Am J Transl Res 2025;17(1):47-59
www.ajtr.org /ISSN:1943-8141/AJTR0162038

Review Article

Regulatory mechanisms of m^{6}A methylation in dilated cardiomyopathy

Hao Zhang, Haiyang Guo, Fengjiao Han, Yang Zheng

Department of Cardiology, The First Hospital of Jilin University, Changchun 130021, Jilin, China

Received November 15, 2024; Accepted December 9, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Dilated cardiomyopathy (DCM) is a complex heart condition marked by genetic mutations, myocardial dysfunction, and progressive heart failure. N6-methyladenosine (m^{6}A) methylation, a key epigenetic modification, plays a crucial role in DCM by regulating gene expression in various pathologic processes, including cardiomyocyte death, inflammation, fibrosis, and mitochondrial dysfunction. m^{6}A modifications influence cardiomyocyte survival by modulating apoptosis, necroptosis, ferroptosis, and autophagy-related genes, balancing cellular death and survival pathways. Additionally, m^{6}A-driven regulation of inflammation and fibrosis contributes to immune microenvironment stability and extracellular matrix remodeling, affecting fibroblast activation and myocardial stiffness. Mitochondrial health, vital for cardiomyocyte energy demands, is also regulated by m^{6}A methylation. Enzymes like methyltransferase-like (METTL) 3 and METTL14 promote mitophagy-related gene expression, while fat mass and obesity-associated protein modulates calcium homeostasis, mitigating oxidative stress and energy imbalances. Targeting m^{6}A-related enzymes with small molecules, gene editing, or RNA interference (RNAi) offers potential for tailored DCM therapy. Emerging technologies, such as nanopore m^{6}A-modified mRNA detection, reveal new insight into cardiomyocyte metabolism, suggesting novel therapeutic avenues. This review underscores m^{6}A methylation as a pivotal epigenetic mechanism of DCM, providing a basis for advanced diagnosis and therapy.

Keywords: Dilated cardiomyopathy, m^{6}A methylation, programmed cell death, mitochondrial dysfunction

Introduction

Dilated cardiomyopathy (DCM) is a chronic heart condition marked by ventricular dilatation and reduced systolic function, ultimately leading to heart failure [1]. In the past, DCM was considered a rare condition. However, recent advancements in epidemiologic studies have revealed a prevalence as high as 1 in 250, making it one of the most common causes of heart failure worldwide and a major indication for heart transplantation [2]. DCM is marked primarily by left ventricular dilatation, thinning of the myocardial wall, and progressive loss of cardiac function [3, 4]. Although various treatment options, including pharmacotherapy and device support, have been developed to slow DCM progression, the overall survival rate of patients remains low, highlighting the urgent need for deeper research into its pathophysiologic mechanisms to identify new therapeutic targets [5, 6].

In recent years, epigenetic research has provided new directions for understanding the pathogenesis of DCM. N6-methyladenosine (m^{6}A) methylation is one of the most common epigenetic modifications of mRNA, playing a key regulatory role in RNA stability, splicing, translation, and degradation [7, 8]. This modification is dynamically regulated by "writer" enzymes that add the modification, "eraser" enzymes that remove it, and "reader" proteins that recognize it, forming a complex and dynamic equilibrium [9-11]. m^{6}A modification is linked to several cardiovascular diseases, including ischemic heart disease and heart failure, suggesting it may have extensive biologic functions in the cardiovascular system [12, 13].

m^{6}A methylation may regulate cardiomyocyte behavior through multiple pathways, by affecting cell proliferation, apoptosis, and metabolism, thereby promoting structural remodeling of the heart [14, 15]. Previous studies have

https://doi.org/10.62347/AOSK8903

demonstrated that m^{6}A-related enzymes play crucial roles in heart-related diseases, with deficiencies in YTHDC1 shown to induce DCM in mice [16]. Furthermore, m^{6}A modification may influence myocardial fibrosis development by modulating fibrosis-related signaling pathways [17, 18]. These studies suggest that m^{6}A methylation may have a regulatory role in the development and progression of DCM, serving as a critical epigenetic regulatory node.

Based on this, the purpose of this review is to systematically summarize the regulatory mechanisms of m^{6}A methylation in DCM and its therapeutic implications. First, we will review and introduce the major pathophysiological mechanisms of DCM and m^{6}A methylation; next, we will delve into the role of m^{6}A methylation in processes such as cardiomyocyte death, myocardial inflammation and fibrosis, and mitochondrial dysfunction; finally, we will discuss the potential of m^{6}A methylation as a therapeutic target for personalized treatment.

DCM

Genetic mutations and epigenetic factors

The pathogenesis of DCM is closely associated with various genetic mutations, particularly those affecting genes encoding structural proteins of the myocardium. The titin gene (TTN) is one of the most significant genes implicated in DCM [19]. It is estimated that 35%-40% of hereditary DCM cases may be caused by mutations in sarcomeric genes, most of which involve truncating mutations in TTN. These mutations alter myocardial fiber compliance, contributing to the development of DCM [20]. Missense and truncating mutations in the gene encoding the nuclear lamina protein, lamin are the second most common cause of familial DCM, responsible for 5%-8% of autosomal dominant cases [21, 22].

In addition to these genetic factors, other mechanisms have been reported to play roles in the progression of DCM. Myocardial connexin (Cx) 43 expression is reduced in the patients with DCM who die suddenly. The alteration of quantity and distribution of myocardial Cx43 expression is probably related to sudden death of the patients with DCM [23]. In clinical trials, increased p53 expression in DCM has been associated with dysregulation of the ubiquitin-proteasome system [24]. Overall, these studies highlight the significant role of post-transcriptional regulation of mRNA in the pathogenesis of DCM.

The role of epigenetic modifications in DCM has also gained increasing attention. Research suggests that DNA methylation, histone modifications, and non-coding RNAs are vital regulators of DCM-related gene expression. For example, abnormal DNA methylation levels of specific genes have been observed in the myocardial tissues of DCM patients, affecting the transcriptional activity of these genes [25, 26]. Recently, m^{6}A methylation has also been identified as a participant in the regulation of DCM. Preliminary studies suggest that it may modulate the pathophysiologic process of DCM through mechanisms such as remodeling the immune microenvironment [27] and influencing the splicing of TTN [16].

Cardiomyocyte death

Cardiomyocyte death is a key feature in the pathologic progression of DCM, involving various regulated cell death mechanisms, including apoptosis, necroptosis, ferroptosis, and pyroptosis. These forms of cell death collectively alter the survival of cardiomyocytes and the overall function of the heart, accelerating disease progression [28].

In DCM, apoptosis is the primary form of cardiomyocyte death, often triggered by oxidative stress, inflammatory factors, and genetic mutations. The intrinsic apoptotic pathway involves mitochondrial damage and activation of the caspase family, leading to programmed cell death in cardiomyocytes [29]. The extrinsic apoptotic pathway, mediated through death receptor signaling, further contributes to myocardial injury [30]. Studies have shown that mutations in genes such as TTN and lamin A/C (LMNA) increase the susceptibility of cardiomyocytes to apoptosis, exacerbating structural and functional cardiac impairment [31].

Beyond apoptosis, necroptosis and ferroptosis also play significant roles in DCM [28]. Necroptosis is characterized by inflammation, where activation of receptor-interacting protein kinase 3 (RIPK3) and mixed lineage kinase domain-like protein (MLKL) results in cell membrane rupture. This form of cell death in DCM is

often accompanied by intense inflammatory responses, aggravating ventricular remodeling [32]. Ferroptosis, on the other hand, is mediated by iron-dependent lipid peroxidation, leading to cell death. This mechanism is closely linked to mitochondrial dysfunction and metabolic dysregulation within cardiomyocytes [33, 34].

In addition, autophagy also plays a dual role in DCM. Autophagy is an intracellular degradation mechanism that helps maintain cellular homeostasis by clearing damaged organelles and proteins [35]. In cardiomyocytes, moderate autophagy is crucial for stress adaptation and the removal of damaged mitochondria [36]. However, when autophagy is excessively activated, it may contribute to cardiomyocyte death. In DCM, autophagy is often incomplete or impaired due to oxidative stress and energy deficiencies, leading to an accumulation of damaged organelles and exacerbating myocardial dysfunction [37].

m^{6}A methylation may play an important role in regulating cardiomyocyte death. For instance, preliminary studies suggest that methyltransferase-like 3 (METTL3) may positively influence cardiomyocyte survival by modulating the mRNA stability of apoptosis- and autophagy-related genes [14, 38].

Inflammation and fibrosis

Myocardial damage, from genetic or environmental factors, triggers inflammation and recruits immune cells to repair the heart; infections and autoimmunity are the primary causes of inflammatory DCM [39]. Fibrosis, resulting from inflammation at injury sites, is a pathologic hallmark of DCM alongside dilatation [1, 40]. Cardiac fibroblasts are central to fibrogenesis, activated by various cellular and humoral factors. Macrophages, CD4+ and CD8+ T cells, mast cells, and endothelial cells promote fibrogenesis by directly activating fibroblasts and indirectly producing profibrotic molecules [41]. Regional dysfunction or volume overload increases cardiac workload and wall stress, activating fetal genes and myocyte reprogramming into myofibroblasts [42]. These processes both result from and drive fibrosis. Over time, fibrotic tissue replaces damaged areas, stiffening the heart and accelerating dilatation and heart failure.

Mitochondrial dysfunction

A notable characteristic of DCM is mitochondrial dysfunction, which has a profound impact on myocardial energy metabolism and overall cardiac function [43]. Mitochondria are the primary sites of ATP production in cardiomyocytes, and their functional integrity is essential for maintaining the energy supply of these cells [44]. In DCM patients, common features include abnormal mitochondrial morphology and structure, reduced mitochondrial numbers, and impaired ATP synthesis capacity [45]. This mitochondrial dysfunction leads to decreased efficiency of fatty acid oxidation and glycolytic pathways, resulting in inadequate energy supply and metabolic imbalance in cardiomyocytes [46].

Mitochondrial dysfunction is closely linked to the regulation of mitophagy. Mutations in the LMNA gene have been shown to affect the mitophagy process, leading to impaired clearance of damaged mitochondria, which further reduces mitochondrial numbers and affects their function [47]. Similarly, mutations in the TTN significantly disrupt mitochondrial bioenergetics, rendering cardiomyocytes unable to produce sufficient ATP under high-energy demand conditions, which manifests as severe energy metabolic dysregulation [48].

Mitochondrial dysfunction also further affects calcium homeostasis in cardiomyocytes. Impaired mitochondrial calcium transport disrupts calcium signaling during cardiomyocyte contraction and relaxation, leading to a deterioration in the mechanical function of the heart. This calcium imbalance exacerbates myocardial cell damage and is a significant factor in the decline of cardiac function in DCM patients [49].

m^{6}A methylation modification

Overview of m^{6}A

m^{6}A methylation is the selective addition of methyl groups to specific adenine bases in RNA by the RNA methyltransferase complex (MTC) [50]. m^{6}A is the most prevalent dynamic and reversible modification in mammalian mRNA, occurring within a conserved DRACH motif (D = A, G, U; R = A, G; H = A, C, U) [51-53]. m^{6}A modification affects mRNA stability, nuclear export,

and translation initiation by interacting with various proteins. Present in almost all RNA types-including mRNA, rRNA, tRNA, snRNA, miRNA, circRNA, and lncRNA-m^{6}A plays essential roles in numerous physiologic and pathologic processes [54].

Regulation of m^{6}A methylation

Similar to other classical epigenetic modifications, m^{6}A RNA methylation is regulated by three enzyme groups: methyltransferases, demethylases, and m^{6}A-binding proteins (or "readers") [55].

Methyltransferases: The "writers" add methyl groups to RNA by forming the m^{6}A MTC [50]. Key writers include Wilms tumor 1-associated protein (WTAP), METTL3, methyltransferase-like 14 (METTL14), and subunits like VIRMA, ZC3H13, and RBM15/15B [56]. METTL3, METTL14, and WTAP are the core MTC components [57]. METTL3 is the catalytic subunit, transferring methyl groups by interaction with S-adenosylmethionine (SAM). METTL14, highly similar to METTL3, binds RNA substrates and activates METTL3 [55]. Together, METTL3 and METTL14 form a catalytic heterodimer. Although WTAP lacks catalytic function, it enhances the methyltransferase activity of the METTL3-METTL14 heterodimer [58].

Demethylases: The "erasers" remove methyl groups from adenosine in RNA, reversing the modifications made by writers. In eukaryotes, the primary erasers are fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), both part of the AlkB family of DNA repair enzymes [59-61]. FTO, as the first identified m^{6}A RNA demethylase, established the concept of reversible RNA modifications. FTO mainly functions in the cell nucleus, where it demethylates m^{6}A marks through selective splicing and processing at the 3'end of mRNA [55, 62]. ALKBH5, another demethylase belonging to the AlkB subfamily in mammals, participates in various physiologic processes by regulating mRNA stability, splicing, and translation efficiency. These processes include fertility, cell survival, and apoptosis [63].

m^{6}A-binding proteins (readers): Readers primarily recognize modifications added by writers, identifying binding sites on RNA and methylated proteins and selectively binding to modified transcripts [64]. When scanning RNA for m^{6}A modifications, readers bind to m^{6}A-modified RNA, recruiting various RNA-binding proteins to target mRNA. Readers may also alter the secondary structure of target mRNA [65, 66].

m^{6}A readers include the YT521-B homology (YTH) protein family-such as YTHDF1/2/3 and YTHDC1/2-and the insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family [67]. YTHDF2 mediates the degradation of m^{6}A-modified mRNA, while YTHDF1 and YTHDF3 enhance mRNA translation, with YTHDF3 also inhibiting RNA eraser activity [68-70]. YTHDC1 regulates mRNA splicing by retaining m^{6}A-modified exons and facilitates nuclear export of modified transcripts [71-73]. YTHDC2 improves translation efficiency and reduces mRNA abundance [72]. Nuclear HNRNP family proteins control RNA processing, and IGF2BP proteins promote the stability and translation of m^{6}A-modified mRNA [56]. Additionally, METTL3, typically a writer, can also act as a reader by promoting translation of certain transcripts [74].

Recent studies suggest that m^{6}A epigenetic modifications, including YTHDC1, may play an important role in the pathogenesis of DCM [16]. m^{6}A methylation can influence several pathophysiologic mechanisms closely related to DCM, such as cardiomyocyte death, inflammation, fibrosis, and mitochondrial metabolic disorders, underscoring its critical regulatory role in DCM progression [15, 27, 28, 44] (**Table 1**).

Pathological regulatory mechanisms of m^{6}A methylation in DCM

m^{6}A modifications in cardiomyocyte death

Cardiomyocyte death is central to the pathologic progression of DCM and involves multiple forms of regulated cell death, such as apoptosis, necroptosis, ferroptosis, and autophagy. As an essential mechanism of epigenetic regulation, m^{6}A modification profoundly influences the expression and stability of key genes involved in these forms of cell death, ultimately determining the fate of cardiomyocytes [28].

Apoptosis: Apoptosis is the primary form of cardiomyocyte death in DCM, regulated by both intrinsic and extrinsic pathways [75]. Intrinsic

Table 1. Types and functions of the m^{6}A enzymes

Type	Regulator	Biological function	References
Writers	METTL3	Engages with SAM to transfer methyl groups, catalyzing the m^{6}A methylation process	[55]
	METTL14	By identifying RNA substrates and forming heterodimers with METTL3, it activates and amplifies METTL3's methylation capacity	[55]
	WTAP	Interacts with the METTL3-METTL14 complex, significantly boosting MTC's methyltransferase function	[58]
	VIRMA (KIAA1429)	Directs the MTC's core components to targeted RNA regions	[56]
	ZC3H3	Plays a role in positioning MTC within the nucleus	[56]
	RBM15/15B	Binds with the METTL3-METTL14 heterodimer to recruit particular RNA sites	[56]
Erasers	FTO	Eliminates m^{6}A modifications to facilitate mRNA splicing and translation	[55, 62]
	ALKBH5	Removes m^{6}A marks, aiding mRNA splicing and export from the nucleus	[63]
Readers	YTHDF1	Enhances both mRNA translation and subsequent protein production	[68-70]
	YTHDF2	Facilitates mRNA breakdown and influences its cellular localization	[68-70]
	YTHDF3	Collaborates with YTHDF1 to boost mRNA translation or supports RNA degradation through YTHDF2	[68-70]
	YTHDC1	Controls both mRNA splicing and its export	[71-73]
	YTHDC2	Elevates target mRNA's translation efficiency while decreasing its quantity	[72]
	IGF2BP	Enhances the translation and stability of modified mRNA	[56]

SAM: S-adenosylmethionine; METTL3: Methyltransferase-like 3; METTL14: Methyltransferase-like 14; WTAP: Wilms tumor 1-associated protein; MTC: m6A methyltransferase complex; VIRMA: KIAA1429; ZC3H13: Zinc Finger CCCH-Type Containing 13; RBM15/15B: RNA-binding motif protein 15/15B; FTO: Fat Mass and Obesity-associated protein; ALKBH5: AlkB homolog 5; YTHDF: YT521-B homology domain family; YTHDC: YT521-B homology domain-containing protein; IGF2BP: Insulin-like Growth Factor 2 mRNA-binding Protein.

apoptosis begins through the mitochondrial pathway, activating caspase-8 and downstream caspase-3, leading to cardiomyocyte apoptosis [76]. Studies indicate that m^{6}A methylation plays a key regulatory role in apoptosis; for instance, m^{6}A-mediated upregulation of miRNA-193a promotes cardiomyocyte apoptosis through the METTL3/miRNA-193a/BCL2L2 pathway [14]. Conversely, Shen et al. demonstrated through a heart failure mouse model that overexpression of FTO could inhibit cardiomyocyte apoptosis by modulating the m^{6}A modification of Mhrt [77]. These findings suggest that the dynamic changes in m^{6}A modifications play a dual role in regulating cardiomyocyte apoptosis.

Necroptosis: Necroptosis, a form of programmed cell death closely associated with inflammation, plays a significant role in the progression of DCM [78]. Necroptosis is typically triggered by the activation of receptor-interacting protein kinase 1 (RIPK1), RIPK3, and MLKL, ultimately causing cell membrane rupture and the release of cellular contents, which leads to an inflammatory response [79]. Studies have found that m^{6}A modification regulates necroptosis by modulating the degradation of m^{6}A-modified mRNA of RIPK3, a necroptosis-associated gene, thereby reducing the occurrence of necroptosis [80].

Ferroptosis: Ferroptosis is an iron-dependent form of cell death characterized by iron-driven lipid peroxidation and failure of compensatory antioxidant systems [81]. In DCM, ferroptosis is triggered by iron metabolism dysregulation and antioxidant system impairment, which exacerbates myocardial damage [82, 83]. Studies have shown that m^{6}A modification influences ferroptosis by regulating the expression of ferroptosis-related genes involved in iron metabolism and antioxidant responses. For instance, METTL3-mediated m^{6}A methylation on the solute carrier family 7 member 11 (SLC7A11) increases the m^{6}A methylation level on its mRNA. YTHDF2 then directly binds to the m^{6}A modification sites of SLC7A11, mediating its mRNA degradation. This recognition and subsequent decay of SLC7A11 mRNA by YTHDF2 promote ferroptosis, thereby exacerbating myocardial injury [14]. Conversely, FTO inhibits ferroptosis in cardiomyocytes by demethylating m^{6}A modifications on P53 or the P21/Nrf2 pathway, thereby activating P21/Nrf2 to counteract ferroptosis [84].

Autophagy: Autophagy is a critical process by which cells maintain homeostasis by degrading

and recycling damaged organelles [85]. In DCM, autophagy acts as a stress response that aids in clearing damaged mitochondria and proteins; however, both excessive and insufficient autophagy can worsen myocardial health [86, 87]. Research indicates that m^{6}A modifications play a significant regulatory role in key genes involved in autophagy. For example, METTL3 suppresses the expression of transcription factor EB (TFEB) by adding m^{6}A modifications to the 3'-UTR of TFEB mRNA, thus inhibiting autophagy. Loss of METTL3 enhances autophagic flux in a TFEB-dependent manner. In turn, TFEB regulates the expression of METTL3 and ALKBH5, creating a feedback loop by activating ALKBH5 transcription and reducing METTL3 mRNA stability [88].

In summary, m^{6}A methylation plays a critical role in DCM through the dynamic regulation of genes involved in apoptosis, necroptosis, ferroptosis, and autophagy. Proper m^{6}A modification helps cardiomyocytes cope with adverse conditions such as metabolic and oxidative stress, thereby supporting cell survival and function. In contrast, imbalances in m^{6}A modifications may intensify cell death and accelerate DCM progression. Therefore, targeting the activity of m^{6}A regulatory factors may provide novel therapeutic strategies for slowing the progression of DCM.

m^{6}A modification in inflammation and myocardial fibrosis

Inflammation: Dysregulation of the inflammation-induced immune microenvironment is a key factor in the pathogenesis of DCM, primarily characterized by abnormal immune cell infiltration and excessive expression of pro-inflammatory cytokines in myocardial tissue. Single-sample gene set enrichment analysis has demonstrated significantly increased infiltration of CD8+T lymphocytes, natural killer (NK) cells, monocytes, and B lymphocytes in the myocardium of DCM patients, indicating a close relationship between changes in the immune microenvironment and DCM development. m^{6}A methylation mediated by insulin-like growth factor-binding protein 2 (IGFBP2) has been found to disrupt the immune microenvironment, increasing the risk of DCM [27]. This abnormal immune activation results in persistent inflammatory stimulation of cardiomyocytes, ultimately leading to myocardial fibrosis and further deterioration of cardiac function [89]. Additionally, miR-193a, enriched through m^{6}A modification, has been identified as an important regulator in the inflammatory response of cardiomyocytes [13].

Fibrosis: Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), exacerbate myocardial fibrosis by activating the transforming growth factor-beta (TGF-β)/SMAD signaling pathway, leading to fibroblast activation and excessive extracellular matrix deposition [17]. Progressive fibrosis increases myocardial stiffness, ultimately resulting in ventricular remodeling and significantly impairing cardiac systolic and diastolic function [18]. m^{6}A modification plays a regulatory role in myocardial fibrosis by modulating the expression of pro-fibrotic factors. For instance, METTL3 binds to the long non-coding RNA (lncRNA) MetBil, which is significantly increased in fibrotic tissue post-myocardial infarction in mice and in cardiac fibroblasts exposed to TGF-β1. Overexpression of MetBil promotes collagen deposition, fibroblast proliferation, and activation, enhancing cardiac fibrosis through interaction with METTL3 and regulating the methylation of fibrosis-related genes [15].

In contrast to the pro-fibrotic actions of m^{6}A methyltransferases, demethylases such as FTO demonstrate protective effects against fibrosis and inflammation. Studies in mouse models of myocardial infarction have shown that overexpression of FTO reduces fibrosis and enhances angiogenesis [62]. Furthermore, increasing evidence indicates that m^{6}A modification mediates programmed cell death (PCD), affecting myocardial fibrosis [17]. Given the relationship between PCD and m^{6}A modification, the role of m^{6}A in myocardial fibrosis warrants significant attention.

In summary, targeting the activity of m^{6}A-related factors may provide a therapeutic strategy to mitigate myocardial fibrosis and inflammation, thereby slowing the pathologic progression of DCM.

Mitochondrial dysfunction and m^{6}A modification

As the primary energy source for cardiomyocytes, mitochondrial dysfunction leads directly

to reduced ATP production and increased oxidative stress, worsening myocardial damage and cardiac dysfunction in DCM, including inflammation and fibrosis [43]. In this context, m6A modification plays a crucial regulatory role in mitochondrial quality control and functional maintenance [44].

Studies have shown that m^{6}A modification profoundly influences mitochondrial health by modulating gene expression related to mitophagy and mitochondrial dynamics [44]. In DCM, m^{6}A methyltransferases such as METTL3 and METTL14 enhance the stability and expression of mitophagy-related genes, such as PTEN-induced kinase 1 (PINK1) and Parkin RBR E3 ubiquitin protein ligase (PRKN), by increasing m^{6}A modification levels on their mRNA. This enhances the clearance of damaged mitochondria, reducing oxidative stress-induced cardiomyocyte damage [90, 91]. This regulatory mechanism is essential for maintaining mitochondrial health, helping to mitigate energy metabolism disorders in DCM.

In addition, m^{6}A modification plays a critical role in regulating mitochondrial calcium homeostasis [92]. During mitochondrial dysfunction, abnormal calcium accumulation can trigger the opening of the mitochondrial permeability transition pore (mPTP), leading to mitochondrial depolarization and increased oxidative stress [93]. METTL3, through m^{6}A modification, regulates the expression of calcium transport-related genes, thereby helping to maintain mitochondrial calcium homeostasis and reducing calcium overload damage to mitochondria. However, the high expression of the demethylase FTO removes m^{6}A modifications from these genes, reducing their expression, resulting in calcium imbalance and exacerbating mitochondrial damage [44].

Mitochondrial dysfunction also causes a significant increase in reactive oxygen species (ROS) levels, creating a vicious cycle of oxidative stress and mitochondrial damage [94]. Using hypoxia-ischemia and TGF-β1-induced fibrosis models, research has shown that inhibiting METTL3 and METTL14 reduces mitochondrial fragmentation and myofibrillar conversion, effectively decreasing cardiomyocyte stress and death [95]. This indicates that m^{6}A modification in DCM not only protects mitochondria by maintaining mitochondrial quality control and calcium homeostasis but also mitigates mitochondrial damage by enhancing antioxidant capacity, thereby slowing myocardial pathologic progression.

Additionally, regulation of the NLRP3 inflammasome mechanism is closely related to mitochondrial function, since mitochondria play a key role in the activation and regulation of the NLRP3 inflammasome. Activation of NLRP3 can further disrupt mitochondrial homeostasis, inducing NLRP3 deubiquitination, releasing mitochondria-derived molecules, and damaging mitochondrial DNA [96]. WTAP has been shown to enhance the activation of the NLRP3 inflammasome by promoting m^{6}A methylation of NLRP3 mRNA, thereby inducing cellular inflammation [97].

In summary, m^{6}A modification profoundly impacts mitochondrial dysfunction in DCM by regulating mitochondrial function and quality control. Targeting the activity of m^{6}A-related factors may offer novel therapeutic strategies to improve mitochondrial function, alleviate metabolic dysfunction, and reduce inflammation in DCM (**Figure 1**).

Conclusion and outlook

DCM is a complex disease caused by various genetic mutations leading to cardiomyopathy. m^{6}A methylation, as a crucial epigenetic mechanism, significantly influences the progression of DCM. In this review, we discussed the regulatory roles of m^{6}A modification in several DCM-related pathologic processes, primarily including cardiomyocyte death, inflammation, fibrosis, and mitochondrial dysfunction.

First, m^{6}A modification directly participates in the pathologic changes in DCM driven by genetic mutations by regulating the expression of key genes. For example, METTL3 influences the expression of crucial genes like TTN and LMNA through m^{6}A modification of mRNA, and mutations in these genes are among the major causes of DCM. m^{6}A modification not only affects gene expression levels but also regulates cardiomyocyte stress responses by altering RNA splicing, post-transcriptional stability, and translational efficiency.

Second, m^{6}A methylation plays a vital role in various forms of cardiomyocyte death, includ-

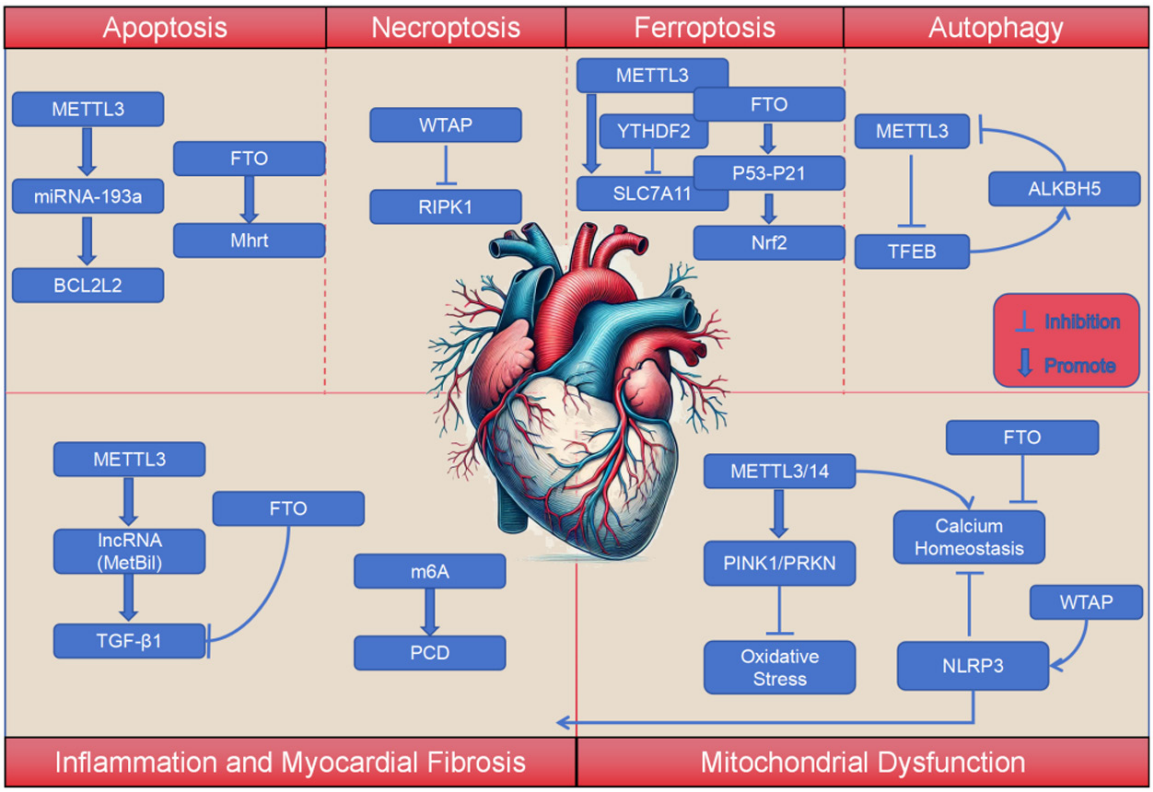

Figure 1. Pathological regulatory mechanisms of m6A methylation in DCM. METTL3: Methyltransferase-like 3; FTO: Fat Mass and Obesity-associated protein; miRNA: MicroRNA; Mhrt: Myosin Heavy Chain-Associated RNA Transcripts; BCL2L2: BCL2-like Protein 2; WTAP: Wilms Tumor 1-Associated Protein; RIPK1: Receptor-Interacting Protein Kinase 1; SLC7A11: Solute Carrier Family 7 Member 11; YTHDF2: YT521-B Homology Domain Family 2; Nrf2: Nuclear Factor Erythroid 2-Related Factor 2; P53-P21: Tumor Protein P53-P21 Pathway; ALKBH5: AlkB Homolog 5; TFEB: Transcription Factor EB; lncRNA: Long Non-Coding RNA; TGF-β1: Transforming Growth Factor Beta 1; PINK1: PTEN-Induced Kinase 1; PRKN: Parkin; NLRP3: NOD-, LRR- and Pyrin Domain-Containing Protein 3; m6A: N6-Methyladenosine; PCD: Programmed Cell Death.

ing apoptosis, necroptosis, ferroptosis, and autophagy. Regulatory factors such as METTL3, FTO, and YTHDF2 influence cardiomyocyte fate through modification or demethylation of cell death-related genes. This underscores m^{6}A modification as a key regulatory factor balancing cardiomyocyte survival and death.

Additionally, m^{6}A methylation also exerts significant effects on DCM-associated inflammation and fibrosis. Inflammation and fibrosis are primary features of DCM pathological remodeling, and m^{6}A modification regulates the inflammatory response and stability of the immune microenvironment by modulating inflammation-related genes such as NLRP3. This, in turn, influences fibroblast activation and the fibrotic process. Overall, m^{6}A modification plays a central role in DCM epigenetic regulation, fine-tuning gene expression across various pathologic processes.

In the future, therapeutic strategies targeting m^{6}A methylation may include small molecule inhibitors or activators to modulate specifically the activity of "writers" or "erasers", thereby restoring gene expression balance in DCM at the cellular level. Furthermore, gene editing technologies or RNA interference could be utilized to precisely regulate m^{6}A-related target genes, offering potential for personalized therapy. Recent studies suggest that nanopore detection of METTL3-dependent m^{6}A-modified mRNA reveals a novel mechanism for regulating mitochondrial metabolism in cardiomyocytes [98]. By targeting the dynamic regulation of m^{6}A modifications, these emerging therapeutic and diagnostic approaches may provide

new clinical tools to effectively slow or even reverse the pathologic progression of DCM.

Limitations

While this review provides a comprehensive overview of the regulatory mechanisms of m^{6}A methylation in DCM, it has several limitations that merit consideration. The discussion focuses predominantly on a narrow range of enzymes, particularly METTL3, METTL14, and FTO, while other regulators, such as ALKBH5, WTAP, and IGF2BP family proteins, received limited attention. Given the complexity of the m^{6}A methylation network, a more holistic examination of these regulators may provide a deeper understanding of the interplay among different methylation factors in DCM pathophysiology.

Moreover, the review briefly touched upon therapeutic strategies, such as small molecule inhibitors and gene editing, but lacked a detailed analysis of their feasibility, safety, or current progress in clinical or preclinical studies. Expanding this discussion would strengthen the practical implications of the findings. Additionally, while the review highlighted the roles of m^{6}A methylation in apoptosis, fibrosis, and inflammation, the underlying mechanistic pathways were not thoroughly explored.

Disclosure of conflict of interest

None.

Address correspondence to: Yang Zheng, Department of Cardiology, The First Hospital of Jilin University, No. 71, Xinmin Street, Chaoyang District, Changchun, Jilin, China. E-mail: zhengyang@jlu.edu.cn

References

[1] Heymans S, Lakdawala NK, Tschöpe C and Klingel K. Dilated cardiomyopathy: causes, mechanisms, and current and future treatment approaches. Lancet 2023; 402: 998-1011.

[2] Haas J, Frese KS, Peil B, Strom TM, Pfeufer A, Kloos W, Ott CE, Gabunia K, Hinzmann C, Fuchs M, Rottbauer W, Wichmann HE, Meitinger T, Stucka R, Kääb S, Katus HA and Keller S. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J 2015; 36: 1123-1135.

[3] Fatkin D, Huttner IG, Kovacic JC, Seidman JG, Seidman CE and Ashley EA. Precision medicine in the management of dilated cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2019; 74: 2921-2938.

[4] Japp AG, Gulati A, Cook SA, Cowie MR and Prasad SK. The diagnosis and evaluation of dilated cardiomyopathy. J Am Coll Cardiol 2016; 67: 2996-3010.

[5] Sarohi V, Srivastava S and Basak T. A comprehensive outlook on dilated cardiomyopathy (DCM): state-of-the-art developments with special emphasis on OMICS-based approaches. J Cardiovasc Dev Dis 2022; 9: 174.

[6] Hershberger RE, Cowan J, Jordan E and Kinnamon DD. The complex and diverse genetic architecture of dilated cardiomyopathy. Circ Res 2021; 128: 1514-1532.

[7] Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, Yi C, Lindahl T and Pan T. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol 2011; 7: 885-887.

[8] Zheng G, Dahl JA, Niu Y, Fedorcsak P, Huang CM, Li CJ, Vågbø CB, Shi Y, Wang WL, Song SH, Lu Z, Bosmans RP, Dai Q, Hao YJ, Yang X, Zhao WM, Tong WM, Wang XJ, Bogdan F, Furu K, Fu Y, Jia G, Zhao X, Liu J, Krokan HE, Klungland A, Yang YG and He C. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. Mol Cell 2013; 49: 18-29.

[9] He L, Li H, Wu A, Peng Y, Ge L, Zhou Q, Mao Z and Hu B. Functions of N6-methyladenosine and its role in cancer. Mol Cancer 2019; 18: 1-15.

[10] Huang H, Weng H and Chen J. m6A modification in coding and non-coding RNAs: roles and therapeutic implications in cancer. Cancer Cell 2020; 37: 270-288.

[11] Li A, Chen YS, Ping XL, Yang X, Xiao W, Yang Y, Sun HY, Zhu Q, Cheng CY, Zhang X, He C and Wang XJ. Cytoplasmic m6A reader YTHDF3 promotes mRNA translation. Cell Res 2017; 27: 444-447.

[12] Kumari R, Ranjan P, Suleiman ZG, Goswami SK, Li J and Kumar S. mRNA modifications in cardiovascular biology and disease: with a focus on m6A modification. Cardiovasc Res 2022; 118: 1680-1692.

[13] Liang L, Liu S, Wu Q, Chen R, Jiang S and Yang Z. m6A-mediated upregulation of miRNA-193a aggravates cardiomyocyte apoptosis and inflammatory response in sepsis-induced cardiomyopathy via the METTL3/miRNA-193a/BCL2L2 pathway. Exp Cell Res 2023; 430: 113712.

[14] Tang Z, Huang X, Mei H and Zheng Z. Silencing of METTL3 suppressed ferroptosis of myocardial cells by m6A modification of SLC7A11 in a

YTHDF2 manner. J Bioenerg Biomembr 2024; 56: 149-157.
[15] Zhuang Y, Li T, Hu X, Ma Y, Wang Y and Chen J. MetBil as a novel molecular regulator in ischemia-induced cardiac fibrosis via METTL3-mediated m6A modification. FASEB J 2023; 37: e22797.
[16] Gao S, Sun H, Chen K, Li L, Liu X, Wang Y and Zhang Y. Depletion of m6A reader protein YTHDC1 induces dilated cardiomyopathy by abnormal splicing of Titin. J Cell Mol Med 2021; 25: 10879-10891.
[17] Li X, Yang Y, Chen S, Zhou J, Li J and Cheng Y. Epigenetics-based therapeutics for myocardial fibrosis. Life Sci 2021; 271: 119186.
[18] Liu ZY, You QY, Liu ZY, Lin LC, Yang JJ and Tao H. m6A control programmed cell death in cardiac fibrosis. Life Sci 2024; 353: 122922.
[19] Guo W, Schafer S, Greaser ML, Radke MH, Liss M, Neuber C, Schaelling B, Mertins P, Gotthardt M and Krüger M. RBM20, a gene for hereditary cardiomyopathy, regulates titin splicing. Nat Med 2012; 18: 766-773.
[20] van den Hoogenhof MMG, Beqqali A, Amin AS, Van Der Made I, Aufiero S, Marsman RF, Pinto YM and Creemers EE. RBM20 mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling. Circulation 2018; 138: 1330-1342.
[21] McNally EM and Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. Circ Res 2017; 121: 731-748.
[22] Lee J, Termglinchan V, Diecke S, Lau E, Greenhaw M, Matsa E and Wu JC. Activation of PDGF pathway links LMNA mutation to dilated cardiomyopathy. Nature 2019; 572: 335-340.
[23] Chen X and Zhang Y. Myocardial Cx43 expression in the cases of sudden death due to dilated cardiomyopathy. Forensic Sci Int 2006; 162: 170-173.
[24] Birks EJ, Latif N, Enesa K, Khan M, Bowles CT, Eastwood M, French B, Mughal M, MacGowan GA and Yacoub MH. Elevated p53 expression is associated with dysregulation of the ubiquitin-proteasome system in dilated cardiomyopathy. Cardiovasc Res 2008; 79: 472-480.
[25] Jo BS, Koh IU, Bae JB, Choi SH, Kim YS, Nam HY and Kang C. Methylome analysis reveals alterations in DNA methylation in the regulatory regions of left ventricle development genes in human dilated cardiomyopathy. Genomics 2016; 108: 84-92.
[26] Koczor CA, Lee EK, Torres RA, Boyd AR, Vega JD and Zile MR. Detection of differentially methylated gene promoters in failing and nonfailing human left ventricle myocardium using computation analysis. Physiol Genomics 2013; 45: 597-605.
[27] Luo Z, Cheng J and Wang Y. m6A regulator-mediated RNA methylation modification remodels immune microenvironment in dilated cardiomyopathy. J Cell Physiol 2023; 238: 2282-2292.
[28] Sheng SY, Li JM, Hu XY and Wang Y. Regulated cell death pathways in cardiomyopathy. Acta Pharmacol Sin 2023; 44: 1521-1535.
[29] Chen SN, Lombardi R, Karmouch J, Shi Y, Heeke B, Gulick J, Aronow BJ, Wang M and Taylor MRG. DNA damage response/TP53 pathway is activated and contributes to the pathogenesis of dilated cardiomyopathy associated with LMNA (Lamin A/C) mutations. Circ Res 2019; 124: 856-873.
[30] Wencker D, Chandra M, Nguyen K, Boehm M, Lesch M and Kitsis RN. A mechanistic role for cardiac myocyte apoptosis in heart failure. J Clin Invest 2003; 111: 1497-1504.
[31] Liu L, Sun K, Zhang X, Tang Y and Xu D. Advances in the role and mechanism of BAG3 in dilated cardiomyopathy. Heart Fail Rev 2021; 26: 183-194.
[32] Park SM, Yoon JB and Lee TH. Receptor interacting protein is ubiquitinated by cellular inhibitor of apoptosis proteins (c-IAP1 and c-IAP2) in vitro. FEBS Lett 2004; 566: 151-156.
[33] Rhee JW, Yi H, Thomas D, Schürer S, Spigolon G, Martinez F, Torok-Storb B and Hsieh PC. Modeling secondary iron overload cardiomyopathy with human induced pluripotent stem cell-derived cardiomyocytes. Cell Rep 2020; 32: 107886.
[34] Fang X, Cai Z, Wang H, Han D, Cheng Q, Zhang P, Gao F and Yu Y. Loss of cardiac ferritin H facilitates cardiomyopathy via Slc7a11-mediated ferroptosis. Circ Res 2020; 127: 486-501.
[35] Sciarretta S, Yee D, Nagarajan N, Bianchi F, Saito T, Valenti V, Knöll R and Sadoshima J. Trehalose-induced activation of autophagy improves cardiac remodeling after myocardial infarction. J Am Coll Cardiol 2018; 71: 1999-2010.
[36] Saito T, Asai K, Sato S, Hayashi M, Takahashi T, Takahashi T, Yoshimoto T and Inagaki T. Autophagic vacuoles in cardiomyocytes of dilated cardiomyopathy with initially decompensated heart failure predict improved prognosis. Autophagy 2016; 12: 579-587.
[37] Muhammad E, Levitas A, Singh SR, Braiman A, Ofir R, Etzion S, Argov Z, Shehadeh W and Parvari R. PLEKHM2 mutation leads to abnormal localization of lysosomes, impaired autophagy flux and associates with recessive dilated cardiomyopathy and left ventricular noncompaction. Hum Mol Genet 2015; 24: 7227-7240.
[38] Song H, Feng X, Zhang H, Luo X, Li C, Yu J, Zhang Y and Han H. METTL3 and ALKBH5 oppositely regulate m6A modification of TFEB

mRNA, which dictates the fate of hypoxia/reoxygenation-treated cardiomyocytes. Autophagy 2019; 15: 1419-1437.
[39] Harding D, Chong MHA, Lahoti N, Ma Z, Siegel D, MacRae CA, Hajjar RJ and Krenz M. Dilated cardiomyopathy and chronic cardiac inflammation: pathogenesis, diagnosis and therapy. J Intern Med 2023; 293: 23-47.
[40] Dilated cardiomyopathy. Nat Rev Dis Primers 2019; 5: 33.
[41] Cojan-Minzat BO, Zlibut A and Agoston-Coldea L. Non-ischemic dilated cardiomyopathy and cardiac fibrosis. Heart Fail Rev 2021; 26: 1081-1101.
[42] Lakdawala NK, Winterfield JR and Funke BH. Dilated cardiomyopathy. Circ Arrhythm Electrophysiol 2013; 6: 228-237.
[43] Wu W, Ziemann M, Huynh K, Long J, Yellon DM and Hausenloy DJ. Activation of Hippo signaling pathway mediates mitochondria dysfunction and dilated cardiomyopathy in mice. Theranostics 2021; 11: 8993-9008.
[44] Chang X, Liu R, Li R, Peng Y, Zhu P and Zhou H. Molecular mechanisms of mitochondrial quality control in ischemic cardiomyopathy. Int J Biol Sci 2023; 19: 426-448.
[45] Tomczyk MM, Cheung KG, Xiang B, Choi B, Balsor JL, Petropolis DB, Tang G, Kozlov G and Al-Omran MG. Mitochondrial sirtuin-3 (SIRT3) prevents doxorubicin-induced dilated cardiomyopathy by modulating protein acetylation and oxidative stress. Circ Heart Fail 2022; 15: e008547.
[46] Wang H, Cai P, Yu X, Shen B, He X, Zhang L, Liu C, Zhang Z and Chen X. Bioinformatics identifies key genes and potential drugs for energy metabolism disorders in heart failure with dilated cardiomyopathy. Front Pharmacol 2024; 15: 1367848.
[47] Bhide S, Trujillo AS, O'Connor MT, Lee CC, Tharp KM, Ayala JE, Barrett JP, Shackelford DA and Shah S. Increasing autophagy and blocking Nrf2 suppress laminopathy-induced age-dependent cardiac dysfunction and shortened lifespan. Aging Cell 2018; 17: e12747.
[48] Verdonschot JAJ, Hazebroek MR, Derks KWJ, Barandiarán Aizpurua A, Merken JJ, Wang P, Weerts J, Gáspárik AS and Heymans S. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur Heart J 2018; 39: 864-873.
[49] Wang H, Cai P, Yu X, Li S, Zhu W, Liu Y and Wang D. Bioinformatics identifies key genes and potential drugs for energy metabolism disorders in heart failure with dilated cardiomyopathy. Front Pharmacol 2024; 15: 1367848.
[50] Huang J, Yang F, Liu Y and Wang Y. N6-methyladenosine RNA methylation in diabetic kidney disease. Biomed Pharmacother 2024; 171: 116185.
[51] Hsu PJ, Zhu Y, Ma H, Guo Y, Shi X, Liu Y, Qi M, Lu Z and He C. Ythdc2 is an N6-methyladenosine binding protein that regulates mammalian spermatogenesis. Cell Res 2017; 27: 1115-1127.
[52] Wei CM, Gershowitz A and Moss B. 5'-terminal and internal methylated nucleotide sequences in HeLa cell mRNA. Biochemistry 1976; 15: 397-401.
[53] Wei CM and Moss B. Nucleotide sequences at the N6-methyladenosine sites of HeLa cell messenger ribonucleic acid. Biochemistry 1977; 16: 1672-1676.
[54] Deng X, Su R, Feng X, Wei M and Chen J. Role of N6-methyladenosine modification in cancer. Curr Opin Genet Dev 2018; 48: 1-7.
[55] Zaccara S, Ries RJ and Jaffrey SR. Reading, writing and erasing mRNA methylation. Nat Rev Mol Cell Biol 2019; 20: 608-624.
[56] Wu J, Frazier K, Zhang J, Gan Z, Wang T and Fan S. Emerging role of m6A RNA methylation in nutritional physiology and metabolism. Obes Rev 2020; 21: e12942.
[57] Huang W, Chen TQ, Fang K, Zeng ZC, Ye H and Chen YQ. N6-methyladenosine methyltransferases: functions, regulation, and clinical potential. J Hematol Oncol 2021; 14: 1-19.
[58] Sorci M, Ianniello Z, Cruciani S, Falbo L, Gallo S, Baltaro R, Bachi A and Bonaldi T. METTL3 regulates WTAP protein homeostasis. Cell Death Dis 2018; 9: 796.
[59] Zhou C, She X, Gu C, Hu Y, Ma M, Qiu Q, Sun T, Xu X, Chen H and Zheng Z. FTO fuels diabetes-induced vascular endothelial dysfunction associated with inflammation by erasing m6A methylation of TNIP1. J Clin Invest. 2023; 133: e160517.
[60] Kaur S, Tam NY, McDonough MA, Schofield CJ and Aik WS. Mechanisms of substrate recognition and N6-methyladenosine demethylation revealed by crystal structures of ALKBH5-RNA complexes. Nucleic Acids Res 2022; 50: 4148-4160.
[61] Zhao S, Devega R, Francois A, Kidane D, Squire JA and Lopez M. Human ALKBH6 is required for maintenance of genomic stability and promoting cell survival during exposure of alkylating agents in pancreatic cancer. Front Genet 2021; 12: 635808.
[62] Mathiyalagan P, Adamiak M, Mayourian J, Liang Y, Agarwal N, Kim R, Zhang S, Nagpal N, Wang K, Sahoo S and Kishore R. FTO-dependent N6-methyladenosine regulates cardiac function during remodeling and repair. Circulation 2019; 139: 518-532.

[63] Chi HC, Tsai CY, Tsai MM and Lin KH. Impact of DNA and RNA methylation on radiobiology and cancer progression. Int J Mol Sci 2018; 19: 555.
[64] Yang Y, Hsu PJ, Chen YS and Yang YG. Dynamic transcriptomic m6A decoration: writers, erasers, readers, and functions in RNA metabolism. Cell Res 2018; 28: 616-624.
[65] Jiang X, Liu B, Nie Z, Duan L, Xiong Q, Lu Z, Peng J and Tang J. The role of m6A modification in the biological functions and diseases. Signal Transduct Target Ther 2021; 6: 74.
[66] Shi H, Wei J and He C. Where, when, and how: context-dependent functions of RNA methylation writers, readers, and erasers. Mol Cell 2019; 74: 640-650.
[67] Liu J, Harada BT and He C. Regulation of gene expression by N6-methyladenosine in cancer. Trends Cell Biol 2019; 29: 487-499.
[68] Wang X, Zhao BS, Roundtree IA, Lu Z, Han D, Ma H, Weng X and He C. N6-methyladenosine modulates messenger RNA translation efficiency. Cell 2015; 161: 1388-1399.
[69] Shi H, Wang X, Lu Z, Zhao BS, Ma H, Hsu PJ, Liu C and He C. YTHDF3 facilitates translation and decay of N6-methyladenosine-modified RNA. Cell Res 2017; 27: 315-328.
[70] Sheng Y, Wei J, Yu F, Xu H, Hu S, Zhu Y, Chen L, Liu Q and Wu C. A critical role of nuclear m6A reader YTHDC1 in leukemogenesis by regulating MCM complex-mediated DNA replication. Blood 2021; 138: 2838-2852.
[71] Roundtree IA, Luo GZ, Zhang Z, Wang X, Zhou T, Cui Y and He C. YTHDC1 mediates nuclear export of N6-methyladenosine methylated mRNAs. Elife 2017; 6: e31311.
[72] Choe J, Lin S, Zhang W, Liu Q, Wang L, Ramirez-Moya J, Du P and Gregory RI. mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. Nature 2018; 561: 556-560.
[73] Lin S, Choe J, Du P, Triboulet R and Gregory RI. The m6A methyltransferase METTL3 promotes translation in human cancer cells. Mol Cell 2016; 62: 335-345.
[74] Wang Y, Sun J, Lin Z, Zhou H, Zhang H, Wang S, Wang J, Tang H and Luo Q. m6A mRNA methylation controls functional maturation in neonatal murine β-cells. Diabetes 2020; 69: 1708-1722.
[75] Moujalled D, Strasser A and Liddell JR. Molecular mechanisms of cell death in neurological diseases. Cell Death Differ 2021; 28: 2029-2044.
[76] Wencker D, Chandra M, Nguyen K, Khoury DS and Kitsis RN. A mechanistic role for cardiac myocyte apoptosis in heart failure. J Clin Invest 2003; 111: 1497-1504.
[77] Shen W, Li H, Su H, Chen K and Yan J. FTO overexpression inhibits apoptosis of hypoxia/reoxygenation-treated myocardial cells by regulating m6A modification of Mhrt. Mol Cell Biochem 2021; 476: 2171-2179.
[78] Fujita Y, Yano T, Kanamori H, Yamauchi-Takihara K, Watanabe T and Funakoshi H. Enhanced nuclear localization of phosphorylated MLKL predicts adverse events in patients with dilated cardiomyopathy. ESC Heart Fail 2022; 9: 3435-3451.
[79] Szobi A, Gonçalvesová E, Varga ZV, Leszek P and Pacher P. Analysis of necroptotic proteins in failing human hearts. J Transl Med 2017; 15: 86.
[80] Calis JJA and van Loosdregt J. N6-adenosine methylation (m6A) is involved in the life and death decisions of T cells. Cell Mol Immunol 2023; 20: 316-317.
[81] Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN and Stockwell BR. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012; 149: 1060-1072.
[82] Fang X, Cai Z, Wang H, Han D, Cheng Q, Zhang P, Gao F and Yu Y. Loss of cardiac ferritin H facilitates cardiomyopathy via slc7a11-mediated ferroptosis. Circ Res 2020; 127: 486-501.
[83] Shen H, Xie K, Tian Y and Wang X. N6-methyladenosine writer METTL3 accelerates the sepsis-induced myocardial injury by regulating m6A-dependent ferroptosis. Apoptosis 2023; 28: 514-524.
[84] Yang Y, Ren J, Zhang J, Shi H, Wang J and Yan Y. FTO ameliorates doxorubicin-induced cardiotoxicity by inhibiting ferroptosis via P53-P21/Nrf2 activation in a HuR-dependent m6A manner. Redox Biol 2024; 70: 103067.
[85] Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV and Kroemer G. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. Cell Death Differ 2018; 25: 486-541.
[86] Muhammad E, Levitas A, Singh SR, Braiman A, Ofir R, Etzion S and Parvari R. PLEKHM2 mutation leads to abnormal localization of lysosomes, impaired autophagy flux and associates with recessive dilated cardiomyopathy and left ventricular noncompaction. Hum Mol Genet 2015; 24: 7227-7240.
[87] Saito T, Asai K, Sato S, Hayashi M, Takahashi T and Inagaki T. Autophagic vacuoles in cardiomyocytes of dilated cardiomyopathy with initially decompensated heart failure predict improved prognosis. Autophagy 2016; 12: 579-587.
[88] Song H, Feng X, Zhang H, Luo X, Li C, Yu J, Zhang Y and Han H. METTL3 and ALKBH5 op-

positely regulate m6A modification of TFEB mRNA, which dictates the fate of hypoxia/reoxygenation-treated cardiomyocytes. Autophagy 2019; 15: 1419-1437.
[89] Bacmeister L, Schwarzl M, Warnke S, Fleischmann BK and Katus HA. Inflammation and fibrosis in murine models of heart failure. Basic Res Cardiol 2019; 114: 19.
[90] Kahl M, Xu Z, Arumugam S and Cho JH. m6A RNA methylation regulates mitochondrial function. Hum Mol Genet 2024; 33: 969-980.
[91] Yu J, Zeng C and Wang Y. Epigenetics in dilated cardiomyopathy. Curr Opin Cardiol 2019; 34: 260-269.
[92] Zhu W, Zhang H and Wang S. Vitamin D3 suppresses human cytomegalovirus-induced vascular endothelial apoptosis via rectification of paradoxical m6A modification of mitochondrial calcium uniporter mRNA, which is regulated by METTL3 and YTHDF3. Front Microbiol 2022; 13: 861734.
[93] Gorski PA, Ceholski DK and Hajjar RJ. Altered myocardial calcium cycling and energetics in heart failure–a rational approach for disease treatment. Cell Metab 2015; 21: 183-194.
[94] Scherz-Shouval R and Elazar Z. Regulation of autophagy by ROS: physiology and pathology. Trends Biochem Sci 2011; 36: 30-38.
[95] Huang B, Xie L, Ke M, Wei Y, Zhang Z and Li J. Programmed release METTL3-14 inhibitor microneedle protects myocardial function by reducing Drp1 m6A modification-mediated mitochondrial fission. ACS Appl Mater Interfaces 2023; 15: 46583-46597.
[96] Traba J and Sack MN. The role of caloric load and mitochondrial homeostasis in the regulation of the NLRP3 inflammasome. Cell Mol Life Sci 2017; 74: 1777-1791.
[97] Lan J, Xu B, Shi X, Pan Q and Tao Q. WTAP-mediated N6-methyladenosine modification of NLRP3 mRNA in kidney injury of diabetic nephropathy. Cell Mol Biol Lett 2022; 27: 51.
[98] Rabolli CP, Naarmann-de Vries IS, Makarewich CA, Baskin KK, Dieterich C and Accornero F. Nanopore detection of METTL3-dependent m6A-modified mRNA reveals a new mechanism regulating cardiomyocyte mitochondrial metabolism. Circulation 2024; 149: 1319-1322.