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REVIEW

METTL3-mediated m^{6}A methylation in cardiac diseases: pathogenic roles and therapeutic potential

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Abstract Cardiac dysfunction is a leading cause of death each year, putting heavy burdens on the global healthcare system. To improve our understanding of cardiac disease, novel perspectives for exploring their pathogenesis mechanisms are needed, which contributes to finding novel diagnoses and therapy targets for cardiac disease. To be noteworthy, researchers have paid great attention to understanding the pathogenesis of cardiac diseases from the perspective of methyltransferase-like 3 (METTL3, the catalytic core)-mediated RNA N^6-methyladenosine modification and targeting METTL3 for therapy. Therefore, we aim to evaluate the significance of METTL3 in cardiac diseases. In the present review, we summarize and analyze all studies reporting the involvement of METTL3 in cardiac diseases (acute myocardial infarction, myocardial ischemia/reperfusion injury, cardiac hypertrophy, and cardiac fibrosis) to interpret their interrelationship. This review suggests that METTL3 is a risk gene for cardiac diseases, which shows great promise as a disease diagnosis and prognosis biomarker and is poised to serve as an important target in drug development. Collectively, this review presents a comprehensive, cutting-edge overview of METTL3 in cardiac diseases, which could be a valuable reference for researchers to understand disease pathogenesis and develop novel drugs.

Ruida Liu and Xiaojuan Su have contributed equally to the manuscript.

Critical points
1. METTL3 induces myocardial diseases by dysregulating CMs.
2. METTL3 disturbs cardiac homeostasis and induces myocardial infarction.
3. METTLL3 contributes to cardiac hypertrophy and cardiac fibrosis.
4. Targeting METTL3 is therapeutic for myocardial regeneration.

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Abbreviations

METTL3, METTL14	Methyltransferase-like 3/14
m^6A	N^6-methyladenosine
WTAP	Wilms tumor 1-associated protein
CM	Cardiomyocyte
TFEB	Transcription factor EB
AMI	Acute myocardial infarction
I/R	Ischemia/reperfusion
IGF2BP1	Insulin-like growth factor 2 mRNA binding protein 1
FTO	Fat mass and obesity-associated protein
TNF-α	Tumor necrosis factor-α
NCBP3	Nuclear cap-binding subunit 3
eIF4 A2	Eukaryotic translation initiation factor 4A2
H/R	Hypoxia/reperfusion
PTEN	Phosphatase and tensin homolog
LncRNA-SNHG8	LncRNA small nucleolus RNA host gene 8
PTBP1	Polypyrimidine tract-binding protein 1
ALAS2	Aminolevulinate synthase 2
ROS	Reactive oxygen species
EVs	Extracellular vehicles
ECs	Endothelial cells
VAs	Ventricular arrhythmias
VF	Ventricular fibrillation
PVN	Paraventricular nucleus
TLR4	Toll-like receptor 4
NF-κB	Nuclear factor kappa-B
IL-1β	Interleukin-1 beta
TRAF6	NF receptor-associated factor 6
ECSIT	Evolutionarily conserved signaling intermediate in toll pathways
UTR	Untranslated regions
MPs	Microplastics
JPH2	Junctophilin 2
Hadh	Hydroxyacyl-CoA dehydrogenase
Kcnn1	Potassium calcium-activated channel subfamily N member 1
Tet1	Ten-eleven translocation 1
YAP	Yes-associated protein
CTNND1	Catenin delta 1
Klf6	Kruppel-like factor 6
Acsl4	Acyl-CoA synthetase long-chain family member 4
DGCR8	Microprocessor complex subunit
PRKCE	Protein kinase c epsilon
SCM	Septic cardiomyopathy
Myh3	Myosin heavy chain 3
CFs	Cardiac fibroblasts
ECM	Extracellular matrix
COL1 A1, COL3 A1	Collagen genes
YTHDF	YTH domain family
TNC	Tenascin-C
TAC	Transverse aortic constriction
CHAPIR	Cardiac-hypertrophy-associated PIWI-interacting RNAs
ADP-ribose	Poly
PARP10	Polymerase family member 10
GSK3β	Glycogen synthase kinase-3 beta
NFATC4	Nuclear factor of activated T cells 4
Ang-II	Angiotensin II
USP12	Ubiquitin-specific protease 12
p300	E1A binding protein p300
DKK2	Dickkopf-related protein 2
ABRO1	Abraxas brother 1
Psph	Phosphoserine phosphatase
CDK2	Cyclin-dependent kinase 2
Fgf16	Fibroblast growth factor 16
DPDMN	Double-layer programmed drug release microneedle
Drp1	Dynamin-related protein 1
MA	Maslinic Acid
FABP1	Fatty acid binding protein 1
FATP1	Fatty acid transport protein 1
CD36	Cluster of differentiation 36
SREBF1	Sterol regulatory element binding transcription factor 1

FAS	Fas cell surface death receptor
ACC	Acetyl-CoA carboxylase
ATGL	Adipose triglyceride lipase
LAL	Lipoprotein A lipase
LPL	Lipoprotein lipase

Introduction

Cardiac diseases currently represent the leading cause of mortality worldwide (Arcidiacono et al. 2020). The etiology of these conditions is underpinned by complex gene regulatory mechanisms, extensively investigated through the lens of N^6-methyladenosine (m^6A), the most abundant RNA modification (Arcidiacono et al. 2020).

The m^6A RNA modification is a posttranscriptional epigenetic alteration that occurs in both coding and non-coding RNAs, influenced by various factors including methyltransferases, demethylases, and m^6A-specific binding proteins (Barnett et al. 2023). These components collectively facilitate RNA processing, cleavage, translation, and degradation of target RNAs (Bassiouni et al. 2023). Methylation is achieved by the addition of a methyl group to the N^6 position of adenosine, mediated by methyltransferase-like 3 (METTL3) in a complex with METTL14 and Wilms tumor 1-associated protein (WTAP) via S-adenosyl methionine (Bhattacharyya et al. 2022). METTL3 serves as the catalytic core, while METTL14 stabilizes substrate RNA binding, and WTAP ensures the nuclear localization and structural integrity of the complex (Bhullar and Dhalla 2022). This tripartite assembly is essential for precise m^6A deposition on target RNAs.

Under normal physiological conditions, METTL3 ensures cardiomyocyte (CM, heart muscle cell) homeostasis by modulating RNA stability and translation. For instance, METTL3-mediated m^6A modifications on ribosomal RNAs enhance ribosome biogenesis, supporting protein synthesis necessary for contractile function (Cheng et al. 2022; Cheng et al. 2023; Christidi et al. 2018). Additionally, METTL3 regulates baseline autophagy by stabilizing transcripts like transcription factor EB (*TFEB)*, ensuring lysosomal efficiency and mitochondrial quality control (Deo 2015). These roles underscore METTL3's dual function as both a modulator of stress responses and a guardian of CM integrity. Notably, elevated expression levels of METTL3 have been frequently observed in patients suffering from cardiovascular diseases, such as acute myocardial infarction (AMI, heart attack), myocardial ischemia/reperfusion (I/R) injury, cardiac hypertrophy, and cardiac fibrosis (Dorn et al. 2019). Moreover, targeting METTL3 holds potential for therapeutic intervention in these heart conditions. Despite the extensive research on METTL3's role in these diseases, there remains a scarcity of comprehensive reviews elucidating their interconnections and assessing the significance of METTL3.

Thus, this review intends to bridge this gap in the literature by summarizing and critically analyzing all studies that report on the involvement of METTL3 in cardiac diseases. Additionally, we will evaluate the feasibility of METTL3 as a clinical target for diagnostic and therapeutic applications in cardiology. In summary, this review aims to enhance the understanding of the mechanisms underlying METTL3-mediated m^6A regulation in cardiac disease.

Functions and mechanism of METTL3 in cardiac diseases

CMs account for around 75% of the heart volume and are the dominant cells responsible for generating contractile forces and controlling the rhythmic beating of the heart (Dragasis et al. 2022). Injuries that affect the structure and function of CMs can cause massive loss of functional CMs, eventually leading to many CM-related disorders (termed cardiac diseases) (Fan et al. 2025). The dysregulation of METTL3 and its-mediated m^6A modification on RNAs contributes to CM dysfunction and subsequently results in cardiac diseases, including AMI, myocardial I/R injury, cardiac hypertrophy, and cardiac fibrosis (Fang et al. 2022). Furthermore, targeting METTL3 is therapeutic for myocardial regeneration.

METTL3 triggers AMI occurrence and development

The coronary arteries supply oxygen and nutrients to the heart to sustain its function throughout life. However, changes in the artery wall narrow the vessel lumen and reduce blood flow, while plaque rupture results in complete thrombotic occlusion that in turn induces AMI (Flamand et al. 2023). AMI can lead to heart failure due to a marked loss of functional CMs.

METTL3 functions in hypoxia and ischemia-induced CM loss

Hypoxia and ischemia are risk factors for CM dysfunction-induced AMI, which is involved in the massive loss of CMs due to hypoxia, as well as the recruitment and activation of myofibroblasts (Frangogiannis 2019). m^6A changes dynamically after AMI. Wang et al. (Gao et al. 2020) found that m^6A regulators are implicated in AMI and may carry prognostic significance. They identified insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1), Fat mass and obesity-associated protein (FTO), RNA binding motif protein 15, METTL3, YTH domain-containing protein 2, Fragile X messenger ribonucleoprotein 1, and heterogeneous nuclear ribonucleoprotein A2/B1 as key regulators associated with the condition. Importantly, patients with high expression levels of METTL3 have an increased level of activated T cells, suggesting a potential immunomodulatory role of METTL3 in AMI (Gao et al. 2020). Mechanistically, METTL3-mediated m^6A methylation may stabilize pro-inflammatory cytokine mRNAs [e.g., Interferon-gamma, tumor necrosis factor-α (TNF-α)] in T cells, enhancing their translation and amplifying inflammatory responses within ischemic myocardium (Gao et al. 2020). This exacerbated T cell activation could aggravate myocardial injury by promoting cytotoxic effector functions and impairing regulatory T cell (Treg)-mediated immunosuppression. Furthermore, METTL3-dependent m^6A modifications on programmed cell death protein 1 mRNA might reduce its stability, dampening inhibitory checkpoint signaling and perpetuating T cell hyperactivity (Gao et al. 2020). Collectively, these mechanisms position METTL3 as a critical regulator of adaptive immunity in AMI, linking RNA epitranscriptomics to inflammatory cardiomyocyte damage. Overall, m^6A regulators prove to be useful in the development of therapy approaches for AMI (Gao et al. 2020). Bioinformatics analysis of m^6A-related genes in patients with AMI indicates that METTL3 could be a novel target for AMI diagnosis (Giacca 2020). Besides, Ye et al. (Gong et al. 2021) demonstrated that in rat H9 C2 CMs undergoing hypoxic stress, METTL3 expression is extensively upregulated by the nuclear cap-binding subunit 3 (NCBP3). METTL3 regulates CM adaptation to hypoxic stress by mediating m^6A modification of eukaryotic translation initiation factor 4 A2 (eIF4 A2) mRNA, thereby enhancing translational efficiency and contributing to AMI pathology (Gong et al. 2021). Therefore, NCBP3 is a novel protein responsive to hypoxic stimulation that acts as a scaffold for coordinating METTL3 and eIF4 A2 to enhance mRNA translation ability in CMs. However, Su et al. (Gong et al. 2023) observed reduced METTL3 levels in adult mouse hearts, differentiated embryonic stem cells, and aged hearts subjected to hypoxia/reperfusion (H/R) injury. Mechanistically, METTL3 modulates H/R-induced stress responses by regulating Bax (a pro-apoptotic gene) (Hayat 2023) and phosphatase and tensin homolog (PTEN) (Gong et al. 2023), a tumor suppressor implicated in cardiomyocyte death. Furthermore, lncRNA small nucleolus RNA host gene 8 (lncRNA-SNHG8), a member of the lncRNA family, is significantly up-regulated in AMI and is a potential biomarker that may be involved in ischemia-induced CM dysfunction (He et al. 2025). Tang et al. (He et al. 2025) reported that METTL3-mediated m^6A modification on lncRNA-SNHG8 binds to polypyrimidine tract-binding protein 1(PTBP1) to regulate aminolevulinate synthase 2 (ALAS2) expression, which in turn increases oxidative stress and promotes AMI occurrence. Knockdown of lncRNA-SNHG8, METTL3, or PTBP1 in CMs enhances CM viability, attenuates reactive oxygen species (ROS) release, and malondialchehyche level, alleviates oxidative stress, protecting myocardium from injury induced by hypoxia–reoxygenation (cellular) or ischemia–reperfusion (tissue/organ) (He et al. 2025). These data may imply that manipulating the effects of METTL3-mediated RNA m^6A modification is beneficial for AMI recovery (Fig. 1A, Table 1).

METTL3 induces CM loss by triggering mitochondrial metabolic dysfunction

Mitochondrial metabolic dysfunction occurs in the early time of AMI, which severely impairs CM survival (Frangogiannis 2019). Intercellular communication mediated by extracellular vehicles (EVs) following AMI is associated with mitochondrial dysfunction, CM loss, and subsequent progression of heart failure (Hollenberg and Singer 2021). EVs containing miRNAs, whose levels markedly vary during pathological processes, exert functions by regulating gene expression at the posttranscriptional

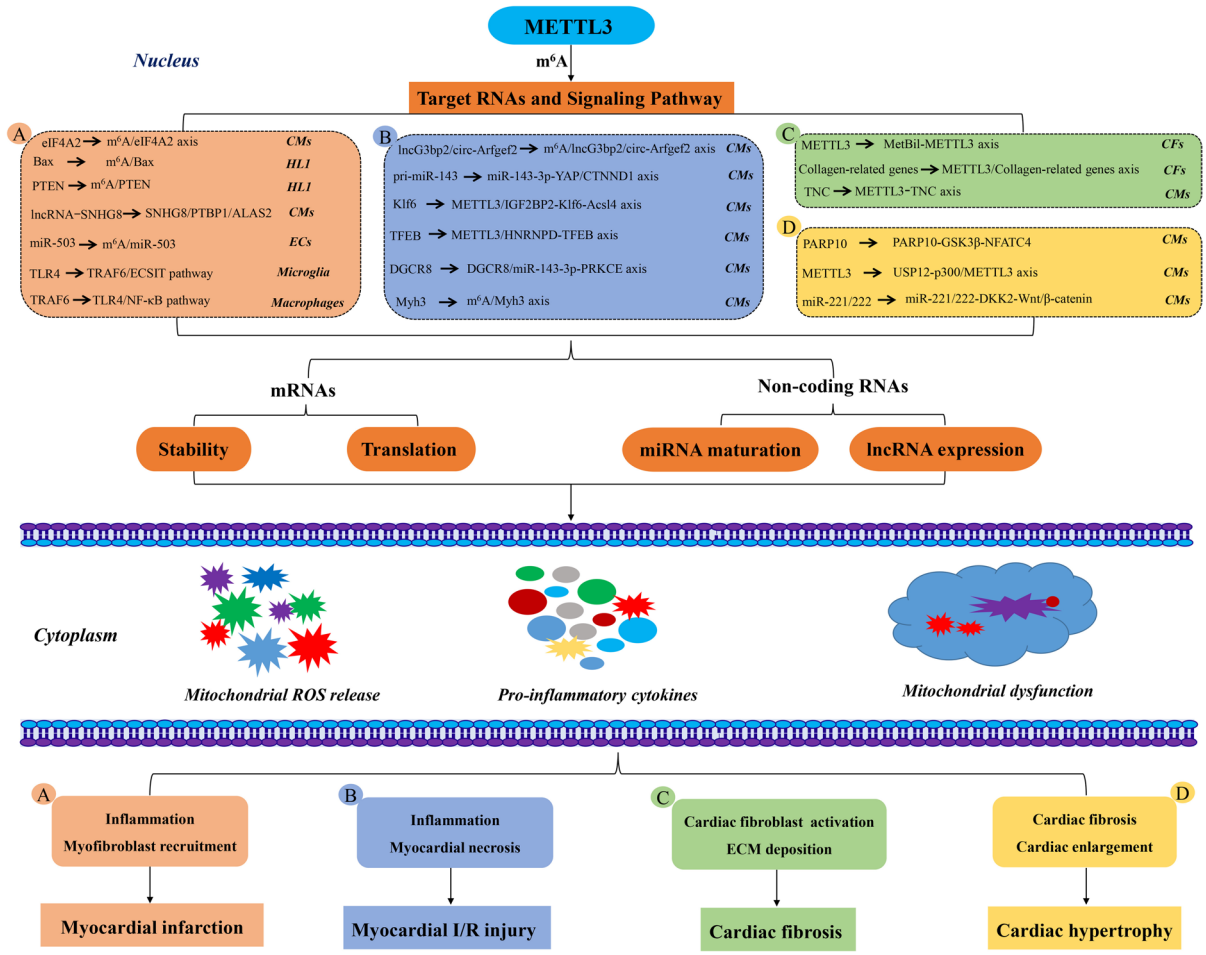

Fig. 1 Mechanisms of METTL3's function in cardiac diseases. The elevated expression of METTL3 promotes cardiomyocyte loss through the modulation of m^6A methylation on diverse target RNAs in different cardiac disorders, which in turn triggers the releases of reactive oxygen species, inflammatory responses, and mitochondrial dysfunction, leading to myocardial infarction, myocardial I/R injury, cardiac fibrosis, and cardiac hypertrophy. Alphabet A indicates the target RNAs and regulatory network diagram of METTL3 in acute myocardial infarction; B indicates the target RNAs and regulatory network diagram of METTL3 in myocardial ischemia/reperfusion injury; C indicates the target RNAs and regulatory network diagram of METTL3 in cardiac fibrosis; D indicates the target RNAs and regulatory network diagram of METTL3 in cardiac hypertrophy. Methyltransferase-like 3 (METTL3). N^6-methyladenosine (m^6A). CM line 1 (HL1). Cardiac fibroblasts (CFs). Endothelial cells (ECs). Cardiomyocytes (CMs). Ischemia/Reperfusion (I/R). Eukaryotic translation initiation factor 4 A2 (eIF4 A2). Phosphatase and tensin homolog (PTEN). LncRNA small nucleolus RNA host gene 8 (lncRNA-SNHG8). Toll-like receptor 4 (TLR4). TNF receptor-associated factor 6 (TRAF6). Nuclear factor-kappa B (NF-κB). Catenin delta 1 (CTNND1). Insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1). Kruppel-like factor 6 (Klf6). Heterogeneous nuclear ribonucleoprotein D (HNRNPD). Transcription factor EB (TFEB). Microprocessor complex subunit (DGCR8). Protein kinase c epsilon (PRKCE). Myosin heavy chain 3 (Myh3). Tenascin-C (TNC). Poly (ADP-ribose) polymerase family member 10 (PARP10). Glycogen synthase kinase-3 beta (GSK3β). Nuclear factor of activated T cells 4 (NFATC4). Ubiquitin-specific protease 12 (USP12). E1 A binding protein p300 (p300). Dickkopf-related protein 2 (DKK2). METTL3 binding lncRNA (MetBil). Reactive oxygen species (ROS)

level (Huang et al. 2023). EV-encapsulated miR-503 enriches during the early phase of AMI, which promotes CM death by directly binding to peroxisome proliferator-activated receptor gamma coactivator-1β and sirtuin 3, a mitochondrial deacetylase, thereby triggering mitochondrial metabolic dysfunction and CM death (Jiang et al. 2021). Sun et al. (Jiang et al. 2021) reported that endothelial cells (ECs)

Table 1 Targets of METTL3's function in the pathogenesis of cardiac diseases

METTL3			
Targets	Functions	Diseases	References
eIF4 A2 mRNA	Enhances *eIF4 A2 mRNA* translation	Acute myocardial infarction	Gong et al. 2021)
PTEN mRNA	Augments m^6A levels of *PTEN mRNA*		Gong et al. 2023)
lncRNA-SNHG8	Promotes lncRNA-SNHG8 expression through m^6A modification		He et al. 2025)
miR-503	Evokes miR-503 biogenesis		Jiang et al. 2021)
TLR4 mRNA	Elevates TLR4 expression by m^6 A modification on *TLR4 mRNA* 3'-UTR region		Li et al. 2021)
TRAF6 mRNA	Promotes TRAF6 translocation		Li et al. 2022b)
TRAF6 mRNA	Increases the m^6A level of *TRAF6 mRNA* on the 3'-UTR		Li et al. 2024a)
lncG3bp2, circ-Arfgef2	Upregulates m^6A modifications on lncG3bp2 and circ-Arfgef2	Myocardial I/R injury	Lu et al. 2021)
JPH2 mRNA	Reduces JPH2 expression		Ozadam et al. 2023)
Hadh, Kcnn1, Tet1 mRNA	Upregulates the m^6A methylation level of *Hadh, Kcnn1,* and *Tet1 mRNA*		Qi et al. 2022a)
pri-miR-143	Facilitates the maturation of pri-miR-143 into miR-143-3p		Qi et al. 2022b)
Klf6 mRNA	Enhances *Klf6 mRNA* stability		Rabolli et al. 2024)
TFEB mRNA	Promotes the association of the HNRNPD with *TFEB pre-mRNA* and upregulates *TFEB mRNA* stability		Deo 2015)
pri-miR-143-3p	Promotes DGCR8 binds to pri-miR-143-3p to enhance miR-143-3p expression		Ritterhoff and Tian 2023)
Myh3 mRNA	Increases *Myh3 mRNA* stability		Shi et al. 2014)
METTL3	Acts as the direct target of MetBil	Cardiac fibrosis	Su et al. 2020)
Collagen-related genes	Modulates the expression and m^6A levels of collagen-related genes		Su et al. 2021)
TNC mRNA	Promotes *TNC mRNA* stability and translation		Tang et al. 2022)
PARP10 mRNA	Impedes m^6A methylation of the *PARP10 mRNA* and upregulates PARP10 expression	Cardiac hypertrophy	Niel et al. 2022)
METTL3 mRNA	Acts as the target of p300		Wang et al. 2016)
pri-miR-221/222	Promotes pri-miR-221/222 binds to DGCR8 to enhances miR-221/222 expression		Wang et al. 2022a)

The elevated expression of METTL3 is identified as a risk factor for cardiac disorders, encompassing acute myocardial infarction, myocardial I/R injury, cardiac fibrosis, and cardiac hypertrophy. METTL3 functions in the pathogenesis of these cardiac diseases through the modulation of m^6A methylation on diverse RNA substrates

Methyltransferase-like 3 (METTL3). N^6-methyladenosine (m^6A). Ischemia/Reperfusion (I/R). Eukaryotic translation initiation factor 4 A2 (eIF4 A2). Phosphatase and tensin homolog (PTEN). LncRNA small nucleolus RNA host gene 8 (lncRNA-SNHG8). Toll-like receptor 4 (TLR4). Junctophilin 2 (JPH2). Untranslated regions (UTR). TNF receptor-associated factor 6 (TRAF6). Nuclear factor-kappa B (NF-κB). Hydroxyacyl-CoA dehydrogenase (Hadh). Potassium calcium-activated channel subfamily N member 1 (Kcnn1). Ten-eleven translocation 1(Tet1). Kruppel-like factor 6 (Klf6). Transcription factor EB (TFEB). Heterogeneous nuclear ribonucleoprotein D (HNRNPD). Microprocessor complex subunit DGCR8 (DGCR8). Myosin heavy chain 3 (Myh3). Tenascin-C (TNC). Poly (ADP-ribose) polymerase family member 10 (PARP10).E1 A binding protein p300 (p300)

are the primary source of miR-503 in EVs after AMI. Hypoxia induces rapid H3 K4 methylation on the *METTL3* promoter, resulting in METTL3 overexpression, which evokes m^6A-dependent miR-503 biogenesis in ECs (Jiang et al. 2021). In summary, this study highlights the mechanism disturbing

CM mitochondrial homeostasis and CM loss during AMI that is linked greatly to METTL3-mediated m^6A modification, wherein EVs aggravate myocardial injury during the AMI onset via EC-secreted miR-503 shuttling (Fig. 1A, Table 1).

METTL3 induces CM loss by triggering microglia-mediated inflammation

Malignant ventricular arrhythmias (VAs), including ventricular tachycardia and ventricular fibrillation (VF), are the leading causes of mortality after AMI. Sympathetic hyperactivity causes VAs in the early stage of AMI by overwhelming local norepinephrine release, which contributes to the high mortality by lowering VF thresholds in AMI and is highly arrhythmogenic in the per-infarct area (Kruszewska et al. 2022). Microglia-mediated inflammation in the paraventricular nucleus (PVN) is involved in the sympathetic hyperactivity of AMI (Li et al. 2018). Qi et al. (Li et al. 2021) found that METTL3-mediated m^6A modification on toll-like receptor 4 (*TLR4*) mRNA is markedly increased in the PVN at 3 days of AMI, and METTL3 is primarily located in microglia. Mechanically, the elevated TLR4 expression, combined with the activated nuclear factor-kappa B (NF-κB) signaling, leads to the overwhelming production of pro-inflammatory cytokines interleukin-1 beta (IL-1β) and TNF-α in the PVN, thus inducing sympathetic hyperactivity and increasing the VA incidence after AMI (Li et al. 2021). Interestingly, targeting METTL3 reduces the inflammatory response, sympathetic hyperactivity, and incidence of VAs after AMI (Li et al. 2021). These data collectively suggest that elevated level of METTL3 in microglia triggers AMI by activating the TLR4/NF-κB signaling pathway. Additionally, TNF receptor-associated factor 6 (TRAF6) is regarded as a protein that integrates with TNF receptors in human and rodent cells, which is rapidly activated and translocated to the mitochondria, augmenting the production of mitochondrial ROS in macrophages (Li et al. 2022a). Therefore, METTL3 stabilizes TLR4 mRNA via m^6A methylation, enabling sustained NF-κB signaling and IL-1β/TNF-α production in microglia. This neuroinflammatory cascade disrupts autonomic balance, lowering the ventricular fibrillation threshold and increasing arrhythmia susceptibility (Li et al. 2021; Li et al. 2022a). Yang et al. (Li et al. 2022b) found that METTL3 is predominantly localized in the microglia and is significantly increased within the PVN at 3 days of AMI. Downregulation of METTL3 prevents TRAF6 translocation to the mitochondria in the microglia and subsequently activates the TRAF6/ECSIT (evolutionarily conserved signaling intermediate in toll pathways) pathway, resulting in decreased mitochondrial ROS production and improved cardiac function (Li et al. 2022b). This study demonstrates that METTL3-mediated m^6A modification promotes sympathetic hyperactivity through the TRAF6/ECSIT pathway and mitochondrial oxidative stress in the PVN, thereby leading to VAs after AMI (Fig. 1A, Table 1).

METTL3 induces CM loss by mediating the inflammatory response of macrophages

Sympathetic neural remodeling caused by inflammation after AMI is closely associated with the occurrence of VAs (Li et al. 2024a). Macrophages are the central link between inflammation and sympathetic remodeling after AMI. Qi et al. (Li et al. 2024a) found that METTL3 is predominantly expressed in macrophages following AMI. Expression of METTL3, TRAF6, NADPH Oxidase 2, and NF-κB was elevated at day 3 and remained high at day 7 post-infarction. Mechanistically, METTL3 binds to the 3'-untranslated regions (3'-UTR) of TRAF6 mRNA, promoting its m^6A methylation. Silencing METTL3 reduced TRAF6 m^6A levels, inhibited NF-κB activation and ROS production, decreased pro-inflammatory cytokine release (TNF-α and IL-1β), and suppressed nerve growth factor expression (Li et al. 2024a). METTL3 knockdown reduces sympathetic remodeling activity and improves cardiac function after AMI (Li et al. 2024a). In summary, METTL3 is critical in mediating inflammatory responses of macrophages, downregulation of METTL3 attenuates the excessive inflammation and sympathetic neural remodeling induced by AMI, further reducing the incidence of VAs and improving cardiac function by targeting the TRAF6/NF-κB pathway (Fig. 1A, Table 1).

Collectively, these findings suggest that METTL3, either acting as a trigger for the occurrence of AMI or a target that confers benefits in maintaining the biological function of CMs and facilitating AMI recovery, is a promising biomarker for AMI diagnosis and target for therapy.

Mechanisms of METTL3's role in myocardial I/R injury

Following AMI, persistent ischemia causes local myocardial necrosis (Li et al. 2024b). The most effective therapeutic intervention is to restore the blood flow in the ischemic area in the early stage of AMI and reduce the myocardial ischemic injury, and infarct size (Liang et al. 2022). However, myocardial reperfusion after AMI activates oxidative stress response that causes massive loss of functional CMs, ultimately leading to myocardial I/R injury (Liu et al. 2014).

METTL3 induces CM loss by mediating oxidative stress response

Microplastics (MPs) exposure induces oxidative stress and inflammation, which stimulate organ damage by regulating the expression of numerous key genes (Liu et al. 2023). Total levels of m^6A and METTL3 are increased in the myocardium after exposure to MPs (Lu et al. 2021). RNA-seq and MeRIP-seq in MP-exposed myocardial tissue screen differentially expressed ncRNAs and their related m^6A modification profiles (Lu et al. 2021). GO and KEGG enrichment analyses show that these altered lncRNAs and circRNAs are closely associated with endocytosis, cellular senescence, and cell cycle signaling pathways, which may cause cardiotoxicity (Lu et al. 2021). Furthermore, MeRIP-seq data show different distributions and abundances of m^6A modifications on lncRNAs and circRNAs. Both m^6A modifications upregulate the expression of lncG3bp2 and circ-Arfgef2 after exposure to MPs (Lu et al. 2021). This suggests that MP-induced METTL3 upregulation contributes to oxidative stress response by mediating m^6A modifications on ncRNAs, which further induces CM loss. Interestingly, another study demonstrated that *Cyclophosphamide* increases the field and action potential durations in CMs by upregulating METTL3, which subsequently reduces junctophilin 2 (JPH2) expression to induce cardiotoxicity and CM death (Ozadam et al. 2023). The pattern of CM death includes apoptosis, ferroptosis, autophagy, and pyroptosis (Prata et al. 2020) (Fig. 1B**,** Table 1).

METTL3 functions by inducing CM apoptosis

According to a combined analysis of MeRIP-seq and RNA-seq for MI tissues, hydroxyacyl-CoA dehydrogenase *(Hadh)*, potassium calcium-activated channel subfamily N member 1 *(Kcnn1)*, and ten-eleven translocation 1*(Tet1)* are identified as hub mRNAs that are associated with apoptosis/angiogenesis (Qi et al. 2022a). Inhibition of METTL3 in CMs downregulates the m^6A methylation level of total RNA and upregulates the expression of these hub mRNAs. Importantly, under the condition of simulated hypoxia, Kcnn1 and Tet1 impact the process of angiogenesis, whereas Hadh, Tet1, and Kcnn1 function in the programmed cell death of apoptosis (Qi et al. 2022a). Furthermore, Gong et al. (Qi et al. 2022b) discovered a significantly upregulated level of METTL3 in CMs following acute cardiac injury. METTL3 promotes neonatal CM death by modulating the m^6A modification of the pri-miR-143 and facilitating the maturation of pri-miR-143 into miR-143-3p, which selectively targets yes-associated protein (YAP) and catenin delta 1(CTNND1). These studies provide a theoretical basis for taking METTL3-mediated RNA m^6A modification as the mechanism of CM death in myocardial I/R injury after AMI (Fig. 1B**,** Table 1).

METTL3 functions by inducing CM ferroptosis

Ferroptosis, a form of programmed cell death featuring lipid peroxidation overload and iron accumulation, has been found in CMs (Qiu et al. 2023). METTL3 regulates CM functions during acute injury. Qiu et al. (Rabolli et al. 2024) found that METTL3/IGF2BP2-mediated m^6A modification on kruppel-like factor 6 (*Klf6*) mRNA enhances *Klf6* mRNA stability and expression in the heart tissues from I/R mice, which directly binds to the Acsl4 promoter and positively regulates its expression, leading to CM ferroptosis. Klf6 knockdown inhibits ferroptosis and improves I/R-induced myocardial injury (Rabolli et al. 2024). Klf6 m^6A modification regulated by METTL3 and IGF2BP2 aggravates myocardial I/R damage through activating acyl-CoA synthetase long-chain family member 4 (Acsl4)-mediated ferroptosis, thereby providing one potential target for the treatment of myocardial I/R (Rabolli et al. 2024) (Fig. 1B**,** Table 1).

METTL3 functions by inducing CM autophagy

Autophagy has been regarded as an important strategy to protect CMs from I/R injury (Rao et al. 2021). Song et al. (Deo 2015) reported an upregulation of METTL3-mediated m^{6}A modification in H/R-treated CMs and I/R-treated mouse hearts, which operates by diminishing autophagic flux while promoting apoptosis in H/R-treated CMs. In this case, METTL3, in conjunction with the RNA-binding protein heterogeneous nuclear ribonucleoprotein D (HNRNPD), modifies TFEB (a master regulator of lysosomal biogenesis and autophagy genes) within its 3'-UTR, ultimately leading to decreased TFEB expression (Deo 2015). This study demonstrates that the METTL3/HNRNPD-TFEB axis mediates the negative regulation of CM autophagy after H/R and I/R, providing novel insights into the mechanism understanding of ischemic heart disease (Fig. 1B, Table 1).

METTL3 functions by inducing CM pyroptosis

CM pyroptosis contributes to CM loss and myocardial I/R injury, which is a complicated pathophysiological process (Rao et al. 2022). METTL3 expression is elevated in myocardial I/R rats and oxygen glucose deprivation/R CMs, which participate in the regulation of CM pyroptosis (Ritterhoff and Tian 2023). Wang et al. (Ritterhoff and Tian 2023) reported that METTL3 increases the total m^{6}A level in myocardial I/R rats and injured CMs, promotes microprocessor complex subunit (DGCR8) binding to pri-miR-143-3p, and enhances miR-143-3p expression, which in turn suppresses protein kinase c epsilon *(PRKCE)* transcription. Therefore, METTL3 promotes DGCR8 binding to pri-miR-143-3p through m^{6}A modification, enhancing miR-143-3p expression to inhibit *PRKCE* transcription and further aggravating CM pyroptosis and myocardial I/R injury. Additionally, pyroptosis not only causes CM death but also participates in the cascade of inflammatory response in ischemic myocardial tissues, affecting the severity and prognosis of myocardial I/R injury (Schäfer et al. 2022). Sepsis is an inflammation syndrome after infection by various pathogenic microorganisms (Scheffer et al. 2022). Cardiac insufficiency caused by sepsis is commonly referred to as septic cardiomyopathy (SCM) and is mainly attributed to LPS-induced systemic inflammation (Sergeeva et al. 2020). Gong et al. (Shi et al. 2014) demonstrated that METTL3 is abnormally upregulated both in samples of patients with SCM and in LPS-treated H9 C2 CMs. In vitro and in vivo, the deficiency of METTL3 improves cardiac function, cardiac tissue damage, myocardial cell apoptosis, and ROS levels in LPS-treated H9 C2 CMs and LPS-induced sepsis rats, respectively (Shi et al. 2014). RNA-seq analysis suggests that the half-life of myosin heavy chain 3 *(Myh3)* mRNA is significantly reduced after METTL3 deletion and that *Myh3* carries several potential m^{6}A modification sites (Shi et al. 2014). In conclusion, METTL3 promotes LPS-induced myocardial damage and cardiac dysfunction by increasing *Myh3* mRNA stability. This study reveals a key role of METTL3-mediated m^{6}A methylation in SCM, which offers a potential mechanism for the therapy of SCM (Fig. 1B, Table 1).

To sum up, high levels of METTL3 contribute to the occurrence and progression of myocardial I/R injury by inducing oxidative stress response in CMs, leading to CM apoptosis, ferroptosis, autophagy, and pyroptosis. Therefore, targeting METTL3 is promising for rescuing CM death.

Functions of METTL3 during cardiac fibrosis

Cardiac fibrosis and CM apoptosis are reparative processes after AMI, which results in cardiac remodeling and heart failure at last (Song et al. 2019). Cardiac fibrosis is a common pathological change in multiple cardiac diseases, which is characterized by aberrant activation of cardiac fibroblasts (CFs) and extracellular matrix (ECM) deposition (Song et al. 2019).

METTL3 induces cardiac fibrosis by over-activating CFs

The activated CF differentiate into myofibroblasts that migrate and concentrate in injured areas of the myocardium and can expand to the border zones in most cardiac pathologic conditions, producing collagens and other ECM as well (Stüdemann et al. 2022). The upregulated level of METTL3 binding lncRNA (MetBil) augments collagen deposition and CF proliferation following AMI (Su et al. 2020). Importantly, the m^{6}A-modified fibrosis-regulated genes mediated by METTL3 are profoundly involved in the regulation of MetBil in cardiac fibrosis following AMI. Zhuang et al. (Su et al. 2020) showed that MetBil

and METTL3 are co-localized in both the nucleus and cytoplasm of CFs. Interestingly, METTL3 binding MetBil directly interacts with METTL3 and promotes its ubiquitin-dependent degradation via the proteasome pathway (Su et al. 2020). Mechanistically, MetBil serves as a scaffold to recruit the E3 ubiquitin ligase TRIM25, which catalyzes K48-linked polyubiquitination of METTL3 at lysine residues 313 and 315, marking it for proteasomal degradation (Su et al. 2020). This reduction in METTL3 protein levels diminishes m^6A methylation on fibrosis-associated transcripts, including collagen genes (COL1 A1, COL3 A1) and TGF-β1 signaling components (SMAD2, SMAD4) (Su et al. 2020). METTL3-mediated m^6A modifications enhance the stability and translation efficiency of these transcripts by recruiting YTH domain family (YTHDF) 1/3 readers, thereby driving collagen deposition and fibroblast-to-myofibroblast transition (Su et al. 2020). Conversely, MetBil knockdown stabilizes METTL3, amplifying m^6A-dependent fibrotic gene expression and exacerbating cardiac fibrosis. In line with this study, Li et al. (Su et al. 2021) reported that the expression level of METTL3 is increased in cardiac fibrotic tissue of AMI mice and CFs treated with TGF-β1, which promotes proliferation and fibroblast transition to myofibroblast and collagens accumulation. Further bioinformatics analyses reveal that METTL3 modulates the expression and m^6A levels of collagen-related genes (Su et al. 2021). These findings suggest that METTL3-mediated m^6A modification triggers the onset and progression of cardiac fibrosis, thereby providing a novel molecular mechanism and therapeutic target for managing fibrosis and associated cardiac disorders (Fig. 1C, Table 1).

METTL3 induces cardiac fibrosis by over-depositing ECM

Excessive ECM deposition contributes to ventricular stiffness and diastolic and systolic dysfunction, which represents a potential risk factor for heart failure (Su et al. 2024). Tenascin-C (TNC) is a large multimodular glycoprotein of the ECM, which serves as a key regulator of CM proliferation and apoptosis and contributes to cardiac fibrosis and CM apoptosis after AMI (Sun et al. 2022). Cheng et al. (Tang et al. 2022) demonstrated that overexpression of METTL3 leads to enhanced m^6A levels of *TNC* mRNA and promotes *TNC* mRNA stability and translation, aggravating cardiac dysfunction and cardiac fibrosis 4 weeks after AMI. In conclusion, METTL3 induces cardiac fibrosis and CM apoptosis by increasing the m^6A levels of *TNC* mRNA and may be a promising target for the therapy of cardiac fibrosis after AMI (Fig. 1C, Table 1).

Collectively, high levels of METTL3 are closely related to the occurrence and progression of cardiac fibrosis, which induces CM apoptosis by over-activating CFs and excessive-depositing ECM, suggesting its potential for the diagnosis and treatment of cardiac fibrosis.

Functions of METTL3 in cardiac hypertrophy

Cardiac enlargement due to myocardial injury, hypertensive stress, or excessive neurohumoral activation is classified as pathological hypertrophy, which is associated with poor cardiac adaptive remodeling and cardiac dysfunction (Tang et al. 2023).

METTL3 induces CM hypertrophy

Comprehensive analysis of RNA m^6A methylation in pressure overload-induced cardiac hypertrophy found that m^6A methylation levels are higher in transverse aortic constriction (TAC) mice hearts (Umei et al. 2023). MeRIP-seq revealed that 1179 m^6A peaks are up-methylated and 733 m^6A peaks are down-methylated. Biological analysis of these genes shows a strong relationship with heart function (Umei et al. 2023). Furthermore, the cardiac-specific deletion of METTL3 in mice causes eccentric CM remodeling during aging and stress-induced heart failure (Cheng et al. 2023). Cardiac-hypertrophy-associated PIWI-interacting RNAs (CHAPIR) are associated with pathological hypertrophy and cardiac remodeling. Gao et al. (Niel et al. 2022) demonstrated that CHAPIR-Piwi-like RNA-mediated gene silencing 4 (PIWIL4) complex directly interacts with METTL3 to impede m^6A methylation of the poly (ADP-ribose) polymerase family member 10 *(PARP10)* mRNA transcript, upregulating PARP10 expression (Niel et al. 2022). Consequently, this upregulation triggers mono-ADP-ribosylation of glycogen synthase kinase-3 beta (GSK3β), inhibiting its kinase activity, causing nuclear accumulation of nuclear factor of activated T cells 4 (NFATC4), and promoting

pathological hypertrophy progression (Niel et al. 2022). Therefore, METTL3 is essential for normal CM hypertrophy and actively regulates cardiac hypertrophy during pathological processes. Besides, dysregulation of METTL3-mediated m^6A methylation on RNAs also plays a crucial role in promoting the occurrence and development of myocardial hypertrophy and cardiac remodeling (Fig. 1D, Table 1).

METTL3 contributes to angiotensin II-induced CM hypertrophy

Angiotensin II (Ang-II) is a vasopressor usually elevated in hypertension, leading to the deterioration of the pressure (Wal et al. 2023). Besides, Ang-II acts directly on the myocardium to promote pathological cardiac hypertrophy and cardiac failure (Wal et al. 2023). Lu et al. (Wang et al. 2016) reported ubiquitin-specific protease 12 (USP12) exacerbates Ang-II-induced cardiac hypertrophy by upregulating METTL3 expression. USP12 binds to and stabilizes E1 A binding protein p300 *(p300)*, activating the transcription of its downstream gene, *METTL3*. This suggests that USP12 promotes myocardial hypertrophy via *p300* stabilization and increased METTL3 expression. USP12 is therefore a pro-hypertrophic deubiquitinating enzyme that exerts its function by promoting the p300/METTL3 axis. Zhang et al. (Wang et al. 2022a) reported that the expression of METTL3 and miR-221/222 and the level of m^6A are significantly increased in response to Ang-II stimulation. The expression of miR-221/222 is regulated by METTL3 positively, and the level of pri-miR-221/222 that binds to DGCR8 or forms m^6A methylation is promoted by METTL3 in neonatal rat CMs, which subsequently activates the Wnt/β-catenin signaling by inhibiting dickkopf-related protein 2 (DKK2) to induce hypertrophy (Wang et al. 2022a). Knockdown of METTL3 or miR-221/222 abolishes the hypertrophy in neonatal rat CM and attenuates Ang-II-induced cardiac hypertrophy in mouse models (Wang et al. 2022a). These findings collectively suggest that METTL3 positively modulates the pri-miR221/222 maturation process in an m^6A-dependent manner and subsequently activates Wnt/β-catenin signaling by inhibiting DKK2, thus promoting Ang-II-induced cardiac hypertrophy. Suppression of cardiac METTL3 could be therapeutic for pathological myocardial hypertrophy (Fig. 1D, Table 1).

In conclusion, the aberrant functions of METTL3-mediated RNA m^6A modification disrupt the delicate balance of cardiac homeostasis and contribute to cardiac hypertrophy development. Consequently, we propose METTL3 as a promising diagnostic biomarker for identifying individuals with cardiac hypertrophy.

Targeting METTL3 rescues cardiac diseases

Although myocardial regeneration is enhanced after AMI, it is unable to compensate for the massive sudden loss of CMs, and it cannot restore the contractile function of the injured heart (Wang et al. 2022b). Moreover, adult mammalian CM lose their mitotic ability shortly after birth, leading to cell cycle stagnation and low renewal rates (Wang et al. 2023a). Therefore, identifying novel molecular mechanisms and regulatory pathways by which adult CM proliferate in tissues with reduced contractility yields promise for cardiac function restoration of AMI-induced heart failure.

Targeting METTL3 ameliorates AMI

M^6A-RIP-seq and RNA-seq suggest that METTL3 is necessary to maintain the proliferation capacity of neonatal CMs after birth (Qi et al. 2022b). Thus, targeting the regulation of METTL3 in CMs after AMI is an attractive strategy for myocardial regeneration. For example, METTL3 expression is upregulated in hypoxia-exposed neonatal rat CMs and AMI-induced rats, which promotes CM proliferation under pathological conditions (Wang et al. 2023b). Zhao et al. (Wang et al. 2023b) reported that silencing METTL3 promotes CM proliferation and inhibits CM apoptosis under hypoxic or AMI conditions, which functions by downregulating miR-17-3p expression in a RNA-binding protein DGCR8 dependent manner (Wang et al. 2023b). Overall, this study indicates that inhibiting METTL3 ameliorates AMI in rats through the METTL3/DGCR8- miR-17-3p axis (Wang et al. 2023b). Furthermore, Su et al. (xxxx) demonstrated that hypoxic preconditioning confers protection against hydrogen peroxide-induced injury in H9 C2 CMs by enhancing cell viability and anti-apoptotic capacity via upregulating METTL3-mediated m^6A modification on lncRNA H19 (Table 2).

Targeting METTL3 ameliorates myocardial I/R injury

Abraxas brother 1 (ABRO1) predominantly expresses in the heart, and its level is upregulated upon myocardial I/R injury (West et al. 2011). Wang et al. (West et al. 2011) found that deletion of ABRO1 increases CM proliferation and cardiac regeneration by targeting METTL3-mediated m^6A methylation on phosphoserine phosphatase *(Psph)* mRNA after myocardial injury. In the early postnatal period, METTL3-dependent m^6A methylation promotes CM proliferation by hypomethylating *Psph* mRNA and upregulating Psph expression, which in turn dephosphorylates cyclin-dependent kinase 2 (CDK2), a positive regulator of the cell cycle, at Thr14/Tyr15 and increases its activity (West et al. 2011). Therefore, ABRO1 negatively regulates cell cycle progression by regulating the METTL3-Psph-CDK2 axis, improving myocardial injury and inducing myocardial regeneration. Additionally, Jiang et al. (Wu et al. 2020) found that the knockdown of *METTL3* significantly increases CM proliferation and accelerates heart regeneration following heart injury in neonatal and adult mice, which upregulates fibroblast growth factor 16 (Fgf16) expression in an m^6A-YTHDF2-dependent manner. *METTL3* overexpression or silencing of *Fgf16* suppresses CM proliferation (Wu et al. 2020). These data demonstrate that METTL3 upregulates Fgf16 through an m^6A-YTHDF2-dependent pathway, thereby controlling CM proliferation and heart regeneration. Targeting the METTL3/m^6A/YTHDF2/Fgf16 pathway may represent a promising therapeutic strategy to promote the proliferation of CMs in myocardial regeneration (Table 2).

Inhibiting METTL3 decreases cardiac infarct size and fibrosis

A balanced mitochondrial fusion and fission is essential to maintain intracardiac homeostasis and reduce myocardial remodeling post-stress (xxxx). Huang et al. (Xu et al. xxxx) found that METTL3-METTL14 inhibition effectively decreases CM death by reducing mitochondrial fragmentation and inhibiting myofibrillar transformation. Double-layer programmed drug release microneedle (DPDMN) treatment of AMI in rat models shows improved cardiac function and decreased infarct size and fibrosis level, demonstrating its superior effectiveness (Xu et al. xxxx). The DPDMN delivers METTL3 inhibitor swiftly in the early phase to rescue dying CMs and slowly in the late phase to achieve long-term suppression of fibroblast over proliferation, collagen synthesis, and deposition (Xu et al. xxxx). METTL3 inhibition reduces the translation efficiency of dynamin-related protein 1 *(Drp1)* mRNA by 5'-UTR m^6A modification, thus decreasing the Drp1 protein level and mitochondrial fragment after hypoxic-ischemic injury (Xu et al. xxxx). This project investigates the efficacy of DPDMN-loaded METTL3 inhibitors in AMI treatment and the downstream signaling pathway proteins, providing an experimental foundation for the translation of the utility, safety, and versatility of METTL3 inhibitors for AMI into clinical applications (Table 2).

Table 2 Methods and targets for cardiac tissue regeneration by modulating METTL3

METTL3			
Methods	Targets	Cardiac diseases	References
METTL3 silencing	*miR-17-3p*	Acute myocardial infarction	Wang et al. 2023b)
Hypoxic-preconditioning	*METTL3*		xxxx)
ABRO1	*METTL3*	Myocardial-ischemia/reperfusion injury	West et al. 2011)
METTL3knockdown	*Fgf16*		Wu et al. 2020)
METTL3 inhibitor	*Drp1*	Cardiac fibrosis	Xu et al. xxxx)
Maslinic Acid	*METTL3*	Cardiac hypertrophy	Yang et al. 2018)
Intermittent fasting	*METTL3*		Yang et al. 2023a)

Inhibition of METTL3 through specific therapeutic approaches effectively mitigates cardiomyocyte apoptosis by targeting various RNA species, ultimately alleviating cardiac pathologies and facilitating myocardial regeneration

Abraxas brother 1 (ABRO1). Fibroblast growth factor 16 (Fgf16). Dynamin-related protein 1 (Drp1)

Targeting METTL3 rescues CM hypertrophy

Manipulating METTL3 expression in human CMs is paramount in preserving cardiac homeostasis and holds great therapeutic potential for managing cardiac hypertrophy. *Maslinic Acid* (MA) treatment rescues cardiac hypertrophy. Fang et al. (Yang et al. 2018) found that MA treatment significantly inhibits Ang-II-induced hypertrophy in neonatal rat CMs and the dosage does not influence the cell viability of rat CMs (Yang et al. 2018). Moreover, the anti-hypertrophy effect of MA is further verified in the TAC-induced hypertrophy mouse model. Further analysis shows that MA administration decreases the total levels of RNA m^6A methylation and METTL3 in Ang-II-treated neonatal rat CMs and TAC-stressed hearts (Yang et al. 2018). Overexpression of METTL3 confirms that METTL3-mediated m^6A methylation is essential for MA treatment of myocardial hypertrophy (Yang et al. 2018). These findings provide a platform for establishing METTL3 as a new target and strategy for cardiac hypertrophy treatment. Furthermore, Xu et al. (Yang et al. 2023a) explored the relationship between intermittent fasting and high-fat diet-induced diseases, demonstrating that intermittent fasting facilitates the functional and structural recovery of cardiac and serum lipid metabolic disorders. Bioinformatic analyses suggest that intermittent fasting suppresses METTL3 expression and enhances FTO expression in high-fat diet-induced obesity-related cardiomyopathy, which subsequently downregulates the expression of genes involved in fatty acid uptake (e.g., fatty acid binding protein 1 [i.e., *FABP1*], fatty acid transport protein 1 [i.e., *FATP1*], and a cluster of differentiation 36 [i.e., *CD36*]) and fatty acid synthesis (e.g., sterol regulatory element binding transcription factor 1 [i.e., *SREBF1*], fas cell surface death receptor [i.e., *FAS*], and acetyl-CoA carboxylase [i.e., *ACC*]) while reducing the levels of genes related to fatty acid catabolism (e.g., adipose triglyceride lipase [i.e., *ATGL*], hormone-sensitive lipase [i.e., *HSL*], lipoprotein A lipase [i.e., *LAL*], and lipoprotein lipase [i.e., *LPL*]) (Yang et al. 2023a) (Table 2).

In summary, these findings suggest that targeting METTL3 is effective for ameliorating heart diseases such as AMI, myocardial I/R injury, cardiac fibrosis, and cardiac hypertrophy, as well as promoting myocardial regeneration. Therefore, METTL3 could be a novel therapeutic target for these heart diseases in human beings.

Discussion

Recent research has focused on the role of METTL3-mediated RNA m^6A modification in the development of cardiac diseases such as AMI, myocardial I/R injury, cardiac fibrosis, and hypertrophy, as well as myocardial regeneration. This review examines how METTL3 influences the pathogenesis and treatment of these conditions, clarifying their interconnections and assessing the clinical potential of METTL3.

The findings suggest that METTL3 regulates CM activity and cardiac stability. When METTL3's RNA m^6A modification functions abnormally, it leads to significant CM loss, disrupting cardiac stability and contributing to heart failure, stemming from AMI, myocardial I/R injury, cardiac hypertrophy, and fibrosis. METTL3's involvement in heart failure involves mechanisms such as CM apoptosis, ferroptosis, autophagy, pyroptosis, oxidative stress, mitochondrial dysfunction, inflammation, endocytosis, cellular senescence, cell cycle regulation, cardiotoxicity, and angiogenesis. For example, circulating METTL3 levels in plasma exosomes correlate with infarct size and left ventricular ejection fraction in AMI patients, suggesting its utility as a non-invasive prognostic biomarker (Yang et al. 2023b; Yankova et al. 2021). Consequently, METTL3 emerges as a risk factor for CM-related heart diseases and shows potential as a diagnostic biomarker. Additionally, nanoparticle-delivered METTL3 siRNA reduces cardiac fibrosis in murine models by silencing COL1 A1 and TNC expression, highlighting its therapeutic promise (Su et al. 2021; Tang et al. 2022). Therefore, regulating METTL3 expression in human CMs is crucial for maintaining cardiac stability and could be a viable therapeutic strategy for these conditions. In conclusion, METTL3 plays a dual role as a contributor to CM loss and as a therapeutic target to enhance CM function and aid in heart failure recovery, making it a promising biomarker for diagnosis and treatment.

Forward-looking perspective and future directions

Recent advances in METTL3-targeted therapy include STM2457 (Ye et al. 2021), a small-molecule inhibitor that disrupts the METTL3-METTL14 interaction, reducing m^6A deposition in CMs (Su et al. 2021; Zhang et al. 2021a; Zhang et al. 2021b). In murine models of pressure overload, STM2457 attenuates cardiac hypertrophy by suppressing *PARP10* and *NFATC4* expression (Niel et al. 2022). However, systemic METTL3 inhibition risks off-target effects, such as impaired hematopoietic stem cell differentiation, underscoring the need for cardiac-specific delivery systems (Zhang et al. 2021a; Zhang et al. 2022). Challenges in METTL3-targeted therapy include: (1) Selectivity: Current inhibitors (e.g., STM2457) lack tissue specificity, potentially causing toxicity; (2) Dosage optimization: METTL3's dual roles in homeostasis and disease necessitate precise dosing to avoid detrimental effects; (3) Biomarker gaps: No validated biomarkers exist to monitor METTL3 inhibition efficacy in patients. Therefore, research should prioritize the development of targeted METTL3 inhibitors or modulators to evaluate their therapeutic potential. These compounds can be tested in preclinical models for their effectiveness and safety. Investigating the effects of METTL3 modulation across diverse patient groups may help in identifying biomarkers for patient stratification and personalized treatment approaches. It's also important to consider the possible side effects of targeting METTL3 due to its involvement in various physiological functions, necessitating comprehensive toxicity assessments to avoid disrupting normal cellular activities. Collaboration among molecular biologists, pharmacologists, and clinicians will be crucial to translate these insights into clinical practice. In summary, while progress has been made in understanding METTL3's association with cardiac diseases, further exploration is needed. Addressing these knowledge gaps through interdisciplinary research could lead to innovative treatments that enhance patient outcomes.

To unravel METTL3's spatiotemporal dynamics, single-cell m^6A sequencing could map cell-type-specific methylomes in developing, adult, and aged hearts (Zhang et al. 2023; Zhao et al. 2021). Coupled with spatial transcriptomics, this approach may resolve how METTL3 activity in cardiac fibroblasts versus CMs dictates fibrosis versus regeneration (Zhaolin et al. 2019). Furthermore, CRISPR-based screening of METTL3-ncRNA interactions in human induced pluripotent stem cell-derived CMs could identify therapeutic targets for congenital heart defects or age-related cardiomyopathy (Zhu et al. 2021). Lastly, leveraging machine learning to integrate multi-omics datasets (epitranscriptomic, proteomic, metabolomic) may predict METTL3-dependent regulatory networks, accelerating the translation of epitranscriptomic insights into precision cardiology (Zhuang et al. 2023).

Conclusion

In conclusion, despite the observable link between METTL3 and cardiac diseases, there are still uncertainties regarding its role as a risk factor. Limited research on treatment failures involving METTL3 hinders a clear understanding of their relationship. While METTL3 is associated with various heart conditions, clinical validation of its potential uses is still insufficient. Additionally, although reducing METTL3 levels has shown promise for certain heart diseases, specific METTL3 inhibitors are not widely available. Future studies should address these gaps to clarify METTL3's role in cardiac diseases. In summary, this review offers a detailed and updated exploration of the link between METTL3 and cardiac diseases, while also evaluating the potential clinical applications of targeting METTL3, thus filling existing literature gaps and providing a valuable reference for researchers in both basic and translational cardiovascular medicine.

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