Review Article

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Research progress on N^6-adenosylate methylation RNA modification in heart failure remodeling

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ABSTRACT

Cardiovascular disease (CVD) is the major cause of disability-adjusted life years (DALY) and death globally. The most common internal modification of mRNA is N^6-adenosylate methylation (m^{6}A). Recently, a growing number of studies have been devoted to researching cardiac remodeling mechanisms, especially m^{6}A RNA methylation, revealing a connection between m^{6}A and cardiovascular diseases. This review summarized the current understanding regarding m^{6}A and elucidated the dynamic modifications of writers, erasers, and readers. Furthermore, we highlighted m^{6}A RNA methylation related to cardiac remodeling and summarized its potential mechanisms. Finally, we discussed the potential of m^{6}A RNA methylation in the treatment of cardiac remodeling.

Key words: RNA modification, m^{6}A RNA methylation, cardiac remodeling, cardiac hypertrophy, heart failure

INTRODUCTION

Cardiovascular diseases result from complicated interactions between multiple genetic variations and environmental factors.[1] Common fatal cardiovascular diseases include ischemic heart disease (IHD),[2,3] hypertensive heart disease,[4] cardiomyopathies,[5] and heart failure (HF),[6,7] among others. One of the global health policy goals launched by World Health Organization is to reduce early mortality from noncommunicable diseases by 25% by 2025.[8] Therefore, it is of great significance to study the mechanisms of cardiovascular disease.

Cardiac hypertrophy is an important factor in the pathogenesis of cardiovascular diseases. Physiological cardiac hypertrophy is typically caused by exercise or pregnancy.[9] It is characterized by a slight increase in cardiac mass (10%–20%) and an increase in the length and width of individual cardiomyocytes.[10] However, the heart shape is normal, and this process is advantageous to the cardiac function. Pathological cardiac hypertrophy includes altered cardiac gene expression, cell death, fibrosis, imbalance in Ca^{2+} transport regulatory proteins, mitochondrial dysfunction, changes in sarcomere structure, and inadequate angiogenesis.[11] The signaling mechanisms that induce these responses contribute to maladaptive heart remodeling and dysfunction, ultimately leading to heart failure. Inhibiting concurrent signaling pathways may also have important therapeutic significance.[9]

RNAs can be modified after transcription, and more than 170 types of RNA posttranscriptional modifications have been discovered to date.[12] An increasing number of inner modifications of eukaryotic epigenetics have been explored in recent studies, including well-known markers named histone tails.[13,14] RNA modifications involve adenosine N^6-methyladenosine (m^{6}A), N^1-methyladenosine (m^{1}A), 5-methylcytosine (m^{5}C), pseudothiopyrimidine (Ψ), N^6, 2'-O-dimethyladenosine (m^{6}A$_m$),[15] the methylation of cytosine to 5-methylcytosine and its oxidation product 5-hydroxymethylcytosine

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Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2022-0025

(hm^{5}C),[13] N^7-methylguanosine (m^{7}G),[16] N^4-acetylcytidine (ac^{4}C),[17] and ribose methylations (N$_m$).[18] The most extensive modification of mammalian mRNA, N6-methyladenosine (m^{6}A), has aroused widespread interest and scrutiny in the field.[19] Scientists have isolated RNA from mammals and discovered that approximately 1‰–4‰ of adenosine was modified as m^{6}A, which made up about half of the total ribonucleotide methylation.[20] m^{6}A is also found in precursor RNAs (pre-RNAs) and long noncoding RNAs (lncRNAs).[21] Generally, m^{6}A is embedded in the conserved sequence 5'-RRACU-3',[22] and it mainly occurs in the beginning segment of the 3'-UTR, which is near the translation end codon.[23] Currently, extensive studies are being conducted to investigate the connection between m^{6}A and various diseases.[24–26] One of the research hotspots is tumorigenesis, but research reports on the relationship between m^{6}A modification and cardiovascular diseases are still limited.[27] This review summarizes m^{6}A RNA methylation and the regulation of RNA stability in cardiac remodeling. It also focuses on how research advances in the relationship between m^{6}A modification and cardiac remodeling provide new ideas for the prevention, early detection, and treatment of cardiac hypertrophy and heart failure.

m^{6}A RNA METHYLATION

RNA modified as m^{6}A refers to the methylation of N^6 in the nitrogenous base adenine.[28] There are three key enzymes mediating this process: methyltransferases (writers), demethylases (erasers), and methylation-reading proteins (readers).[29] We summarized their participation in biological dynamic modification and function, as shown in Figure 1.

Writers

"Writers" refer to methyltransferases. Enzymes of this class mainly contain methyltransferase-like 3 (METTL3), methyltransferase-like 14 (METTL14), methyltransferase-like 16 (METTL16), Wilms tumor 1-associated protein (WTAP),[30] vir-like m^{6}A methyltransferase associated (KIAA1429/VIRMA),[31] zinc finger protein (ZFP217),[32] RNA-binding motif protein 15 (RBM15),[33] zinc finger CCCH-type containing 13 (ZC3H13),[34] zinc finger CCHC-type containing 4 (ZCCHC4),[35] and other components. They exist in the form of complexes and jointly catalyze the m^{6}A modification of adenine on RNA. A steady formation can be achieved with METTL3 and METTL14,[36] which catalyze the epigenetic modification of m^{6}A RNA *in vitro* and *in vivo*.[37] WTAP has no methyltransferase activity but can bind to METTL3 and METTL14.[38] These three proteins are colocalized in nuclear speckles and play important roles in regulating gene expression and alternative splicing.[39] METTL3, an m^{6}A methyltransferase, also plays a key role in autophagy in non–small-cell lung cancer (NSCLC) cells.[40-42] This process reverses gefitinib resistance through β-elemene. Compared to paired normal tissues, METTL3 expression was increased in lung adenocarcinoma tissues and participated in gefitinib drug tolerance of NSCLC cells. The key genes in autophagy pathways, such as ATG7 and ATG5, are upregulated by METTL3.[43] The upregulation of inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and interleukin 18 (IL-18), and the inflammatory proteins TNF receptor associated factor 6 (TRAF6) and nuclear factor of kappa light polypeptide gene enhancer in B cells 1 (NF-κB) was observed in a microglial inflammation model mediated by lipopolysaccharide (LPS). Surprisingly, METTL3 expression levels were also upregulated alongside TRAF6 in this model. The TRAF6-NF-κB pathway is also activated when METTL3 is overexpressed. Therefore, METTL3 activates the TRAF6-NF-κB pathway and accelerates LPS-induced microglial inflammation.[44]

Erasers

Demethylases, also known as the "erasers," remove the m^{6}A modification of RNA. This process demonstrates the dynamic and reversible modification of m^{6}A. It has been found that demethylases mainly include the genes Fat Mass and Obesity Associated (FTO)[45] and ALKBH5 (alkane hydroxylase homolog 5).[46] These two molecules are part of the α-ketoglutarate-dependent dioxygenase family.[47] m^{6}A demethylation can be catalyzed in an Fe^{2+}- and α-ketoglutarate-dependent manner.[48] A decrease in FTO and ALKBH5 expression was found to be coupled with an increase in m^{6}A modification in mRNA.[45] FTO is associated with human obesity and is considered an obesity susceptibility gene.[49] It is related to body mass index through energy expenditure and intake.[50] Several studies have revealed that FTO is involved in m^{6}A modifications. m^{6}A demethylation catalyzed by FTO can regulate the stability of mRNA, regulate the efficiency of degradation and translation, and control the expression of protein levels. Research has shown that FTO is necessary for the normal development of the central nervous system[51] and the cardiovascular system.[52] This confirms that mutations in the alkb-related dioxygenase family of genes could cause severe polymalformation syndrome.[53] The Alkb family, which is enriched with iron- and 2-oxoglutarate-dependent nucleic acid oxygenase (NAOX), contains a member named ALKBH5. ALKBH5 catalyzes m^{6}A demethylation.[54] According to a report, the double-stranded β-helix domain of ALKBH5 has a mutual effect on the ATP domain of the DEAD (Asp-Glu-Ala-Asp) box polypeptide 3 (DDX3). This domain participates in critical biological processes, such as the cell cycle, metabolism, and apoptosis.[55] Furthermore, it was revealed that both FTO and ALKBH5 are closely associated with single-nucleotide

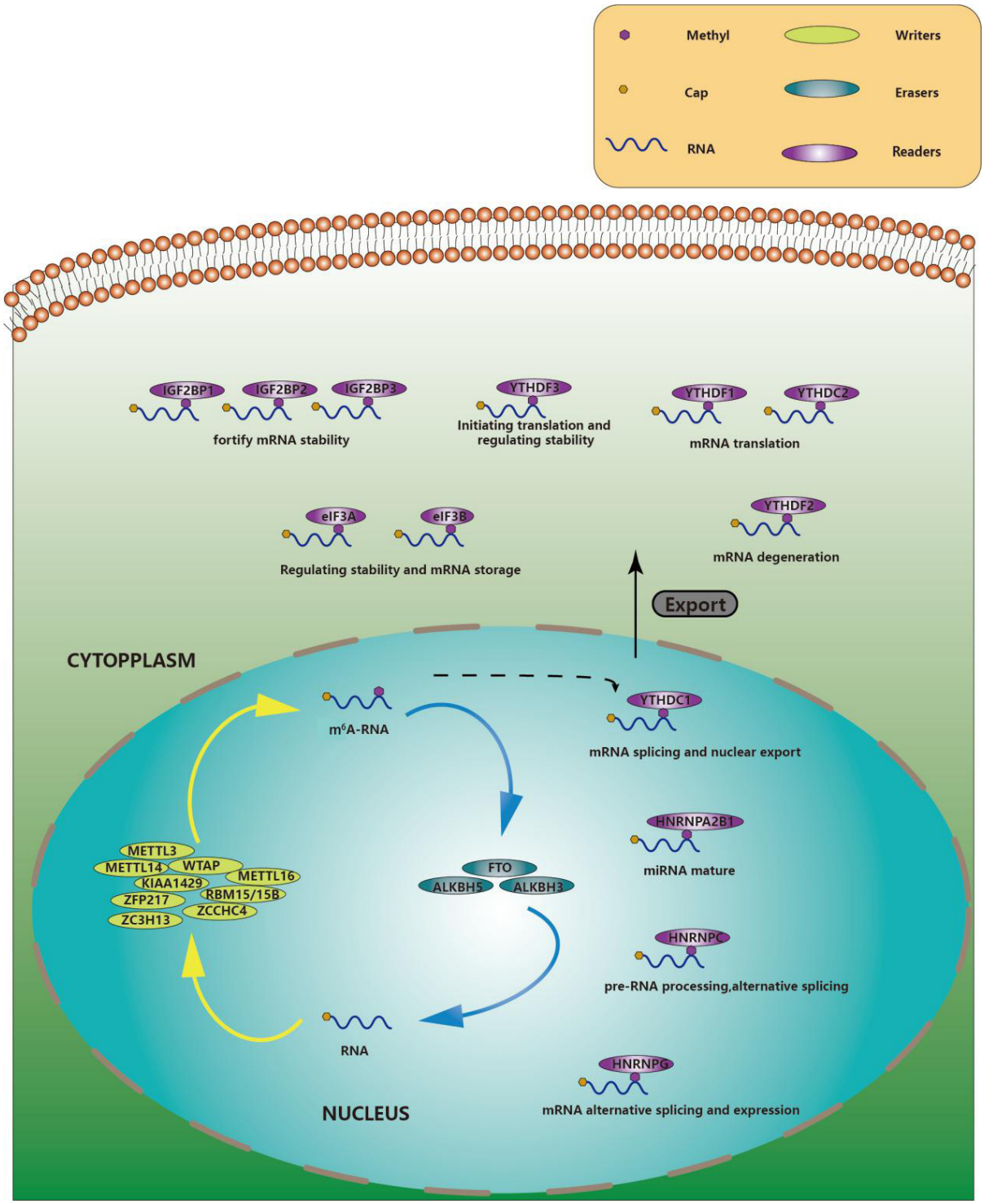

Figure 1: The dynamic modification of m⁶A. Writers (METTL3, METTL14, WTAP, METTL16, KIAA1429, RBM15/15B, ZFP127, ZC3H13, and ZCCHC4) can identify and methylate the N6 of RNA. Erasers (FTO, ALKBH5, ALKBH3) can catalyze m⁶A-RNA demethylation. m⁶A-RNA can be discerned by readers such as YTHDC1 for mRNA splicing. Other readers of m⁶A are located in the cytoplasm; for instance, YTHDF1, YTHDF2, YTHDF3, YTHDC2, HNRNPA2B1, HNRNPC/G, and IGF2BP1/2/3 are involved in the splicing, processing, translation, and degradation of m⁶A RNAs. METTL3: methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit; METTL14: methyltransferase 14, N6-adenosine-methyltransferase subunit; METTL16: methyltransferase 16, N6-methyladenosine; WTAP: WT1-associated protein; KIAA1429/VIRMA: vir-like m⁶A methyltransferase-associated; RBM15/15B: RNA-binding motif protein 15/15B; ZFP127/MKRN3: makorin ring finger protein 3; ZC3H13: zinc finger CCCH-type containing 13; ZCCHC4: zinc finger CCHC-type containing 4; FTO: FTO α-ketoglutarate dependent dioxygenase; ALKBH5: alkB homolog 5, RNA demethylase; ALKBH3: alkB homolog 3, RNA demethylase; YTHDC1/2: YTH domain-containing 1/2; YTHDF1/2/3: YTH N6-methyladenosine RNA binding protein 1/2/3; HNRNPA2B1: heterogeneous nuclear ribonucleoprotein A2/B1; HNRNPC/G: heterogeneous nuclear ribonucleoprotein C/G; IGF2BP1/2/3: insulin-like growth factor 2 mRNA-binding protein 1/2/3.

polymorphisms (SNPs).[56] In addition, it was reported that ALKBH3 could demethylate 1-meA and 3-meC; thus, the damage and incomplete methylation of DNA/RNA could be repaired.[57]

Readers

The major function of m^{6}A-reading proteins is to recognize the bases that have been modified by m^{6}A and to regulate the processing, transportation, translation, and stability of the modified RNA.[58] To date, the m^{6}A reading proteins that have been identified include the YT521-B homology (YTH) family (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2),[59] HNRNP family (HNRNPA2B1, HNRNPC, and HNRNPG),[60-62] IGF2BP (IGF2BP1, IGF2BP2, and IGF2BP3),[63] and eIF3A/B.[64] The YTHDFs, YTHDC2, IGF2BP, and eIF3A/B proteins are located in the cytoplasm,[65] whereas the YTHDC1 and HNRNP families can be found in the nucleus.[66] YTH N6-methyladenosine RNA-binding protein 2 (YTHDF2) was the first m^{6}A reader to be discovered.[67] YTHDF2 accelerates the degradation of transcripts modified by m^{6}A by directly enlisting the glucose-repressible alcohol dehydrogenase transcriptional effector (CCR4-NOT) deadenylase complex. In contrast, YTH N6-methyladenosine RNA binding protein 1 (YTHDF1) was initially shown to combine with the m^{6}A site near the stop codon and then bind to the translation origination mechanism to enhance the translation efficiency of specific RNA in mammals.[68] YTH N6-methyladenosine RNA-binding protein 3 (YTHDF3) plays a crucial role in the original stages of translation and stability.[69] The YTH domain-containing 1 (YTHDC1) mediates m^{6}A-regulated mRNA splicing,[70] nuclear transport, and gene translation silencing[71] as a nuclear RNA-binding protein.[72] YTH domain-containing 2 (YTHDC2) increases mRNA translation efficiency.[73] HNRNPA2B1 promotes miRNA maturation.[74] Heterogeneous nuclear ribonucleoprotein C (HNRNPC) participates in pre-mRNA processing[75] and alternative splicing.[76] Heterogeneous nuclear ribonucleoprotein G (HNRNPG) regulates alternative splicing and the abundance of target mRNAs.[77] Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs), located in the cytoplasm as m^{6}A readers, preferentially recognize m^{6}A-modified mRNAs. They can reinforce mRNA stability and promote translational efficiency.[78]

m^{6}A RNA METHYLATION AND PATHOLOGICAL CARDIAC REMODELING

Cardiac remodeling includes changes in genomic expression, molecules, cells, and the mesenchyme that clinically manifest as changes in cardiac size, shape, and function after injury.[79] Cardiac remodeling can be categorized into physiological remodeling and pathological remodeling. Physiological cardiac remodeling is often caused by exercise or pregnancy.[80] It manifests as a slight (15%) increase in heart weight and an increase in the length and width of individual cardiomyocytes. The shape of the heart is normal, which is beneficial to its function.[81] However, pathological cardiac hypertrophy can manifest as changes in cardiac gene expression, cell death, fibrosis, Ca^{2+} transport regulatory protein disorders,[9] mitochondrial dysfunction, metabolic maladjustment, restoration of antenatal gene expression, damaged protein quality assurance mechanisms, changes in sarcomere structure, and lack of angiogenesis.[82] The signaling mechanism inducing these reactions promotes maladaptive cardiac remodeling and dysfunction, eventually leading to heart failure (HF).[83] It has been reported that heart failure (HF) is a chronic disease that inflicts more than 20 million patients worldwide.[84,85] In the past several years, a growing number of studies have revealed the relationship between m^{6}A modifications and cardiovascular diseases, including cardiac hypertrophy,[86] heart failure,[19] atherosclerosis, coronary heart disease,[87] ischemic cardiomyopathy, hypertension, and vascular disease.[88] Therefore, inhibiting concurrent signaling pathways will have important therapeutic significance for interventions in these cardiac diseases.

Cardiac hypertrophy

In the presence of hemodynamic stress, cardiomyocytes adapt by becoming hypertrophic. This reaction plays a reparative role in improving cardiac function, decreasing the strain on the ventricular wall and oxygen expenditure.[89] Cardiac hypertrophy can be divided into two types: physiological and pathological. Physiological cardiac hypertrophy, which can maintain normal morphology and play a beneficial role in the heart, mostly results from exercise training or pregnancy.[90] In contrast, pathological cardiac hypertrophy causes many cardiovascular pathophysiological changes, such as ventricular remodeling, fibrosis, and cardiac gene expression alteration.[91]

Hinger *et al.*[92] found an increase in m^{6}A content in human heart failure samples but showed a preserved distribution. The protein level of METTL3 was increased, and that of FTO was decreased, while there was no change in ALKBH5 levels. Afterward, human and hypertrophic neonatal rat ventricular myocytes obtained from heart failure samples were used to investigate whether there was conserved specificity in m^{6}A events in cardiomyocytes across species. Their results showed stress-responsive m^{6}A-transcripts between rats and humans were conservative. In both human hearts and rat cardiomyocytes, Western blotting showed that coronin 6 (CORO6) levels were reduced, whereas the expression of RE1 silencing transcription factor (REST) was increased. However, the mRNA levels

of these two genes remained unaffected. Furthermore, they detected m^{6}A content in both human heart failure samples and hypertrophic cardiomyocytes. They found that REST expression was increased, while CORO6 had greater m^{6}A content in nonfailing heart and normal cardiomyocytes. Upon upregulation of METTL3, the translation levels of REST and CORO6 increased. Hence, posttranscriptional modifications may play a direct role in gene expression in cardiomyocytes.

Gao *et al.*[93] revealed a piRNA (PIWI-interacting RNA) named CHAPIR (cardiac-hypertrophy-associated piRNA), which regulates cardiac hypertrophy. Overexpression of CHAPIR using a mimic aggravated pathological hypertrophic response in a TAC mouse model, while the downregulation of CHAPIR notably attenuated cardiac hypertrophy and recovered cardiac function. In terms of mechanism, METTL3 combined with CHAPIR–PIWIL4 complexes suppressed *Parp10* mRNA m^{6}A methylation. The mRNA and protein expression levels of poly(ADP-ribose) polymerase family member 10 (PARP10) increased, which promoted mono-ADP-ribosylation of GSK3β and suppressed its kinase activity.[94] This process increased nuclear NFATC4 levels and led to the progression of pathological hypertrophy. Therefore, targeting the CHAPIR-METTL3-PARP10-NFATC4 signaling axis could be a therapeutic mechanism for improving cardiac hypertrophy.

Dorn *et al.*[95] discovered that the extent of m^{6}A methylation increases in response to hypertrophic stimulation. The growth of hypertrophic cardiomyocytes was fully abolished upon stimulation, and they did not undergo hypertrophy when METTL3 was suppressed *in vitro*. However, the overexpression of METTL3 can cause spontaneous and compensatory hypertrophy. *In vivo*, cardiac-specific METTL3-knockout mice showed cardiac remodeling and heart failure followed by cardiac homeostasis disorders, whereas increased METTL3 levels caused cardiac hypertrophy.

Kmietczyk *et al.*[96] showed that the mechanism of m^{6}A RNA methylation is dynamic and effective in cardiomyocytes undergoing pressure[97] and regulates gene expression and cellular proliferation in the heart. They found that METTL3 and FTO could participate in m^{6}A RNA methylation by influencing transcript stability and regulating translational efficiency. In an *in vitro* model of neonatal rat cardiomyocytes (NRCM), the knockdown of METTL3 reduced m^{6}A levels[98] and increased the cell size and the expression of the hypertrophic markers ANP and BNP. However, FTO-KO mice exhibited enhanced m^{6}A levels and weakened NRCM hypertrophy. In an *in vivo* model of AAV9-mediated METTL3 overexpression in C57Bl6/N mice and TAC mice, METTL3 overexpression shrank the cross-sectional area of the myocytes and suppressed pathological hypertrophic cellular growth. Nevertheless, how METTL3 and FTO regulate gene expression and cellular growth and which specific target genes play an essential role in cardiomyocyte hypertrophy are still under study.

Heart failure

Berulava *et al.*[99] discovered that the level of m^{6}A RNA methylation decreases during heart failure. The mRNA level of calmodulin 1 (calm1) remained unchanged, while the protein expression level of calm1 was reduced. In other words, m^{6}A RNA methylation levels influenced protein levels rather than mRNA levels. m^{6}A RNA methylation is directly proportional to ribosomal occupancy, indicating increased protein levels of hypermethylated transcripts and decreased protein levels of hypomethylated transcripts. A worsened cardiac phenotype in the FTO-knockout mice model after TAC was also observed, as the ejection fraction was reduced and the degree of dilatation was increased.

Mathiyalagan *et al.*[100] discovered that the demethylase FTO was associated with cardiac function during cardiac remodeling and repair. They detected reduced FTO expression levels in failing mammalian hearts and hypoxic cardiomyocytes; therefore, m^{6}A RNA methylation increased. Sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) is a contractile protein that exhibits less stability and lower efficiency to regulate translation when hypermethylated, eventually resulting in cardiomyocyte contractile function. However, FTO overexpression in human myocytes led to SERCA2a demethylation. Furthermore, cardiac contractile function improved with an increase in SERCA2a expression. They also found that FTO overexpression reduced fibrosis and promoted angiogenesis in mouse models of myocardial infarction. Hence, this mechanism provides novel insights into cardiac remodeling and repair.

RESEARCH PROGRESS ON NEW TECHNIQUES IN DETECTING m^{6}A RNA METHYLATION

Researchers are actively exploring the role of m^{6}A modification-related molecules in cardiovascular disease; however, many problems and challenges still need to be resolved. For example, transcriptome-wide mapping used in m^{6}A can help us better understand catalog m^{6}A targets and reveal the underlying epigenetic modification mechanisms. In 2012, *Nature* and *Cell* published a method for the whole transcriptome sequencing of m^{6}A modification via m^{6}A-specific antibody enrichment (MeRIP-seq or m^{6}A-seq);[19,101] however, MeRIP-seq has an insufficient resolution (about

100 nt). However, insurmountable weaknesses in principle, such as low repeatability, large sample demand, and cumbersome operation, have caused significant problems in m^{6}A research in recent years.

In 2015, *Nature Methods* proposed a new method for the high-resolution detection of the localization of N^6-methyladenosine in eukaryotic RNA called m^{6}A single-nucleotide resolution cross-linking and immunoprecipitation (miCLIP).[102] Mutations would occur when the cross-linking of the RNA-m^{6}A antibody-binding sites is reverse-transcribed. The mutated sequences had unique features (*e.g.*, C-T transition or truncation) that could pinpoint m^{6}A. miCLIP can perform high-resolution detection of individual m^{6}A residues and m^{6}A cluster analysis of the total RNA. In particular, miCLIP is suitable for small nucleolar RNA (snoRNA).

In a recent study, Zhang *et al.* published a research paper titled "Single-base mapping of m^{6}A by an antibody-independent method,"[103] which described a new principle of m^{6}A detection technology named m^{6}A-REF-seq (m^{6}A-sensitive RNA-endoribonuclease-facilitated sequencing). This technology used the sensitivity of the newly discovered RNA endonuclease to m^{6}A, which eliminated the dependence of traditional methods on antibodies and achieved accurate detection of m^{6}A across the transcriptome.[104] New methods must be implemented in the m^{6}A field with the development of better scientific methods and technological advances. However, whether other types of m^{6}A modification have some links to cardiac remodeling is still to be discovered. Finally, drugs targeting m^{6}A are promising for the clinical treatment of cardiovascular diseases.

We hope that consistent studies in this field can further deepen our understanding of the processes surrounding heart failure and approach the reality of discovering new treatments, thereby improving the quality of life of patients with heart failure.

CONCLUSIONS AND FUTURE PERSPECTIVES

The most abundant RNA modification in RNA epigenetics is m^{6}A methylation.[105] m^{6}A methylation studies have currently gained significant popularity in scientific research.[106] In this review, we focused on cardiac remodeling, summarized the

Table 1: m^{6}A and cardiac remodeling

Types of cardiac remodeling	Effector	Type of effector	Expression	Target genes	Mechanism	Reference
Cardiac hypertrophy	METTL3 FTO	Writer Eraser	Upregulation Downregulation	REST CORO6	Protein expression was higher in condition of greater m^{6}A content, and overexpression of METTL3 was sufficient to positively affect the translation of REST and CORO6	[92]
	METTL3	Writer	Reduce activity of METTL3	PARP10	CHAPIR-PIWIL4 → METTL3 → m^{6}A-PARP10 → PARP10 (mRNA and protein) → mono-ADP-ribosylation of GSK3β → GSK3β kinase activity → NFATC4 → pathological hypertrophy	[93]
	METTL3	Writer	Upregulation	MAP3K6/ MAP4K5/ MAPK14/ Nppa/Nppb	*In vitro*: METTL3 → prevent pathological hypertrophy METTL3 → spontaneous and compensate hypertrophy *In vivo*: METTL3-KO → remodeling and heart failure → cardiac homeostasis disorder METTL3 → cardiac hypertrophy	[95]
	METTL3	Writer	Downregulation	Unknown	*In vitro*: METTL3-KO → m^{6}A level → cell size and level of Nppa/Nppb; FTO-KO → m^{6}A level → hypertrophy of NRCM *In vivo*: METTL3-overexpression → myocytes cross-sectional area → pathological hypertrophic cellular growth	[96]
Heart failure	FTO	Eraser	Downregulation	Calm1	Calm1 protein expression regulation in heart failure occurs partially only on translational level and without changes in DNA to RNA transcription	[99]
	FTO	Eraser	Downregulation	SERCA2a	In failing mammalian hearts and hypoxic cardiomyocyte, FTO SERCA2a mRNA is hypermethylated cardiomyocytes contractile function	[100]

METTL3: methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit; REST: RE1 silencing transcription factor; CORO6: coronin 6; PARP10: poly (ADP-ribose) polymerase family member 10; MAP3K6/5/14: mitogen-activated protein kinase kinase kinase 6/5/14; Nppa: natriuretic peptide A; Nppb: natriuretic peptide B; FTO: FTO α-ketoglutarate-dependent dioxygenase; Calm1: calmodulin 1; SERCA2a: sarco/endoplasmic reticulum Ca^{2+}-ATPase.

classification of m^{6}A RNA methylases, and discussed their dynamic modification (Figure 1) in detail. Furthermore, we surveyed m^{6}A RNA modifications in cardiac remodeling, including cardiac hypertrophy and heart failure (Table 1). The mechanisms regarding the development of cardiac hypertrophy are intricate; however, what we currently know is just the tip of the iceberg, and further research is needed to elucidate the epigenetic mechanisms underlying heart failure.[107] In the past few years, we have opened new areas for advancing the known mechanisms and identifying the unknown pathways involved in cardiac remodeling. Heart failure is still difficult to cure in the clinical setting and its prevalence rate increases with age.[108] m^{6}A has potential applications in the diagnosis and treatment of heart failure. Research focus should be placed on the abnormal expression of some m^{6}A enzymes, such as METTL3 and FTO, because they are related to cardiac hypertrophy or heart failure since the early detection of these abnormalities will help in the early diagnosis of heart failure. It is also possible that we interfere with the expression of methylases, such as METTL3 and FTO, to prevent heart failure.

Source of Funding

This study was funded by the National Natural Science Foundation of China (No. 8197021725) and the Shenyang Science and Technology Project (No. 19-112-4-003).

Conflict of Interest

Yingxian Sun is an Associate Editor-in-Chief of the journal. The article was subject to the journal's standard procedures, and peer review was handled independently of this editor and his research groups.

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How to cite this article: Yang Y, Muisha MB, Zhang J, Sun Y, Li Z. Research progress on N^6-adenosylate methylation RNA modification in heart failure remodeling. J Transl Intern Med 2022; 10: 340-348.