD. Inflammatory adipose tissue releases free fatty acids and inflammatory cytokines, which promote insulin resistance. These changes notably impact tissue homeostasis and the progression of metabolic diseases. Recent research has highlighted the role of m^{6}A modification and its associated regulatory proteins in various biological functions. The level of m^{6}A modification, along with its corresponding effects, largely depends on the regulation of the local microenvironment. A study has shown that m^{6}A levels increase or decrease in conjunction with the development of obesity and related metabolic disorders (10). Furthermore, m^{6}A modifications are significantly altered in the context of T2DM (21), MASLD (22) and atherosclerosis (23) and play roles in the regulation of adipose tissue dysfunction, insulin resistance, liver fibrosis and other related pathological processes (36,50,67,127). The discovery of how m^{6}A influences adipose tissue inflammation has gradually elucidated its potential to alleviate MASLD and T2DM. In this section, the regulatory functions of m^{6}A-mediated epigenetic modifications in metabolic diseases are further explored, with a particular focus on adipose tissue inflammation and its implications for the treatment of T2DM and MASLD.

m^{6}A in adipose tissue inflammation-associated MASLD. MASLD refers to a range of liver conditions that occur when >5% of liver cells become fatty, typically in individuals who consume little or no alcohol (128). MASLD is a multisystem disease that affects various organs outside the liver as well as different regulatory pathways within the body (129). If left untreated, MASLD can progress to non-alcoholic steatohepatitis (NASH), which is characterized by the inflammation and swelling of liver cells. This condition can further lead to cirrhosis and hepatocellular carcinoma (HCC), both of which pose serious threats to human health (130). According to epidemiological statistics and analyses, the global prevalence of MASLD is ~25% and is continuously increasing, and the prevalence of NASH in these patients is also gradually increasing (131,132). Compared with other liver diseases, HCC is more common in patients with NASH (133,134). Current treatment methods for MASLD include several mechanism-based approaches. Key classes of pharmacological agents in clinical development include glucagon-like peptide-1 receptor agonists such as semaglutide (135,136), liver-directed thyroid hormone receptor-β agonists such as resmetirom (137,138) and farnesoid X receptor agonists such as obeticholic acid (139).

Adipose tissue is a crucial metabolic organ in the body, influencing the metabolic state of the liver and the development and progression of MASLD through various pathways. One major factor involved in this process is the inflammation of adipose tissue caused by obesity, which significantly contributes to insulin resistance (140). In cases of obesity and insulin resistance, lipolysis is increased, leading to increased production of free fatty acids. Additionally, the efficiency of fatty acid release from adipose tissue and fatty acid uptake by the liver is increased in most patients with MASLD. As these fatty acids enter liver cells (hepatocytes), they promote the liver accumulation of TGs, which contributes to increased lipid deposition. This accumulation of lipids is a key factor in the development of MASLD (5). Moreover, previous studies and database analyses have revealed several inflammatory cytokines that play a role in the onset and progression of MASLD, including IL-1β, IL-6, TNF-α, C-reactive protein and intercellular adhesion molecule-1 (141-143). Under conditions of adipose tissue inflammation, the release of inflammatory cytokines such as TNF-α and IL-6 from adipose tissue increases. This promotes insulin resistance and contributes to the occurrence and progression of MASLD (4,7,8,144). Additionally, adipose tissue plays a role in regulating liver metabolism and insulin resistance through the secretion of numerous adipokines, including leptin and adiponectin (145-147). From the above, it can be observed that inflammation in adipose tissue plays significant roles in the onset and progression of MASLD. Elucidating communication between adipose tissue inflammation and liver metabolic function holds considerable research significance.

Numerous studies have demonstrated that m^{6}A-mediated epigenetic changes can contribute to the development of MASLD by influencing the expression of genes in the liver involved in lipid metabolism. For instance, a study utilizing methylated RNA immunoprecipitation sequencing alongside RNA transcriptome sequencing in MASLD mice fed a high-fructose diet revealed a large number of m^{6}A-modified genes, including lipid metabolism-related genes such as fatty acid synthase, ACC1, CD36, apolipoprotein A-IV and PPARγ, and glucose metabolism-related genes such as PGC-1α and sirtuin 1. These modifications play crucial roles in the progression of MASLD (148). Changes in m^{6}A modification play important roles in the progression of MASLD by influencing lipid metabolism in the liver. For example, in an *in vivo* and *in vitro* study using mouse models, mouse 3T3-L1 cells and porcine primary preadipocytes, FTO was shown to modulate the expression of the autophagy-related genes, ATG7 and ATG5. Such regulation facilitates the fusion of autophagosomes and lysosomes, which is essential for the effective clearance of LDs in the context of MASLD (32). METTL3 and YTHDF1 produce the same effect by regulating the expression of Rubicon (149). Research has demonstrated that METTL3 plays crucial roles in regulating hepatic lipid and glucose metabolism in mice with high-fat-diet-induced obesity, further influencing the progression of MASLD (67). Adipose tissue inflammation is a significant factor that affects both the onset and progression of MASLD. Recent studies have indicated that m^{6}A plays a role in these processes from various perspectives. For example, in *in vivo* and *in vitro* studies using mouse models, Hepa1-6 cells and HepG2 cells, research has demonstrated that FTO promotes lipid accumulation and lipogenesis in hepatocytes through sterol regulatory element-binding protein 1c (SREBP1c)/cell death-inducing DFF45-like effector C and SREBF1/carbohydrate response element-binding protein signalling pathways. These findings suggest that FTO is crucial for both insulin-regulated hepatic lipogenesis and the development of MASLD (150,151). In addition, analyses of patients with MASLD-driven HCC and

in vivo studies using animal models of HCC have revealed that ALKBH5-, METTL3- and YTHDF1-mediated m^{6}A modifications are involved in regulating *de novo* lipid biosynthesis in the liver and HCC progression through the activation of the phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin and stomatin-like protein 2/c-Jun NH2-terminal kinase signalling pathways (152,153).

Research has demonstrated that m^{6}A regulation plays a crucial role in the release of inflammatory factors during adipose tissue inflammation, which affects MASLD. Notably, *in vivo* studies using HFD mouse models have demonstrated that, when METTL3 is knocked down in ATMs, the mRNA level of DNA damage-inducible transcript 4 increases. This alteration leads to a decrease in the proinflammatory cytokine IL-1β and an increase in the anti-inflammatory markers IL-10 and IL-1 receptor antagonist. These changes contribute to the improvement of metabolic health in patients with MASLD associated with HFD-induced obesity (22). Additionally, altered m^{6}A modification influences the progression of MASLD by regulating hepatic insulin resistance. For example, the expression of YTHDC2 is significantly decreased in the livers of obese mice and patients with MASLD. YTHDC2 upregulation in the livers of obese mice is associated with the activation of adipogenic genes. YTHDC2 binding to mRNA promotes steatosis and insulin resistance in the liver (127). Furthermore, hepatocyte-specific knockout of METTL3 in HFD-fed mice leads to a reduction in lipid accumulation and an improvement in insulin sensitivity (67). MASLD also has the potential to progress to liver fibrosis. An *in vivo* study using obese mouse models revealed that promoting YTHDC1-containing proteasome degradation while suppressing nuclear receptor subfamily 1 group D member 1 degradation can ameliorate liver fibrosis (154).

These findings highlight the significant roles of m^{6}A in regulating the development and progression of MASLD. Additionally, these data underscore m^{6}A modification as a potential intervention to alleviate liver lipid accumulation, metabolism and insulin resistance linked to inflammation in adipose tissue. In summary, the onset and progression of MASLD is a complex process that includes various molecular mechanisms. At present, m^{6}A is considered the most important epigenetic modification. By exploring these molecular mechanisms through the lens of m^{6}A, we can elucidate how MASLD develops and progresses. However, whether m^{6}A influences MASLD through its effects on other key factors remains unclear, and further research is needed to develop more effective prevention and treatment strategies.

m^{6}A in adipose tissue inflammation-associated T2DM. Diabetes and its complications pose notable threats to global health. According to the International Diabetes Federation, the global prevalence of diabetes was estimated to be 9.3% (463 million people) in 2019; this figure is projected to increase to 10.2% (578 million people) by 2030 and further to 10.9% (700 million people) by 2045 (155). At present, T2DM accounts for >90% of all diabetes cases, making it a major global health issue (156,157). Key factors contributing to the development of T2DM include increasing rates of obesity, the lack of physical activity, the consumption of high-calorie diets and an ageing population (158). Adipose tissue inflammation plays a role in influencing the onset and progression of T2DM through various mechanisms. For instance, adipose tissue induces insulin resistance through the release of adipokines under chronic inflammatory conditions. The insulin secreted by pancreatic β cells is not sufficient to adequately counteract this insulin resistance, leading to pancreatic β-cell dysfunction, glucose intolerance and ultimately T2DM (6,159). Understanding the mechanisms that connect adipose tissue inflammation to T2DM, particularly concerning the regulation of m^{6}A, is highly important.

Research has shown that m^{6}A is important in the development of T2DM (160,161). Numerous studies have demonstrated that changes in m^{6}A levels in adipose tissue can contribute to the development and progression of T2DM by influencing insulin resistance and sensitivity. For example, the adipocyte-specific deletion of METTL14 leads to a reduction in the m^{6}A content of these transcripts, which results in their decreased translation. This reduction inhibits β-adrenergic signalling and lipolysis in WAT, thereby providing protective effects against obesity and insulin resistance induced by a HFD in mice (50). *In vivo* research has also indicated that the deletion of WTAP in brown adipocytes reduces EP3 levels in these cells, disrupting the development of interscapular BAT and exacerbating obesity and insulin resistance induced by a HFD in mice (95). Additionally, METTL14-mediated m^{6}A modification increases the degradation of prostaglandin E synthase type-2 and carbonyl reductase 1 in brown adipocytes through YTHDF2/3, worsening insulin resistance in mice fed a HFD (162). Further research has indicated that the upregulation of IGF2BP3 in adipose tissue extends the half-life of myosin light-chain kinase mRNA, which in turn inhibits the phosphorylation of factors in the extracellular regulated kinase 1/2 pathway. This process leads to weight loss and improved insulin sensitivity in HFD-fed mice (163). In summary, alterations in m^{6}A modifications within adipocytes influence insulin resistance through various pathways.

Insulin resistance plays a crucial role in the development of T2DM. In particular, the cytokines and inflammatory factors (such as TNF-α and IL-6) secreted from adipose tissue cells due to inflammation can significantly affect insulin sensitivity and fat metabolism (164,165). It is therefore important to further investigate how m^{6}A modification in inflammatory adipose tissue regulates the transcription and translation of these factors. Additionally, future research should further investigate the molecular networks and dynamic changes involved in m^{6}A modification during adipose tissue inflammation and its role in the pathogenesis of T2DM. Such studies should focus specifically on how m^{6}A modification functions in different types of adipose tissues (white, brown and beige) and how it interacts synergistically with other metabolic organs, such as the liver, muscle and pancreas. Such investigations could provide a new perspective on our understanding of the pathogenesis of T2DM. Additionally, an *in vivo* study using type 2 diabetes cardiac fibroblast-specific NOTCH1 conditional knockout mouse models has shown that m^{6}A is closely involved in the complications of diabetes, specifically diabetic cardiomyopathy. This is primarily reflected in how ALKBH5 deficiency increases NOTCH1 methylation to promote mitochondrial fission (166). Finally, examining the specific regulatory molecules that influence m^{6}A modification-related enzymes (including METTL3,

METTL14 and WTAP) could lead to the development of potential therapeutic strategies aimed at alleviating adipose tissue inflammation and improving insulin resistance. The development of small molecule inhibitors or activators in this area holds notable research value.

4. Conclusion and outlook

The present review systematically examined and analysed recent research on m^{6}A modifications in adipose tissue inflammation and related metabolic diseases, highlighting the crucial role of m^{6}A as an important epigenetic regulatory mechanism in obesity and metabolic disorders. Specifically, m^{6}A is involved in the onset and progression of adipose tissue inflammation by influencing adipocyte generation and hypertrophy, the transition between brown and white adipose tissue, the infiltration and phenotypic polarization of immune cells and angiogenesis. These findings not only increase our understanding of the role of m^{6}A in adipose tissue function but also offer new perspectives for targeting m^{6}A as a means of regulating inflammation in adipose tissue.

Despite advancements in recent research, a number of questions remain unanswered regarding the specific roles of m^{6}A in adipose tissue inflammation and related metabolic diseases. First, how m^{6}A modification influences the inflammatory response and metabolic functions of adipose tissue through the regulation of gene expression in various types of adipocytes and immune cells remains unclear. Second, the dynamic changes in m^{6}A regulators in the context of obesity and metabolic diseases, along with the complexity of their regulatory networks, necessitate further experimental data to provide clarity. Additionally, there may be notable differences in m^{6}A modifications and their regulatory mechanisms across different tissues and cell types. Moreover, current insights into the roles of m^{6}A in adipose tissue inflammation and associated metabolic disorders are predominantly derived from mouse or pig models. While these animal studies are instrumental for elucidating underlying mechanisms, certain differences in fat distribution, immune responses and the m^{6}A regulatory network exist in these species. Therefore, the translation of these findings into human clinical applications requires careful consideration and further validation.

With the development of new technologies, m^{6}A and adipose tissue inflammation will be further explored in the future. In recent years, the rapid development of single-cell sequencing technology has provided new opportunities for revealing the role of m^{6}A in adipose tissue inflammation. Single-cell RNA sequencing can reveal heterogeneity among cell types and even distinguish the different roles of different immune cells, fat cells and other cell types in inflammation. For example, researchers can use single-cell sequencing technology to identify specific cell populations in obesity-associated adipose tissue (such as M1-type and M2-type macrophages) and further explore the regulatory role of m^{6}A modifications in these cells in inflammatory responses. In addition, by combining transcriptomic data with m^{6}A methylation analysis, whole-gene expression maps of m^{6}A modifications in adipose tissue could provide a more systematic understanding of the potential role of m^{6}A in metabolic diseases. More notably, emerging oligonucleotide-based strategies, such as antisense oligonucleotides and small activating RNAs, offer promising prospects for the precise intervention of m^{6}A regulators, thereby promoting our understanding of the role of m^{6}A in adipose tissue inflammation. Given that dysregulated m^{6}A modification is a key factor in chronic inflammation of metabolic tissues, selectively targeting writers, erasers or readers via these intervention strategies could precisely regulate local immune cell function and have significant translational potential in the development of new therapies for metabolic diseases related to obesity. Therefore, future research should combine multi-omics approaches and bioinformatics analyses for more detailed and comprehensive exploration.

The clinical translation of m^{6}A regulatory therapies faces a major challenge: Achieving cell type- or tissue-specific targeting to minimize toxic effects. Core m^{6}A regulatory factors, such as METTL3 and FTO, are generally expressed in different tissues and exert pleiotropic effects. Therefore, systemic inhibition of these factors may disrupt their fundamental physiological processes, leading to unacceptable toxicity. To overcome this limitation, future strategies must focus on spatial accuracy. Promising approaches include developing tissue-specific lipid nanoparticles or exosome-based delivery systems and designing oligonucleotides with activatable cell-specific promoters or binding targets to confine activity to specific cells, such as ATMs (167). In addition, fusing the CRISPR/Cas9 system with m^{6}A for site-specific editing is a more precise, although technically complex, long-term strategy (168). Successfully overcoming this obstacle is a fundamental prerequisite for modulating m^{6}A regulation in the treatment of complex metabolic diseases.

In conclusion, m^{6}A methylation is a reversible epigenetic regulatory modification that has a crucial role in adipose tissue inflammation and related metabolic diseases. By further investigating the molecular mechanisms and functional networks associated with m^{6}A modification, we hope to discover more effective intervention strategies to combat obesity and its associated metabolic disorders, ultimately promoting improved human health. This research is significant not only for basic science purposes but also for providing new ideas and directions for clinical treatments. Future breakthroughs in this field will help establish a solid foundation for precision medicine and personalized treatment.

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Authors' contributions

XY and HT conceived the review. XW and ST wrote the first version of the manuscript. XY and HT jointly oversaw the writing of all versions following the initial draft. XZ and KY revised the manuscript. XY was responsible for all revisions and refinements after the manuscript was submitted. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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