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REVIEW

Regulation of Methylase *METTL3* on Fat Deposition

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Abstract: N6-methyladenosine (m^6A) is the most prevalent and abundant type of internal post-transcriptional RNA modification in eukaryotic cells. *METTL3* is a methylation modifying enzyme, which can directly or indirectly affect biological processes, such as RNA degradation, translation and splicing. In addition, it was found that 67% of 3'-UTR regions containing m^6A sites had at least one miRNA binding site, and the number of m^6A at 3'-UTR sites was closely related to the binding sites of miRNA. With the improvement of human living standards, obesity has become a very serious and urgent problem. The essence of obesity is the accumulation of excess fat. Exploring the origin and development mechanisms of adipocyte from the perspective of fat deposition has always been a hotspot in the field of adipocyte research. The aim of the present review is to focus on *METTL3* regulating fat deposition through mRNA/adipocyte differentiation axis and pri-miRNA/pre-miRNA /target genes/adipocyte differentiation and to provide a theoretical basis according to the currently available literature for further exploring this association. This review may provide new insights for obesity, fat deposition disease and molecular breeding.

Keywords: METTL3, m^6A methylation, miRNA, adipocyte differentiation, intramuscular fat

Introduction

In the early 1970s, a novel RNA epigenetic modification, N6-methyladenosine (m^6A), was first discovered and proposed in eukaryotic messenger RNA (mRNA) from Novikoff hepatoma cells.[1] N6-methyladenosine (m^6A) is one of the most abundant internal modifications in eukaryotic messenger RNA that affects a variety of cellular biological processes, including splicing, processing, nuclear export, stability and decay, translation, cellular differentiation and metabolism.[2,3] M^6A modification refers to the methylation of the 6th N of adenine on mRNA under the action of methyltransferase complex (MTC), which is a dynamic and reversible process regulated by both methyltransferase and dimethyl transferase,[4] such as methyltransferase like 3 (METTL3) and methyltransferase like 4 (METTL4).[5,6]

METTL3 was discovered and named from Hela cells in 1994[7] and was conserved from yeast to human, including leading spiral structure LH, nuclear localization signal NLS, Methyltransferase domain MTD containing SAM binding domain and zinc finger motif ZFD.[6,8] Studies have shown that zinc finger participates in RNA binding, ZNF1 interacts with RNA electrostatically, whereas ZNF2 interacts with RNA hydrophobically, which suggests that zinc finger is responsible for specifically recognizing RNA and making *METTL3* play a role.[9] The formation of miRNA requires the cutting of the complex composed of *DGCR8* and *DROSHA*, and *METTL3* deletion reduced the binding of *DGCR8* to pri-miRNA.[10] According to its function, RNA can be divided into two broad categories, including noncoding

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RNA and encoding protein mRNA. MiRNAs are a group of conservative, small and non-coding RNAs inhibiting translation of or degrading target mRNAs by binding to the complementary sequences in the 3'untranslated region.[11] It has been proved that miRNAs play important roles in energy homeostasis,[12] sugar and lipid metabolism,[13] insulin secretion,[14] pancreatic β-cell development,[15] and adipocyte differentiation.[16] More and more studies have shown that miRNA can interact with transcription factors and important signal molecules related to adipocyte differentiation.[17] Adipose tissue deposition is characterized by increased cell size (hypertrophy) and increased cell numbers (hyperplasia) at the cellular level, which indicates that cell differentiation is a necessary process of fat deposition. In addition, studies found the formation of *METTL3* and *METTL14* heterodimers played an important role in adipocyte differentiation.[18] Another study also found *METTL3* regulates adipocyte differentiation by regulating genes alone.[19] So, *METTL3* plays an important role in fat deposition. However, the specific mechanism by which *METTL3* regulates fat deposition remains unclear.

Despite recent progress in *METTL3* research, the presence and functionality of *METTL3* remains largely unknown. Recent studies have reported the emerging roles of *METTL3* in the development of fat deposition. The present review focuses on the latest progress in made *METTL3* research and provides an up-to-date summary of the association between *METTL3* and fat deposition, which may provide insight into *METTL3*-related molecular biomarkers and increase of fat deposition in animals.

M^6A Methylation

Epitranscriptomic m^6A modification is dynamically and reversibly regulated by modulators characterized as dedicated demethylases (erasers), m^6A binding protein (readers) and methyltransferases (writers), according to their functions,[20] Erasers (FTO, ALKBH5) and writers (METTL3, METTL14, WTAP) are responsible for catalyzing and removing m^6A, respectively.[21–24] In complex *METTL3/METTL14/ WTAP, METTL3* and *METTL14* form a heterodimer complex and interact with *WTAP*. *METTL3* is identified as a SAM-binding component of the complex and has its own catalytic ability, which is highly conserved in eukaryotes.[25] It has been reported that m^6A can label pri-miRNAs and identify *DGCR8* molecules by *METTL3*/m^6A, participating in the mature process of miRNAs and leading to differential expression of miRNAs in many biological processes.[10,26] In addition, it was found that *METTL3* knockout decreased the binding activity between *DGCR8* and pri-miRNA, leading to decreased expression of mature miRNAs.[10] So, understanding the structure of *METTL3* and its interaction mechanism with target RNA will help to further understand the post transcriptional regulation level of genetic information.

METTL3 Promoted the Transformation of pri-miRNA into Mature miRNA (miR-21, miR-25, miR-34a, miR126, miR-143-3p, miR-221/222 and miR-320)

MicroRNAs (miRNAs) are a group of single-stranded, non-coding small RNAs that are broadly present in eukaryotic cells and are highly conserved during evolution with a length of 19–24nt.[27] As miRNAs are critical in development, differentiation, and fat deposition, their mature are controlled by multiple ways during their biogenesis cascade. Figure 1 shows the role of *METTL3* in miRNA maturation. Alarcon et al demonstrated that m^6A modification could mark pri-miRNA for processing by recognizing *DGCR8* in a *METTL3*-dependent manner,[10] indicating that altered *METTL3* mediated m6A modification might be responsible for the aberrant expression of miRNAs in many biological processes. In addition, it was shown that depletion of *METTL3* leads to decreased accumulation of miRNAs and to an overaccumulation of pri-miRNAs due to their impaired processing.[10,28] Similar to previous results,[1] miR-21 was up-regulated when *METTL3* was overexpressed.[10,29] METTL3-dependent m^6A methylation promoted primary miR-34a (pri-miR34a)[30] and miRNA-126 (pri-miR126)[31] maturation through *DGCR8*. Other researchers have demonstrated that upregulation of *METTL3*/m^6A modification promotes pri-miR-25,[32] pri-miR-221/222[33] and pri-miR-143-3p[34] maturation (decreasing the expression of pri-miRNA but increasing the expression of pre-miRNA and miRNA). In addition, pre-miR-320 was much less enriched after *METTL3* inhibition, indicating that pre-miR-320 was a target of *METTL3*.[35]

MiRNA (miR-21, miR-25, miR-34a, miR126, miR-143-3p, miR-221/222 and miR-320) Regulated Adipocyte Differentiation by Targeting Target Genes

MicroRNAs (miRNAs), a novel class of endogenous, non-coding, single-stranded RNAs, have emerged as a group of

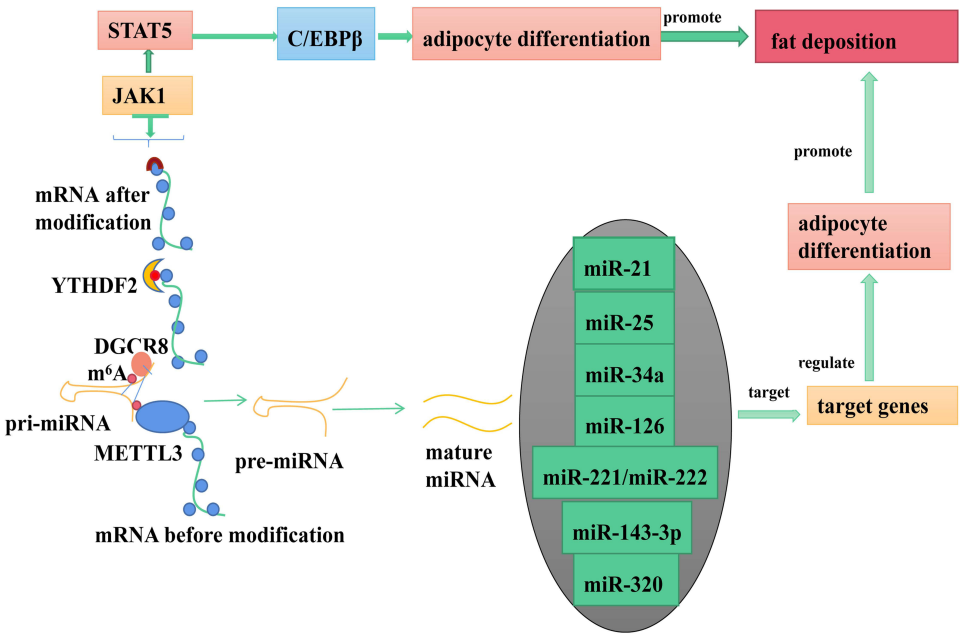

Figure 1 METTL3 regulates fat deposition by coding RNA and non-coding RNA.

important regulators via degradation or translational inhibition of their target mRNAs.[36] As shown in Table 1, miRNA regulates adipocyte differentiation by targeting multiple target genes.

MiR-21 Regulated Adipocyte Differentiation

It was found that nearly 25% of miRNA targets are conserved in the 3' noncoding region of human, mouse and rabbit.[37] In addition, highly conserved miR-21 recognition elements were found in the analysis of *PTEN* 3'UTR of different species, indicating that *PTEN* can be combined with mir-21.[38] At the same time, the results presented here indicated that the potential signal pathway of miR-21 protection might be achieved by targeting *PTEN*/*AKT* signaling pathway. *PTEN* was the main regulator of the *PI3K* signaling pathway, which was involved in lipid metabolism and glucose transport in 3 T3-L1 adipocytes.[39] Previous studies have also shown that endogenous *PTEN* expression is down-regulated during 3T3-L1 differentiation,[40] and knockdown of *PTEN* potentiated the increase in insulin-mediated phosphorylation of *AKT*/*ERK* and promoted adipogenesis of 3T3-L1 cells.[41] The study also indicated that miR-21 directly targets the 3′-UTRs of *SMAD7*, and negatively regulates mRNA and protein expression levels.[42] In addition, *SMAD7* regulated 3T3-L1 preadipocyte differentiation and adipogenesis through *TGFβ*/*SMAD* and *WNT* signaling pathway.[43]

MiR-25 Regulated Adipocyte Differentiation

MiR-25, a member of miR-106b-25 cluster, was significantly downregulated during the differentiation from 3T3-L1 preadipocytes towards mature adipocytes.[44] In addition, this study confirmed *BTG2*,[45] *FBXW7*,[46] *LATS2*[47] and *PTEN*[48] are targets of miR-25 and had binding sites with miR-25 in the 3'-UTR. Further experiments demonstrated that miR-25 Suppresses 3T3-L1 Adipogenesis by directly targeting *KLF4* and *C/EBPα*.[44] *FBXW7* inhibits *C/EBPα*-dependent transcription and inactivation of *FBXW7* results in the accumulation of *C/EBPα*.[49] *LATS2* regulates the balance between proliferation and differentiation during adipose development. Interestingly, studies provided evidence that *LATS2* not only negatively modulates cell proliferation but also positively regulates cell differentiation.[50] In addition, a recent study showed that *BTG2* downregulates interleukin-6 expression by inhibiting the signal transducer and activator of transcription 3 (STAT3) signaling pathway, which is known to regulate adipocyte differentiation.[51] So, miR-25 can regulate adipocyte differentiation through multiple pathways.

Table 1 METTL3 Regulates Adipocyte Differentiation Through Target Genes

miRNA	Promoting Targeted Genes	Inhibitory Target Gene	Regulation of Target Genes on Adipocyte Differentiation
miR-21		PTEN[84]	Down regulate[85]
		SMAD7[86]	Down regulate[43]
miR-25		BTG2[87]	Down regulate[88]
		LATS2[47]	Up regulate[50]
		PTEN[89]	Down regulate
		FBXW7[90]	Down regulate[49]
		KLF4[44]	Up regulate[44]
		C/EBPα[44]	Up regulate[44]
miR-34a		AMPK[55]	Down regulate[91]
		SIRT1[53]	Down regulate[92]
		HDAC1[93]	Up regulate[94]
mir-126		VEGF[95]	Down regulate[65]
		IGF-1[96]	Up regulate[97]
	CRK[98]		Up regulate[62]
		IRS-1[99]	Up regulate[100]
	AKT[101]		Up regulate[102]
		PI3K[103]	Up regulate[78]
mir-143-3p		MAPK7[73]	Down regulate[73]
		MAP3K7[68]	Up regulate[74]
		AKT[71]	Up regulate
		KLF5[70]	Up regulate[76]
		PI3K[71]	Up regulate
		EZH2[72]	Up regulate[104]
mir-221/mir-222		PTEN[105]	Down regulate
		TIMP3[79]	Down regulate[106]
	AKT[107]		Up regulate
		p27Kip1[82]	Down regulate[108]
mir-320		ERK1/2[109]	Down regulate[110]
		PI3K[111]	Up regulate
		adipoR1[112]	Up regulate[113]

MiR-34a Regulated Adipocyte Differentiation

In recent years, reports on miR-34a in human fat have found that miR-34a can target *PPARα* Gene regulation of human fat deposition in liver,[52] which indicated miR-34a played an important role in fat deposition. miR-34a was revealed to directly target *SIRT1* by binding to its 3'-untranslated region[53] and *SIRT1* can promote fat mobilization in white adipocytes by repressing *PPAR-γ*.[54] The study provides evidence that miR-34a decreases the mitochondrial content and increases TAG via *PPARα* and *AMPK* pathways by targeting the *AdipoR2* gene.[55] A number of factors regulate the transcriptional activation potential of *C/EBP-β* in stimulated preadipocytes. DNA binding of *C/EBP-β* is facilitated by *MAPK* phosphorylation beginning at 4 h post-stimulation and *GSK3β* phosphorylation-14 h into differentiation. MiR-34a regulates therapy resistance by targeting *HDAC1*.[56] We have shown that the ability of *C/EBP-β* to activate *C/EBP-β* expression in preadipocytes stimulated to differentiate is initially reduced through the interaction of *C/EBP-β* with an mSin3A/histone deacetylase 1 (HDAC1) complex.[57] *PPAR-γ* and *C/EBP-β* are marker genes of adipocyte differentiation. So, miR-34a can regulate adipocyte differentiation by targeting target genes.

MiR-126 Regulated Adipocyte Differentiation

MiR-126 is a single stranded small RNA molecule with a length of 23 nucleotides encoded by endogenous genes,[58] which can widely mediate the regulation of physiological reactions such as cell differentiation, proliferation and migration.[59] Functional analysis of miR-126 demonstrated that its overexpression conveys neurotoxicity by impairing *IGF-1*/*PI3K*/*AKT* signaling, and that its inhibition increases the trophic effects of *IGF-1*.[60] Studies also confirmed that miR-126 exerted these pivotal functions by down-regulating the expression of *CRK*.[61] During 3T3-Ll cell differentiation induction, *C-CRK* is phosphorylated on tyrosine by *IGF-1* receptor kinase and dephosphorylated by PTPase.[62] In addition, overexpression of miR126 down-regulated *IRS-1* expression, suppressed *AKT* and *ERK1/2* activation. Decreased expression of *IRS-1* in embryonic fibroblast cells severely decreased the expression of *C/EBPα* and *PPARγ*.[63] The inhibitory effect of mir-126 on *VEFG* expression was investigated and indicated that *VEGF* is a target of miR-126.[64] Retrovirus-mediated restoration of *VEGF* expression in mutant cells reduced adipocyte differentiation to the levels exhibited by control cells.[65] In a word, miR-126 played an important role in adipocyte differentiation.

MiR–143-3p Regulated Adipocyte Differentiation

miR-143 was identified to promote adipocyte differentiation by using antisense oligonucleotides.[66] There are many target genes of miR-143-3p that play a regulatory role in adipocyte differentiation, such as *MAPK7*,[67] *MAP3K7*,[68] *AKT*,[69] *KLF5*,[70] *PI3K*[71] and *EZH2*.[72] Firstly, *MAPK7* inhibited adipocyte differentiation[73] and *MAP3K7* induces adipocyte differentiation through *PPARγ* signaling.[74] Secondly, *AKT*/*PKB* may play a role in suppression of apoptosis and negatively regulate preadipocyte differentiation.[75] *KLF5* is also induced by *C/EBPβ/δ*, and

that it then acts in concert with *C/EBPβ/δ* to regulate *PPARγ2* expression[76] and *EZH2*-induced H3K27me3 of *WNT* gene promoters facilitated adipogenic differentiation of murine preadipocytes.[77] Finally, *IRSs*/*PI3K* signal pathway may play an important role in the differentiation of 3T3-L1 preadipocytes by regulating the expression of *C/EBPα* and *PPARγ*.[78] These results suggest that miR-143-3p can regulate adipocyte differentiation.

MiR–221/222 Regulated Adipocyte Differentiation

miR-221/222, located in a cluster on chromosome Xp11.3, are considered part of the same family. They share the same'seed' sequence, short regions at their 5' ends through which they bind their target sites in mRNA 3'-UTRs. Studies showed that miR-221 and 222, by targeting *PTEN* and *TIMP3* tumor suppressors, induce *TRAIL* resistance and activate the *AKT* pathway.[79,80] *SH2-B* is a key regulator of adipogenesis both in vivo and in vitro by regulating the insulin/*IGF-I* receptor-*AKT-FOXO1-PPARγ* pathway,[81] which indicates *PTEN, TIMP3* and *AKT* genes play an important role in adipogenesis. In addition, miR-221 and 222 inhibited the expression of $p27^{Kip1}$[82] and Genetic ablation of $p27^{Kip1}$ in mice leads to adipocyte hyperplasia.[83] In a word, miR–221/222 can regulate adipocyte differentiation by multiple pathways.

MiR-320 Regulated Adipocyte Differentiation

MiR-320 is involved in a variety of pathological processes, including cell proliferation and differentiation.[114] The present results provided evidence that the miR-320/*ELF3* axis regulated tumor progression via the *PI3K*/*AKT* signaling pathway.[111] Activated form of *PI3K*, a critical target of *IRS1* downstream, led to phosphorylation of phosphatidyl inositides and then activated the downstream main target *AKT*, which is pivotal in regulating 3T3-L1 preadipocyte differentiation.[115,116] In addition, Data study indicates that miR-320 negatively regulates expression of *ET-1, VEGF*, and *FN* through *ERK1/2*.[109] The adipocyte-specific transcription factor *PPARγ* can be phosphorylated by *ERK1/2* to decrease its transcriptional activity and inhibit adipocyte differentiation.[117] Finally, A luciferase assay confirmed that miR-320 binds to the 3'-untranslated regions of *AdipoR1*, which indicated *AdipoR1* is a target gene of miR-320.[112] *CTRP6* regulates proliferation and differentiation of intramuscular and subcutaneous adipocytes through the *AdipoR1 (*Adiponectin Receptor 1)/*MAPK* pathway.[118] So miR-320 can regulate adipocyte differentiation by targeting *ERK1/2, PI3K* and *adipoR1*.

METTL3 Regulated Adipocyte Differentiation by Directly Modifying Key Genes

Methyltransferase-like 3 (METTL3), a key RNA methyltransferase, has been demonstrated to regulate neurogenesis,[119] spermatogenesis,[120,121] early embryonic development,[122] stem cell pluripotency in mice,[122,123] and white fat cell differentiation in vitro.[18] Recently, Yao et al found that *METTL3* plays an important role in BMSCs differentiation and adipogenesis and there was a negative correlation between *METTL3* expression and porcine BMSCs (pBMSCs) adipogenesis.[124] It was demonstrated that the deletion of *METTL3* significantly promoted the pBMSCs adipogenesis process and janus kinase 1 (JAK1) protein expression via an m6A-dependent way.[124] Specifically, *METTL3* inhibited pBMSCs adipogenic differentiation by targeting the *JAK1*/*STAT5*/*C/EBPβ* pathway via an m^6A-*YTHDF2*–dependent manner.[124] C/EBPβ is a marker gene of adipocyte differentiation, which indicates METTL3 plays an important role in regulating adipocyte differentiation.

Effect of Adipocyte Differentiation and on Fat Deposition

Fat deposition is the main means of energy storage in animals. Mammalian adipose tissue mainly exists in four forms: subcutaneous, visceral, intermuscular and intramuscular fat. Generally, the differentiation of adipocytes refers to the process of preadipocytes differentiating into multi compartment adipocytes.[125,126] After 8 days of culture in vitro, precursor adipocytes were induced to differentiate into mature adipocytes by *PPARγ, CEBP/a* and *FABP4*.[127] The number and volume of lipid droplets in mature adipocytes increased. At the same time, the volume of mature adipocytes also increased significantly, which also increased the content of adipose tissue. So, adipocyte differentiation promoted fat deposition.

Conclusions

In summary, although the correlation between m6A modification and fat deposition, as a hotspot in the field of genetics, has been extensively explored, most studies

concentrated on gene sequencing analysis, differential expression analysis, and modification site analysis. There are few studies on the functional phenotypes and mechanisms of action at the cell level, but studies in this field are likely to be key to revealing the origin of fat deposition, especially the origin and development of obesity. With a deep understanding of mechanism of fat deposition and the targeted study for m^6A modification, m^6A modification then provides a new perspective for elucidating the occurrence and development of related obesity diseases, providing a new direction for guiding the diagnosis and treatment of obesity diseases.

Data Sharing Statement

All of the data used in this research appears in the manuscript and is available at request from corresponding author.

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 declare no conflict of interest.

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