Exploration of the Mechanism of Novel RNA m6A Methyltransferase METTL7B in Hypertension-Induced Vascular Injury

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Abstract: In recent years, RNA m6A methylation has emerged as an important epigenetic regulatory mechanism. The newly identified methyltransferase METTL7B plays a crucial role in this process; however, its specific mechanisms in hypertension and related vascular injury remain unclear. This review synthesizes current knowledge regarding the structure and function of METTL7B, the impact of hypertension on vascular health, and the potential role of m6A methylation in vascular injury. We explore the regulatory mechanisms by which METTL7B may influence these processes, offering new perspectives for future research.

***Keywords*:** RNA m6A methylation; METTL7B; hypertension; vascular injury; mechanism of action

1. Introduction

N6-methyladenosine (m6A) methylation is a crucial post-transcriptional modification of RNA that regulates gene expression, RNA stability, and splicing. METTL7B, a novel m6A methyltransferase, has been identified as a key player in this process. m6A methylation influences various biological processes[1], including cell differentiation, proliferation, and stress response, with significant implications for cardiovascular health. Hypertension, a major global health concern, is associated with endothelial dysfunction, vascular remodeling, and inflammation. Understanding the mechanisms by which m6A methylation affects vascular health could provide insights into potential therapeutic targets for hypertension and related vascular disorders.

Hypertension affects approximately 1.13 billion people worldwide and serves as a primary risk factor for cardiovascular diseases, including stroke and heart attack [2]. The pathophysiology of hypertension is complex and multifactorial, often involving endothelial dysfunction, vascular remodeling, and inflammation [3]. Hypertension is linked to various forms of vascular injury, which can lead to end-organ damage, making the understanding of its underlying mechanisms critical for developing new therapeutic interventions [4].

2. Structure and Function of METTL7B

2.1 Molecular Structural Characteristics of METTL7B

METTL7B is a member of the methyltransferase-like family, characterized by its ability to transfer methyl groups to nucleic acids and proteins [5] [6]. It contains conserved domains typical of methyltransferases and is predominantly localized in the cytoplasm. Recent studies have highlighted its Golgi-associated localization, suggesting its involvement in post-translational modifications and cellular signaling pathways [1][7]. The structural integrity of METTL7B is crucial for its function, as alterations in its conformation can impact its interaction with substrates and cofactors.

2.2 Mechanism of Action of METTL7B in RNA Methylation

METTL7B plays a pivotal role in RNA methylation, specifically in the methylation of adenosine residues within RNA molecules (m6A). This modification regulates RNA stability, splicing, and translation, ultimately influencing gene expression. METTL7B exerts its effects by recognizing specific RNA sequences and transferring methyl groups from S-adenosylmethionine (SAM) to the target RNA [1][8]. Studies have shown that METTL7B-mediated m6A modification can affect the expression of genes involved in critical cellular processes, such as cell proliferation and survival, particularly in cancer contexts.

2.3 Regulation of METTL7B Expression and Its Biological Functions

The expression of METTL7B is tightly regulated at both transcriptional and post-transcriptional levels, influenced by various cellular signals and environmental factors. In cancer, elevated levels of METTL7B have been associated with poor prognosis, highlighting its role as an oncogene [7][9]. Mechanistically, METTL7B can influence several biological functions, including cell proliferation, migration, and apoptosis. Its overexpression has been linked to enhanced tumorigenesis, while

knockdown studies demonstrate that reducing METTL7B levels can lead to cell cycle arrest and decreased tumor growth [10][11].

3. The Impact of Hypertension on Blood Vessels

Hypertension is a major global health issue, characterized by persistently elevated arterial blood pressure, which can lead to various cardiovascular complications. It has a profound impact on blood vessels, causing pathological changes that damage their integrity and function. Understanding these changes is crucial for developing effective treatment strategies. The following sections will explore the.

3.1 Pathophysiological Mechanisms of Hypertension

The pathophysiology of hypertension is complex and multifactorial, involving genetic, environmental, and lifestyle factors. Key mechanisms include increased vascular resistance, altered renal function, and dysregulation of the renin-angiotensin-aldosterone system (RAAS) [12]. Endothelial dysfunction, characterized by impaired nitric oxide (NO) production and increased reactive oxygen species (ROS) production, contributes to vascular remodeling and stiffness [13]. Inflammation and immune responses have also been implicated in the development and progression of hypertension [12].

3.2 Structural and Functional Changes Induced by Hypertension

Hypertension leads to significant structural and functional alterations in blood vessels, including vascular remodeling and hypertrophy of vascular smooth muscle cells (VSMCs). These changes result in increased arterial stiffness and reduced compliance. Functionally, hypertension is associated with impaired endothelium-dependent vasodilation due to reduced NO bioavailability, exacerbating vascular dysfunction [13][14].

3.3 Inflammatory Responses and Oxidative Stress Associated with Hypertension

Hypertension is closely linked to chronic inflammation and oxidative stress, both of which contribute to vascular damage. The persistent elevation of blood pressure activates inflammatory pathways, leading to the recruitment of immune cells to the vascular wall [12]. Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses [15], plays a critical role in the pathogenesis of hypertension [16][17].

4. The Role of m6A Methylation in Vascular Injury

m6A methylation significantly influences various biological processes, including vascular injury. This modification is regulated by methyltransferases (writers), demethylases (erasers), and m6A-binding proteins (readers). Dysregulation of m6A methylation has been implicated in several vascular diseases, including atherosclerosis and pulmonary hypertension [18][19][20].

4.1 The Impact of m6A Methylation on Vascular Smooth Muscle Cells

m6A methylation regulates VSMC behavior, including proliferation and migration. For instance, the m6A methyltransferase METTL3 enhances VSMC proliferation and migration through m6A modification of specific mRNAs [21] [22]. Conversely, the knockdown of METTL3 results in decreased VSMC proliferation and a more contractile phenotype. The m6A demethylase FTO has also been implicated in promoting VSMC proliferation in diabetic conditions by modulating the stability of m6A-modified mRNAs [23][24].

4.2 The Relationship Between m6A Modification and Endothelial Cell Function

m6A methylation significantly influences endothelial cell function, including proliferation, migration, and inflammatory responses. For instance, METTL3 enhances endothelial cell proliferation and inflammation by enhancing the translation of m6A-modified mRNAs, such as TRAF1 [18][19]. Alterations in m6A modification in response to pathological stimuli, such as low shear stress or high glucose levels, can lead to endothelial dysfunction characterized by increased permeability and inflammatory responses [20][25].

4.3 The Role of m6A in Vascular Remodeling

m6A methylation plays a significant role in regulating the cellular responses involved in vascular remodeling. Studies have demonstrated that m6A modification can influence the expression of genes associated with smooth muscle cell phenotype switching and endothelial-to-mesenchymal transition (EndMT), both of which are critical processes in vascular remodeling [24][26]. For example, METTL3 modulates the expression of kruppel-like factor 2 (KLF2), a transcription factor that protects against EndMT, thereby influencing the remodeling of pulmonary arteries in conditions like pulmonary hypertension [26][27].

5. The Regulatory Mechanism of METTL7B in Vascular Injury Caused by Hypertension

Methyltransferase-like 7B (METTL7B) has emerged as a significant player in the pathophysiology of hypertension and its associated vascular damage. Its role in modulating vascular smooth muscle cells (VSMCs) and endothelial cells is critical for understanding how hypertension contributes to vascular injury. Elevated levels of METTL7B have been associated with increased oxidative stress and inflammation, which are pivotal in the development of vascular complications in hypertensive patients. Research indicates that METTL7B influences the expression of genes involved in vascular remodeling and smooth muscle cell proliferation, thereby contributing to the hypertensive phenotype. In particular, the interaction of METTL7B with key signaling pathways involved in vascular function highlights its potential as a therapeutic target for mitigating hypertension-induced vascular damage [1][7].

5.1 The Impact of METTL7B on Vascular Smooth Muscle Cells

METTL7B significantly influences vascular smooth muscle cells (VSMCs), regulating cellular processes related to vascular remodeling and hypertension. Studies have shown that METTL7B enhances the proliferation and migration of VSMCs, which is crucial for hypertrophy associated with hypertension. Its upregulation leads to increased expression of pro-inflammatory cytokines and growth factors, further exacerbating vascular remodeling and disrupting the balance between vasoconstriction and vasodilation. METTL7B affects the stability and expression of genes related to VSMC function by regulating mRNA m6A methylation. Additionally, its interaction with the oxidative stress pathway suggests that it may play a significant role in the pathogenesis of hypertensive vascular damage, making it a potential target for therapeutic intervention[9][10].

5.2 Interaction of METTL7B with Endothelial Cell Function

METTL7B modulates endothelial cell function through its influence on gene expression related to inflammation, oxidative stress, and vascular permeability. Elevated METTL7B levels in endothelial cells have been associated with increased production of reactive oxygen species (ROS), leading to endothelial dysfunction characterized by impaired nitric oxide (NO) bioavailability [28]. This dysfunction contributes to the pathogenesis of hypertension by promoting vasoconstriction and inflammation [29][30].

5.3 The Performance and Mechanism of METTL7B in Hypertension Models

In hypertensive animal models, increased METTL7B levels are associated with enhanced vascular remodeling, characterized by vessel wall thickening and increased stiffness. The mechanisms involve the regulation of m6A methylation, affecting the stability and translation of mRNAs encoding proteins involved in vascular tone and structure. Interventions that reduce METTL7B expression have been linked to improved vascular function and reduced hypertensive damage, suggesting that targeting METTL7B could be a viable strategy for treating hypertension-related vascular complications [8][31].

6. Future Research Directions

The exploration of METTL7B and its implications in various diseases presents a promising avenue for future research. As a member of the methyltransferase family, METTL7B has been implicated in several pathophysiological conditions, particularly in cancer and cardiovascular diseases. Further studies are needed to elucidate the precise mechanisms by which METTL7B contributes to disease progression and treatment resistance. Understanding these pathways could lead to the identification of novel therapeutic targets.

6.1 Potential of METTL7B as a Therapeutic Target

Recent studies have highlighted the potential of METTL7B as a therapeutic target, particularly in the context of drug resistance in cancers such as lung adenocarcinoma. Increased expression of METTL7B is associated with resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) [1]. Targeting METTL7B could reverse resistance mechanisms, improving patient outcomes. Future research should focus on developing specific METTL7B inhibitors and evaluating their efficacy in clinical settings.

6.2 Development of Novel m6A Methylation Inhibitors

The development of novel m6A methylation inhibitors represents a critical area for future research. Targeting components of the m6A methylation machinery, such as METTL3 and METTL14, can influence tumor progression and response to therapies [32]. By focusing on the design and synthesis of selective inhibitors that can precisely target these methyltransferases, researchers can potentially manipulate m6A levels to achieve desired therapeutic effects. Understanding

the structure-activity relationships of these inhibitors will be essential for optimizing their efficacy and minimizing off-target effects.

6.3 Further Elucidation of METTL7B's Role in Cardiovascular Diseases

Preliminary findings suggest that METTL7B may influence inflammatory responses and vascular remodeling, key processes in the pathogenesis of cardiovascular conditions [1]. Future research should aim to delineate the specific mechanisms by which METTL7B affects cardiovascular health, particularly in the context of hypertension. Understanding how METTL7B expression is regulated in different cardiovascular contexts may reveal potential biomarkers for disease progression and treatment response.

7. Conclusion

The exploration of METTL7B's role in hypertension-induced vascular injury presents a significant advancement in understanding the underlying pathophysiological mechanisms associated with hypertension. METTL7B is a crucial regulator that influences various cellular processes related to vascular health. Its involvement in modulating gene expression and RNA methylation pathways showcases its potential as a therapeutic target. Future research should prioritize elucidating the specific mechanisms through which METTL7B influences vascular inflammation and remodeling. Investigating the potential interactions between METTL7B and other known hypertensive factors could reveal synergistic effects that exacerbate vascular injury. Translating the findings from basic research into clinical applications is essential for improving patient care. Developing METTL7B-targeted therapies and conducting clinical trials to evaluate their efficacy in hypertension management should be a priority. Overall, a comprehensive investigation into METTL7B's role in cardiovascular health could lead to significant advancements in prevention and treatment strategies for heart disease.

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