Research Progress of N6-Methyladenosine in the Cardiovascular System

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According to the World Health Organization cardiovascular disease risk charts, the mortality rate of cardiovascular diseases in people is still high. The medical expenses caused by cardiovascular diseases are increasing daily, and the medical burden is becoming heavier; as such, it is imperative to prevent and cure cardiovascular diseases. A large number of scholars are analyzing the pathogenesis of cardiovascular diseases from various perspectives. Recent findings suggest that N6-methyladenosine (m6A) plays a multifaceted role in the cardiovascular system. m6A is a methylated modification product on RNA molecules and exists on various RNA molecules. It is one of the most common epigenetic modifications discovered to date. It regulates the expression of genes and subsequent responses. The amount of m6A is determined by methylases (writers) and demethylases (erasers). The third type of proteins, readers, selectively bind to m6A to regulate RNA stability and gene expression. In this paper, the relationship between m6A and related enzymes and cardiovascular structure and function was reviewed based on recent research results regarding the cardiovascular system.

MeSH Keywords: Cardiovascular System • Heart Diseases • Lipid Metabolism

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Background

In this paper, the relationship between m6A and related enzymes and cardiovascular structure and function was reviewed based on the results of recent research regarding the cardiovascular system.

Epidemiology of Cardiovascular Diseases

In recent years, international research on cardiovascular diseases has been ongoing. Cardiovascular disease has always ranked high in total disease mortality [1]. The medical expenses caused by cardiovascular diseases are increasing, and the medical burden is becoming more oppressive. It is imperative to prevent and treat cardiovascular diseases. Researchers are not only studying cardiovascular functions and morphological changes; more and more scholars in recent years have begun to study the role of epigenetics in disease. They recently discovered that m6A might be associated with many fundamental changes in the heart or blood vessels.

The Modifications on RNA

More than 100 modifications of RNA molecules have been discovered so far, and the number is still increasing [2]. Post-transcriptional modification of RNA gives it more functional diversity, enabling alteration of the original function of the 4 basic ribonucleotides, similar to the role of amino acid side chains. Nucleotide modifications can affect function by affecting RNA structure. Similarly, these modifications can also affect the interaction of RNA with other molecules, particularly proteins. In general, they create molecular diversity of RNA molecules, especially in complex regulatory networks. In these regulatory networks, changes in the structure and function of RNAs can lead to changes in various subsequent processes, such as transcription.

There are many post-transcriptional modifications, like 5-methylcytosine (m5C), and N1-methyladenosine (m1A) [3]. N6-methyladenosine (m6A) is a methylation modification of the 6th N of adenine (A) catalyzed by a methyltransferase.

N6-Methyladenosine and Its Related Enzymes

m6A was initially discovered in the 1970s. The research found that m6A is one of the most abundant modifications after transcription. It accounts for approximately 50% of methylated RNA in cellular RNA and is most commonly found at the 3' end of the RNA and near the stop codon [4–6]. m6A is a modification of not only mRNAs (messenger RNAs) but also tRNAs (transfer RNAs), rRNAs (ribosomal RNAs), and lncRNAs (long noncoding RNAs). Multiple experiments have shown that the amount of m6A in the heart, kidney, and brain is much greater than that in other tissues. In different tumor cell lines, the amount of m6A is also different. Its generation, elimination, and actions are mainly related to 3 types of proteins.

The first class of proteins is methyltransferases, which promote the methylation of adenine in RNA. A transferase is composed of multiple components, and the components, which have been previously identified, including METTL3 (methyltransferase-like 3), METTL14 (methyltransferase-like 14), and WTAP (Wilms tumor suppressor-1-associated protein) [7–9]. Among them, METTL3 interacts with S-adenosylmethionine, which was the first essential component to be discovered. METTL14 is another active component that was discovered later. The difference between the 2 writers is that METTL3 is mainly used as the catalytic core of the complex, while METTL14 mainly assists in the binding of the transferase to the RNA [10]. After knocking out METTL3 and METTL14, the amount of m6A in various cells was significantly reduced. The upregulation of METTL3-METTL14 and m6A can be found in tissues repaired after UV (ultraviolet) damage. It demonstrates that, in the number of m6A changes, METTL3-METTL14 dimers play a key role. WTAP is also a vital component of the transferase complex. It has no direct effect on the methylation of adenine. However, it can interact with the 2 joint components of the transferase, METTL3 and METTL14, resulting in a change in the catalytic activity of the transferase, ultimately affecting the entire methylation process [11].

In more recent years, new transferase components, such as METTL16 (methyltransferase-like 16), KIAA1429, and RBM15/15B (RNA binding motifs protein 15/15B), were discovered [12–15].

Methyltransferases, such as METTL16, are closely related to methionine adenosyltransferase II (MAT2a). METTL16 can change the amount of m6A in the 3’UTR of MAT2a, thereby regulating the metabolism of SAM [16,17].

These functional components are involved in the operation of the enzyme complex. However, their mutual connection and respective roles are still not fully understood and are still under further study.

The second class of proteins is m6A demethylases, which selectively remove methyl groups from m6A. FTO (fat mass and obesity-associated protein) was the first m6A demethylase identified. Since then, people have realized that the process of demethylation is reversible, so more attention has been devoted to researching the process of demethylation. In 2013, the second RNA demethylase, ALKBH5 (α-ketoglutarate-dependent
dioxidogenase homolog 5), was discovered [18–20]. The researchers found that m6A levels were increased in total mRNA isolated from the organs of ALKBH5-deficient mice and that ALKBH5 deficiency resulted in impaired sperm production and development. Recently, the size of the testes of ALKBH5 knockout mice was found to be smaller than that of normal mice. ALKBH5 is also necessary for the later stages of meiosis [21]. All of these findings indicate that ALKBH5 may affect the physiological activities of the organism, and this effect is likely caused by the change in the amount of m6A.

Another m6A demethylase, ALKBH3 (α-ketoglutarate-dependent dioxygenase homolog 3), has recently been discovered. Interestingly, ALKBH3 has a greater affinity for m6A in tRNA than for m6A in mRNA or rRNA.

The discovery of demethylases indicates that the conversion between adenine and N6-methyladenosine is a reversible process. This process is first initiated by the methylase, which catalyzes the production of m6A based on physiological regulations and external stimuli. Demethylases can selectively remove methyl groups. After the completion of methylation and demethylation, the final number of m6A alterations is changed, which can regulate the expression of several genes.

The third class of proteins binds to specific sites on N6-methyladenosine in RNAs, allowing the methylation to serve its function. This type of protein is a reader. YTH family proteins are the first known reader proteins. This includes YTHDF3, YTHDF2, and YTHDF1. YTHDF2 was the first m6A reader protein to be discovered. YTHDF3 and YTHDF1 can synergistically promote the translation of methylated RNA and can directly interact with YTHDF2 to accelerate the decay of mRNA [22–24].

The Impact of m6A Modification on the Cardiovascular System

Many studies have shown that m6A has a specific relationship with cardiovascular risk factors and structural functions. Cardiovascular disease is closely related to risk factors and structural functions. At present, in the cardiovascular field, the relationship between m6A and cardiovascular risk factors and structural functions is mainly studied to explore the relationship between the occurrence and development of diseases.

m6A and Cardiovascular Risk Factors

Hyperlipidemia is a definite risk factor for coronary atherosclerotic heart disease [25]. In clinical treatment, lipid-lowering therapy is now an essential strategy. Therefore, in the occurrence and treatment of coronary heart disease or other vascular plaque diseases, studying the mechanisms of blood lipid production and elimination can help us solve many clinical problems. m6A has been confirmed to be closely related to blood lipids. Zhong et al. [26] found that m6A is associated with lipid metabolism mechanisms. They knocked down the methyltransferase METTL3 to reduce the amount of N6-methyladenosine in mice and found that the lipid accumulation in the cells was significantly reduced. The entire lipid metabolism pathway was also affected. When the reading protein YTHDF2 binds to the m6A site on the RNA of PPARα, the downstream lipid metabolism pathway can also be regulated. Sheng et al. found that YTHDF2 directly binds to the m6A modification site to promote 6PGD (6-phosphogluconate dehydrogenase) mRNA translation [27] and increase the amount of 6PGD in cells. The cholesterol level of people with 6PGD deficiency is significantly lower than that of normal people. In addition, 6PGD-deficient cells have significantly less cholesterol than normal cells [28]. Further studies have shown that 6PGD deficiency can cause cells to absorb more cholesterol in the plasma, leading to lower blood cholesterol, and reduce the risk of cardiovascular disease. Therefore, YTHDF2 might be a target for lowering cholesterol.

Similarly, the role of overweight and obesity in the development of cardiovascular disease cannot be ignored. Many research reports have noted that obese people can reduce the incidence of cardiovascular disease if they reduce their body weight and abdominal circumference [25]. It has also been found that m6A plays a vital role in the process of obesity. Fischer et al. [30] found that in mice, loss of FTO led to growth retardation after birth and a marked reduction in adipose tissue. In the human body, it was also found that the variation or loss of FTO led to an increase in basic energy consumption, resulting in a decrease in adipose tissue and a weight reduction effect [30]. Later, FTO was confirmed to be positively correlated with changes in body mass index (BMI) [31]. The upregulation of FTO can increase an individual’s food intake and increase the accumulation of white adipose tissue in the abdomen [32,33].

Hypertension can be seen in the development of most cardiovascular diseases [1,25]. The incidence of hypertension worldwide is not encouraging, and the number of patients with hypertension is increasing rapidly. Although the mechanism of hypertension is unclear, it has been confirmed that hypertension is associated with obesity and metabolic syndrome. Therefore, the regulation of m6A in adipose tissue and its relationship with cardiovascular diseases have been widely studied. The expression of FTO, which is associated with obesity, was confirmed to be positively correlated with changes in body mass index [29].

In addition, the size of the testis of ALKBH5 knockout mice was reduced [26]. Further studies have shown that m6A levels were increased in total mRNA isolated from the organs of ALKBH5-deficient mice. ALKBH5 deficiency resulted in impaired sperm production and development. The size of the testes of ALKBH5 knockout mice was found to be smaller than that of normal mice. ALKBH5 is also necessary for the late stages of meiosis [21]. All of these findings indicate that ALKBH5 may affect the physiological activities of the organism, and this effect is likely caused by the change in the amount of m6A.

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Previously, Lu et al. [29] found that curcumin could affect METTL3, METTL14, ALKBH5, FTO, and YTHDF2 when curcumin in the study diet was used to treat LPS (lipopolysaccharide)-induced liver injury. The expression of these proteins changed, thereby increasing the amount of m6A in the liver. Finally, they found that the protective effect in regulating lipid metabolism was derived from the increase in m6A.

These results all illustrate the critical role of m6A in the overall lipid metabolism mechanism.
cardiovascular disease is increasing each year [34]. Mo et al. confirmed that there is a clear relationship between m6A on multiple RNAs and systolic and diastolic blood pressure. m6A can affect the regulation of blood pressure [35].

Hyperlipidemia, hypertension, and obesity are clear risk factors for cardiovascular and cerebrovascular diseases, and these relationships have been confirmed. Many studies have shown that m6A has a clear relationship with these risk factors, and some studies have even examined whether there is a relationship between m6A and cardiovascular disease: the answer is yes [35]. These studies confirmed that coronary heart disease and stroke are associated with m6A, but the specific mechanism is still unclear. However, the aforementioned risk factors may be one of the answers.

**Effect of m6A on Heart Structure and Function**

In the development of heart diseases, changes in cardiac structure can play a critical role, and we focus here on the underlying cardiac hypertrophy and the underlying mechanisms of myocardial structural changes in ischemic heart disease.

Cardiac hypertrophy is the response of the cardiomyocyte to stress and other factors, which can compensate for the ejection fraction. Donald Teare first proposed this concept in 1958. At the cellular level, cardiac hypertrophy is the reaction of cardiomyocyte under the influence of external factors: the size becomes larger, the protein content increases, and the contraction ability is stronger [36].

At the same time, as a compensatory adaptation to the needs of the body, cardiac hypertrophy can lead to myocardial ischemic diseases, hypertension, arrhythmia, and similar issues. Chronic heart failure, which still has high associated morbidity and mortality, has also been shown to be associated with chronic cardiac hypertrophy [37]. Therefore, studying cardiac hypertrophy has become a hot topic in the medical field.

Dorn et al. [38] found that the response of the myocardium to hypertrophic stimulation increased significantly with the increase of m6A, which, to some extent, suggested the role of m6A in cardiac hypertrophy. They confirmed that this effect was achieved through METTL3. Adenovirus transfection artificially increased the expression level of METTL3 in the myocardium. By observing the level of m6A methylation on mitogen-activated protein kinases (MAPKs), the researchers found that the expression levels of MAP3K6, MAP4K5, and MAPK14 were increased. In addition, the size of the myocardial cells also increased. When the methyltransferase METTL3 is inhibited, the myocardium loses its ability to hypertrophy under-stimulation. That is, under the normal stresses of the outside world or the body itself, the process of METTL3 generating m6A modifications is regulated [38]. Interestingly, Kmietczyk et al. found that overexpression of METTL3 blocked the progression of cardiomyocyte hypertrophy. m6A can affect the amount of RNA in cardiomyocytes and can regulate translation efficiency. It can regulate cell growth and hypertrophy in this way [39]. These 2 results seem to be conflicting, and perhaps the experimental design differences can explain some of the discrepancies in the data. However, this also shows that the adaptation mechanism is still unknown, and there may need to be some minor adjustments to the model. See Figure 1 [38,39].

On the other hand, changes in myocardial structure or changes in function may be closely related to myocardial ischemia. Long-term changes in blood supply may cause subsequent changes in highly aerobic myocardial tissue. These changes can affect short-term cardiovascular function and long-term prognosis. In ischemic myocardium, the researchers compared the expression of major methylases, demethylases, and reader proteins and found that FTO expression was significantly reduced in ischemic cardiomyocytes. That is, the low expression of FTO in the myocardium after ischemia and hypoxia led to subsequent changes in myocardial structure and function. This regulation is mainly accomplished by regulation of the model. See Figure 1 [38,39].
the changes of myocardial structure to a certain extent and plays a role in improving clinical prognosis [40]. On the other hand, FTO has been shown to inhibit intracellular p53 (the tumor suppressor gene) expression [41]. Low expression of p53 has also been shown to inhibit coronary endothelial cell apoptosis, increase coronary flow, and improve cardiac contractility in diabetic patients [42]. It is still uncertain whether there is a link between the different ways in which FTO functions.

In addition, Song et al. [43] found that the amount of m6A was increased in ischemic myocardium, but they believed that the enhanced effect of METTL3 mainly caused this increase. Silencing METTL3 can inhibit cardiomyocyte apoptosis after ischemia-reperfusion injury and improve subsequent structural changes. ALKBH5 can also reverse this effect to a certain degree. The transcription factor EB is a crucial link. It is a downstream target of METTL3 and ALKBH5 and is an essential factor for achieving the reversal of myocardial function.

The enzymes that played a major role in these studies were different, but ultimately, the changes in m6A content were consistent and increased. Interestingly, one effect is an enhanced effect on the methylase, and the other is a decrease in the level of demethylases. However, the combined effects of the 2 enzymes still have different mechanisms, and these are still unknown.

### m6A in the Blood Vessels of the Brain

Stroke cannot be ignored in cardiovascular disease. It is the second most common cause of cardiovascular disease-related mortality, preceded by only ischemic heart disease. The number of cases has increased each year, causing a substantial worldwide medical burden [44]. The cause of stroke has been studied, but the relationship of stroke with different genes is still under study. Mo et al. [45] found several m6A-related single-nucleotide polymorphisms (SNPs) that can affect the incidence of stroke. The mechanism may be that these m6A-SNPs affect the expression of disease-causing genes [31,45]. However, stroke can also lead to changes in the number of m6A alterations, and the researchers initially suspected that these changes might be caused by alterations in the physiological mechanisms of the brain after a stroke [46]. The relationship between these factors still needs further research because they are not fixed causal relationships, and the reverse relationship may be the real one.

### Conclusions

Cardiovascular diseases are common disorders, and efforts must be made to reduce the burden of medical expenses. The current research on the mechanism of m6A in cardiovascular disease is limited. It remains to be unclear that FTO, METTL3, ALKBH5, or other methylases and demethylases would affect organ function by acting on m6A levels or downstream targets such as the transcription factor EB. Reader proteins can also influence the process of gene expression through binding to m6A. However, the relationship between m6A and heart or cerebral vascular disease would be interpreted by future studies.

### Outlook

Although some of the above results are consistent, the process is not exactly the same, which has caused us to consider whether there are still some unknown downstream targets that affect the final result and whether m6A can be used as a regulatory target for blood lipid regulation or a marker of heart failure stage. Can the processes of remodeling after myocardial infarction artificially increase the levels of FTO, reduce the level of fibrosis in the heart, and benefit prognosis and subsequent rehabilitation process? In the setting of heart hypertrophy caused by hypertension, after determining the specific mechanism, we can suppress hypertrophy of the myocardium by suppressing METTL3 or activating METTL3. Moreover, m6A can be used as a novel disease predictor or disease-related substance.

In general, an understanding of the quantitative changes in the amount of m6A in RNA and the dual regulation of gene expression may be used to answer some questions that could not be answered before and provide new ideas for the treatment of various cardiovascular diseases.

### Conflict of interest

None.
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