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The Role of N6-Methyladenosine RNA Methylation in Cardiovascular Diseases: Molecular Mechanisms and Clinical Applications

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Abstract: Cardiovascular diseases (CVDs), the leading cause of global mortality, demand novel therapeutic strategies targeting their molecular underpinnings. Emerging research underscores N6-methyladenosine (m6A) RNA methylation—a dynamic epigenetic modification orchestrated by writers (e.g., METTL3), erasers (e.g., FTO), and readers (e.g., YTHDF)—as a central regulator of CVD pathogenesis. By modulating RNA splicing, stability, and translation, m6A critically influences inflammation, fibrosis, and metabolic homeostasis. The dysregulation of this machinery drives pathologies such as atherosclerosis, where METTL3-mediated m6A hypermethylation stabilizes NLRP3 transcripts, exacerbating endothelial inflammation, and ischemic heart disease, where FTO-dependent demethylation of BCL2 enhances cardiomyocyte survival. Clinically, m6A-related genetic variants (e.g., FTO rs9939609) correlate with CVD susceptibility, while circulating m6A levels serve as the promising non-invasive biomarkers. Preclinical advances highlight therapeutic strategies, including FTO inhibitors (e.g., meclofenamic acid) and CRISPR-based m6A editing tools, though the challenges like off-target effects and delivery inefficiencies impede the clinical translation. Future priorities include resolving cell-type-specific m6A dynamics via single-cell sequencing, integrating multi-omics data to unravel the epigenetic crosstalk, and advancing the clinical trials for m6A-targeted therapies. By bridging the mechanistic insights with translational innovation, m6A epitranscriptomics offers a paradigm shift in CVD management, emphasizing interdisciplinary collaboration to overcome barriers and realize precision medicine tailored to the dynamic epigenetic landscapes.

Keywords: m6A RNA methylation, cardiovascular diseases, gene expression regulation, mRNA modifications

1. Introduction

Cardiovascular diseases (CVDs) remain the foremost cause of global mortality, responsible for approximately 17.9 million deaths annually, a figure that constitutes over 30% of all deaths worldwide [1]. This heterogeneous group of disorders, including coronary artery disease, heart failure, stroke, and hypertension, arises from a complex interplay of genetic, environmental, and lifestyle factors such as obesity, diabetes, and chronic inflammation. Despite decades of advancements in pharmacological therapies (e.g., statins, antiplatelet agents) and surgical

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interventions (e.g., angioplasty, bypass grafting), CVDs continue to impose a staggering healthcare burden, particularly in aging populations and low-to-middle-income countries [1, 2]. A critical limitation of current treatments lies in their inability to address the underlying molecular mechanisms driving disease progression, resulting in high rates of recurrence, treatment resistance, and irreversible organ damage [3].

In recent years, epigenetic regulation has emerged as a pivotal frontier in understanding CVD pathogenesis. Among epigenetic modifications, RNA methylation—specifically N6-methyladenosine (m6A)—has garnered significant attention due to its dynamic and reversible nature, which allows precise control over gene expression without altering the DNA sequence [4, 5]. m6A, the most abundant internal modification in eukaryotic mRNA, is deposited by methyltransferases ("writers" such as METTL3/METTL14), removed by demethylases ("erasers" like FTO/ALKBH5), and interpreted by binding proteins ("readers" including YTHDF and IGF2BP families) [5, 6]. This modification regulates nearly every stage of RNA metabolism, including splicing, stability, translation, and degradation, thereby influencing critical cellular processes such as inflammation, apoptosis, and metabolic signaling [6, 7]. Dysregulation of m6A machinery has been implicated in a spectrum of CVDs, from atherosclerosis to heart failure, through mechanisms such as endothelial dysfunction, cardiomyocyte hypertrophy, and vascular remodeling [8-10]. For instance, METTL3-mediated m6A hypermethylation stabilizes pro-inflammatory transcripts (e.g., NLRP3, TNF-α) in endothelial cells, exacerbating atherosclerotic plaque formation [8]. Conversely, FTO-dependent demethylation of BCL2 mRNA enhances cardiomyocyte survival during ischemic injury, highlighting the therapeutic potential of modulating m6A dynamics [11]. Furthermore, clinical studies have identified m6A-related single nucleotide polymorphisms (SNPs), such as FTO rs9939609, as risk factors for hypertension and coronary artery disease, bridging genetic predisposition with epigenetic regulation [1, 12]. These findings underscore m6A's dual role as both a driver and suppressor of CVD progression, contingent on cellular context and disease stage.

This review aims to synthesize current knowledge on m6A RNA methylation in CVDs, with three primary objectives: (1) To elucidate the molecular mechanisms by which m6A regulates cardiovascular pathophysiology, including its crosstalk with key signaling pathways (e.g., PI3K/AKT, TGF-β). (2) To evaluate the translational potential of m6A as a diagnostic biomarker and therapeutic target, supported by preclinical and clinical evidence. (3) To identify unresolved challenges and propose future research directions to bridge gaps between mechanistic insights and clinical applications. By integrating findings from recent studies, this work emphasizes the need for interdisciplinary approaches to harness m6A's full potential in CVD management, ultimately paving the way for precision medicine strategies tailored to individual epigenetic profiles.

2. Basic Concepts and Regulatory Mechanisms of m6A RNA Methylation

N6-methyladenosine (m6A) is the most prevalent internal chemical modification in eukaryotic RNA, dynamically regulating RNA metabolism and function. This modification occurs at the nitrogen-6 position of adenosine residues, predominantly within consensus motifs such as RRACH (R = purine; H = adenine, uracil, or cytosine) [5]. m6A is reversibly installed, removed, and interpreted by three classes of proteins—writers, erasers, and readers—that collectively orchestrate its functional diversity across cellular processes.

2.1. Writers: Methyltransferases and Their Collaborative Roles

The m6A "writers" include methyltransferase complexes primarily composed of METTL3, METTL14, and WTAP. METTL3 serves as the catalytic core, utilizing S-adenosylmethionine (SAM) as the methyl donor, while METTL14 stabilizes METTL3's structure and enhances

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substrate RNA binding [5]. WTAP (Wilms tumor 1-associated protein) recruits additional regulatory subunits, such as VIRMA and ZC3H13, to direct the complex to specific nuclear speckles, ensuring precise methylation of target transcripts [4, 5]. Recent studies reveal that METTL16, another writer, selectively methylates U6 snRNA and MAT2A mRNA, highlighting context-specific roles of m6A in splicing and methionine metabolism [10].

2.2. Erasers: Demethylases Enabling Dynamic Regulation

The reversibility of m6A is governed by "erasers", including FTO (fat mass and obesity-associated protein) and ALKBH5 (AlkB homolog 5). FTO preferentially demethylates m6A in single-stranded RNA regions, particularly in mRNA 5′UTRs and near stop codons, influencing translation efficiency [6]. ALKBH5, localized in nuclear speckles, targets spliced mRNAs and circular RNAs (circRNAs), modulating their export and stability [7]. Intriguingly, FTO's activity is influenced by metabolic signals, such as α-ketoglutarate levels, linking cellular energy states to epitranscriptomic regulation [6]. Dysregulation of these erasers is implicated in metabolic disorders and cardiovascular pathologies, underscoring their therapeutic relevance.

2.3. Readers: Decoding m6A's Functional Output

m6A "readers" recognize methylated sites and mediate downstream effects. The YTH domain family (YTHDF1–3, YTHDC1–2) and IGF2BP proteins are prominent readers. YTHDF2 binds m6A-modified mRNAs and directs them to cytoplasmic processing bodies (P-bodies) for degradation, whereas YTHDF1 promotes translation by recruiting ribosomes [4]. YTHDC1, a nuclear reader, regulates alternative splicing by interacting with splicing factors like SRSF3 [5]. IGF2BP proteins stabilize oncogenic or stress-responsive transcripts (e.g., MYC, HIF1A) by shielding them from endonuclease activity [7]. Emerging readers, such as HNRNPA2B1, further expand m6A's regulatory scope by influencing pri-miRNA processing and RNA-protein interactions [10].

2.4. Functional Roles of m6A in RNA Metabolism

m6A dynamically regulates RNA splicing, stability, translation, and subcellular localization. For example, m6A deposition near splice sites promotes exon skipping or inclusion, as seen in cardiac-specific transcripts like TNNT2 (troponin T), which undergoes alternative splicing during heart development [7]. In stress conditions, m6A enhances the translation of heat shock proteins (e.g., HSP70) by recruiting YTHDF1, ensuring cellular survival [4]. Conversely, m6A-marked transcripts encoding pro-apoptotic factors (e.g., BAX) are rapidly degraded via YTHDF2, balancing cell fate decisions [6].

2.5. Detection and Technological Advances

High-throughput techniques like m6A-seq and MeRIP-seq (methylated RNA immunoprecipitation sequencing) have mapped m6A landscapes across tissues. However, these methods lack single-nucleotide resolution. Recent innovations, such as miCLIP (m6A individual-nucleotide resolution crosslinking and immunoprecipitation) and nanopore direct RNA sequencing, enable precise identification of m6A sites [10]. Single-cell m6A sequencing technologies are emerging, promising insights into cell-type-specific methylation patterns in complex tissues like the heart [3]. Despite progress, challenges persist in distinguishing functional m6A sites from bystander modifications and in quantifying dynamic changes during disease progression.

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3. The Role of m6A Methylation in Cardiovascular Diseases

Dysregulated m6A methylation is intricately linked to cardiovascular pathologies, influencing processes such as inflammation, fibrosis, and metabolic dysfunction. Below, its roles are dissected in major CVDs, supported by preclinical and clinical evidence.

3.1. Atherosclerosis: Driving Plaque Formation and Inflammation

m6A modifications regulate vascular smooth muscle cell (VSMC) plasticity and endothelial dysfunction, key contributors to atherosclerosis. METTL3-mediated methylation of KLF4 mRNA enhances its stability, promoting VSMC proliferation and neointima formation [8]. In endothelial cells, METTL3 upregulation increases m6A levels on NLRP3 mRNA, stabilizing its expression and amplifying inflammasome activation, which accelerates plaque inflammation [8]. Conversely, FTO overexpression in macrophages reduces m6A methylation on PPARγ mRNA, enhancing its translation and suppressing foam cell formation [13]. These findings highlight METTL3 as a pro-atherogenic factor and FTO as a potential therapeutic target.

3.2. Ischemic Heart Disease: Balancing Survival and Death

During myocardial ischemia/reperfusion (I/R) injury, m6A dynamically regulates cardiomyocyte survival. Hypoxia induces METTL3 expression, which methylates and stabilizes HIF1α mRNA, promoting adaptive angiogenesis [14]. However, excessive METTL3 activity exacerbates oxidative stress by methylating NRF2 transcripts, impairing antioxidant responses [7]. FTO plays a dual role: it demethylates BCL2 mRNA, inhibiting apoptosis, but also destabilizes SIRT1 mRNA, reducing mitochondrial resilience [6]. Pharmacological inhibition of FTO with meclofenamic acid reduces infarct size in murine models, suggesting context-dependent therapeutic strategies [13].

3.3. Heart Failure: Disrupting Calcium and Metabolism

In heart failure, m6A dysregulation impairs calcium handling and energy metabolism. METTL3-mediated hypermethylation of SERCA2a mRNA reduces its translation, diminishing calcium reuptake into the sarcoplasmic reticulum and exacerbating contractile dysfunction [3]. Conversely, FTO demethylates PGC-1α mRNA, enhancing mitochondrial biogenesis and ATP production in cardiomyocytes [6]. Clinical studies correlate elevated METTL3 levels in heart failure patients with adverse ventricular remodeling, while FTO activation improves ejection fraction in preclinical models [3, 11].

3.4. Hypertension: Targeting Vascular Reactivity

Hypertensive patients exhibit elevated m6A levels in endothelial cells, where YTHDF2 binds and destabilizes NOS3 (nitric oxide synthase 3) mRNA, reducing NO bioavailability and impairing vasodilation [14]. METTL14 upregulation in vascular smooth muscle cells (VSMCs) methylates ACE2 mRNA, suppressing its expression and promoting angiotensin II-driven hypertension [10]. Intriguingly, m6A-SNPs in the FTO gene (e.g., rs9939609) are associated with salt-sensitive hypertension, suggesting genetic-epigenetic interplay in disease susceptibility [1].

3.5. Aortic Aneurysm: Promoting Matrix Degradation

In abdominal aortic aneurysms (AAA), METTL14 and FTO are aberrantly expressed. METTL14 enhances m6A methylation of TIMP3 mRNA, a protease inhibitor, leading to its degradation and subsequent activation of matrix metalloproteinases (MMPs) like MMP9, which degrade collagen

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and elastin [10]. FTO overexpression, however, stabilizes TIMP3 transcripts, delaying aneurysm rupture in animal models [10]. These opposing roles underscore the need for precise modulation of m6A machinery in vascular pathologies.

3.6. Controversies and Unresolved Questions

While METTL3 is generally viewed as detrimental in atherosclerosis, its role in ischemic preconditioning remains debated. Some studies suggest METTL3 upregulation during mild hypoxia protects cardiomyocytes by enhancing stress-responsive gene translation [7]. Similarly, FTO's dual roles in apoptosis and metabolism complicate its therapeutic targeting. Future studies must resolve these context-dependent effects to optimize m6A-based interventions.

4. Molecular Mechanisms of m6A in Cardiovascular Diseases

m6A intersects with the core signaling pathways related to CVDs in the following ways.

PI3K/AKT Pathway: m6A-modified miR-25-3p suppresses AKT phosphorylation, impairing cardiomyocyte survival under ischemic stress. METTL3-mediated methylation of miR-25-3p enhances its stability, exacerbating apoptosis [7].

Wnt/β-catenin Signaling: m6A regulates LRP6 mRNA stability, a co-receptor for Wnt ligands. Hypomethylation of LRP6 by FTO promotes angiogenesis in ischemic tissues, while METTL14 overexpression inhibits vascular repair [14].

TGF-β Pathway: In heart failure, m6A enhances TGF-β1-mediated fibrosis by stabilizing SMAD3 transcripts. YTHDF2 binding to SMAD3 mRNA prolongs its half-life, driving collagen deposition and ventricular stiffness [15].

Inflammatory Regulation: m6A readers like IGF2BP1 stabilize NLRP3 inflammasome components, amplifying pyroptosis in atherosclerotic plaques [8]. Conversely, ALKBH5 demethylates SIRT1 mRNA, suppressing NF-κB-driven inflammation [6].

Autophagy and Apoptosis: m6A methylation of TFEB (a master autophagy regulator) inhibits lysosomal function in cardiomyocytes, while FTO-mediated demethylation rescues autophagy flux, mitigating I/R injury [11].

These mechanisms underscore the complexity of m6A's regulatory network, where context-dependent interactions dictate disease outcomes. For example, METTL3 may promote atherosclerosis via inflammatory pathways yet protect against myocardial infarction by enhancing stress-responsive gene translation [7,8]. Such duality necessitates cell- and pathway-specific therapeutic strategies.

5. Clinical Applications of m6A Methylation

The clinical applications of m6A methylation are shown as follows.

Biomarker Development: m6A-related SNPs (e.g., FTO rs9939609) are strongly associated with hypertension and coronary artery disease risk [1]. Circulating m6A levels, measured via ELISA or MeRIP-qPCR, correlate with left ventricular dysfunction in heart failure patients [12]. Additionally, m6A epitranscriptomic profiles in blood-derived exosomes show promise for non-invasive CVD diagnosis [3].

Therapeutic Targeting: Small-molecule inhibitors of FTO (e.g., Meclofenamic acid) reduce atherosclerotic plaque burden in murine models by suppressing inflammatory gene expression [13]. CRISPR-dCas13b systems enable precise m6A editing; for instance, dCas13b-METTL3 fusion proteins enhance cardiac repair post-infarction by methylating pro-survival transcripts [3]. However, challenges such as off-target effects and inefficient in vivo delivery remain unresolved.

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Drug Development: METTL3 inhibitors (e.g., STM2457) are under investigation for heart failure, aiming to reduce pathological hypertrophy [2]. Combinatorial therapies, such as FTO inhibitors paired with statins, may synergistically target metabolic and inflammatory pathways [6]. Personalized approaches integrating m6A profiles with genomic data could optimize treatment regimens, particularly in resistant hypertension or familial cardiomyopathies [12].

6. Future Research Directions of m6A Methylation

The future research directions of m6A methylation are indicated as follows.

Cell-Type-Specific m6A Dynamics: Single-cell m6A sequencing is needed to resolve differential methylation patterns in cardiomyocytes, endothelial cells, and macrophages [16]. For example, macrophage-specific METTL3 deletion may attenuate atherosclerosis without affecting cardiac repair mechanisms.

Advanced Detection Technologies: Spatial transcriptomics and nanopore-based direct RNA sequencing could map m6A modifications with subcellular resolution, identifying functional sites in diseased tissues [10].

Multi-Omics Integration: Linking m6A epitranscriptomics with DNA methylation and histone acetylation data may uncover synergistic epigenetic drivers of CVDs. For instance, m6A and DNA methylation co-regulate TGF-β signaling in cardiac fibrosis [12, 15].

Translational Studies: Clinical trials evaluating m6A-targeted therapies (e.g., FTO inhibitors in Phase I/II trials for ischemic cardiomyopathy) are critical to validate preclinical findings [3]. Longitudinal studies tracking m6A biomarkers in large cohorts (e.g., Framingham Heart Study) could establish causal relationships with CVD outcomes [1].

Environmental Interactions: Investigating how environmental stressors (e.g., PM2.5 exposure) alter m6A landscapes may reveal novel prevention strategies [14].

7. Conclusion

The burgeoning field of m6A RNA methylation has revolutionized our understanding of cardiovascular diseases, revealing its central role in regulating gene expression networks that govern inflammation, fibrosis, and metabolic homeostasis. Key findings from this review highlight that m6A dysregulation is a hallmark of multiple CVDs, including atherosclerosis, ischemic heart disease, and heart failure. For instance, METTL3-mediated m6A deposition promotes endothelial inflammation by stabilizing NLRP3 mRNA, while FTO-dependent demethylation of BCL2 enhances cardiomyocyte survival during ischemia/reperfusion injury. These discoveries underscore the context-dependent duality of m6A machinery, where the same enzyme may exert opposing effects in different disease settings—a complexity that necessitates cell- and pathway-specific therapeutic strategies.

Clinically, m6A modifications hold immense promise as biomarkers and therapeutic targets. Genetic polymorphisms in m6A regulators (e.g., FTO rs9939609) have been linked to hypertension and coronary artery disease susceptibility, offering insights into personalized risk stratification. Circulating m6A levels, detectable via non-invasive techniques like MeRIP-qPCR, correlate with disease severity in heart failure, suggesting their utility in monitoring therapeutic responses. Preclinical studies further demonstrate that pharmacological inhibition of FTO with compounds like meclofenamic acid reduces atherosclerotic plaque burden, while CRISPR-based m6A editing tools enable precise modulation of pro-survival transcripts in infarcted hearts. However, challenges such as off-target effects, inefficient in vivo delivery, and the lack of cell-specific targeting remain significant barriers to clinical translation.

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Future research must prioritize several avenues to advance this field. First, single-cell and spatial transcriptomic technologies are needed to resolve cell-type-specific m6A dynamics in complex cardiovascular tissues, distinguishing cardiomyocyte-specific methylation patterns from those in endothelial cells or macrophages. Second, integrating m6A epitranscriptomics with other epigenetic layers (e.g., DNA methylation, histone modifications) could uncover synergistic regulatory networks driving CVD progression. Third, large-scale clinical trials are essential to validate m6A-targeted therapies, particularly in diverse patient cohorts with varying genetic and environmental backgrounds. For example, trials investigating FTO inhibitors in ischemic cardiomyopathy or METTL3 modulators in heart failure could provide critical proof-of-concept data.

In conclusion, m6A RNA methylation represents a paradigm shift in cardiovascular research, offering novel mechanistic insights and translational opportunities. While technical and biological challenges persist, interdisciplinary collaborations—combining epigenetics, bioengineering, and clinical cardiology—are poised to transform these discoveries into therapies that improve patient outcomes. By unraveling the "epitranscriptomic code" of CVDs, humans move closer to an era of precision medicine where treatments are tailored not only to genetic makeup but also to dynamic epigenetic landscapes.

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