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Molecular Mechanisms of the Interaction between m6A Modification and Endoplasmic Reticulum Stress and Their Regulatory Roles in Disease Progression

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Abstract

N6-methyladenosine (m6A), the most prevalent post-transcriptional modification in eukaryotic messenger RNA (mRNA), plays a pivotal role in the regulation of gene expression. Endoplasmic reticulum stress (ERS) serves as a critical defensive mechanism for cells responding to the disruption of internal homeostasis and is intimately associated with the initiation and progression of various major diseases. In recent years, accumulating evidence has revealed a complex bidirectional regulatory network between m6A modification and ERS. On one hand, m6A modification directly modulates the initiation and intensity of ERS by regulating the translation efficiency or mRNA stability of unfolded protein response (UPR)-related genes. On the other hand, ERS signaling exerts feedback regulation on the expression and activity of the m6A methyltransferase machinery (the "writers", "erasers", and "readers"), thereby reshaping the cellular transcriptomic landscape. This review summarizes the regulatory mechanisms underlying the interaction between m6A modification and ERS, explores how this dynamic network influences cell fate, and further elaborates on their pathophysiological roles in tumors, neurodegenerative diseases, and metabolic diseases, aiming to provide a theoretical basis and potential strategies for targeted therapies against these diseases.

Keywords

m6A Modification, Endoplasmic Reticulum Stress, Unfolded Protein Response, Cell Fate, Disease Mechanisms

1. Introduction

Epitranscriptomics represents a focal point of research in the post-genomic era, among which N6-methyladenosine (m6A) modification has garnered significant attention due to its dynamic reversibility and extensive biological functions. M6A modification predominantly occurs at the conserved RRACH motif and is catalyzed by the methyltransferase complex (comprising METTL3, METTL14, WTAP, etc., known as "writers") [1]. This modification can be removed by demethylases (such as FTO and ALKBH5, known as "erasers") and recognized by specific binding proteins (such as YTHDFs and YTHDCs, known as "readers"), thereby regulating RNA splicing, nuclear export, stability, and translation efficiency [2].

As the primary site for protein synthesis, folding, and secretion, the endoplasmic reticulum (ER) plays a critical role in maintaining cellular homeostasis, which is vital for cell survival. When cells are subjected to stimuli such as hypoxia, nutrient deprivation, and oxidative stress, the accumulation of unfolded or misfolded proteins within the ER lumen triggers endoplasmic reticulum stress (ERS) [3]. Cells attempt to restore homeostasis by activating the unfolded protein response (UPR), a process primarily mediated by three transmembrane sensors: inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor 6 (ATF6) [4]. If the stress persists and remains unresolved, the UPR signaling shifts from promoting survival to inducing apoptosis, ultimately determining cell fate [3].

Recent studies have revealed that m6A modification and ERS do not exist in isolation but rather constitute an intricate molecular interaction network. This crosstalk not only finely regulates UPR signal transduction but also functions as a "molecular rheostat" when cells respond to external stress. A comprehensive understanding of the interplay between these two mechanisms is of great significance for elucidating the fundamental logic underlying cell fate decisions and for developing novel therapeutic strategies.

2. Regulation of Endoplasmic Reticulum Stress by m6A Modification

As a dynamic mechanism of gene expression regulation, m6A modification participates in the initiation, transduction, and effector phases of ERS [5]. By modulating the expression of key UPR molecules, m6A modification influences cell survival or apoptosis under stress conditions [6]. The three canonical UPR pathways (IRE1, PERK, and ATF6) and their downstream signaling axes are all subject to regulation by m6A modification [5].

Within the PERK pathway, the regulation of downstream key molecules-eukaryotic translation initiation factor 2*α* subunit (eIF2*α*) and activating transcription factor 4 (ATF4)-by m6A modification is characterized by high precision. Under persistent stress, eukaryotic translation initiation factor 3 subunit d (eIF3d) not only activates the translation of general control nonderepressible 2 (*GCN2*) to

promote eIF2*α* phosphorylation but also upregulates AlkB homolog 5 (ALKBH5) to drive the demethylation of *ATF4* mRNA 5' UTR and facilitates the selective translation of ATF4, thereby potentially promoting the transition of cells from adaptation to apoptosis [7]. Furthermore, YTHDC2 indirectly enhances eIF2*α* phosphorylation by stabilizing LIM domain kinase 1 (*LIMK1*) mRNA, leading to chemoresistance in colorectal cancer cells; this mechanism reflects a malignant phenotype characterized by an imbalance between pro-survival and pro-death signaling [8]; in renal cell injury, m6A modification levels are also significantly positively correlated with the expression of UPR signaling molecules, implying its involvement in the initiation of injury [9]. Regarding the IRE1 pathway, a positive feedback regulation exists between m6A modification and X-box binding protein 1s (*XBP1s*), which aims to alleviate ERS. During ERS, XBP1s transcriptionally upregulate methyltransferase-like 3/methyltransferase-like 14 (*METTL3/METTL14*), enhancing the mRNA stability of calcium binding and coiled-coil domain 1 (*CALCOCO1*) and *p62* to promote ER-phagy and alleviate ERS [10]. In the ATF6 pathway, the regulatory role of m6A modification is primarily manifested in its indirect effects on downstream effector molecules and upstream regulators. On one hand, m6A modification directly targets ATF6 downstream signals; for instance, METTL3 regulates the expression of the ATF6 target gene hyaluronan synthase 2 (*HAS2*) via the m6A modification/YTH domain-containing family protein 1 (YTHDF1) axis, thereby mediating specific cellular functions of the ATF6 branch [11]. On the other hand, m6A modification participates in ATF6-associated cellular processes through non-coding RNAs. Studies have confirmed a close association between long non-coding RNA (lncRNA) X-inactive specific transcript (*XIST*), m6A methylation, and ATF6-related autophagy, indicating that m6A modification can indirectly maintain (or interfere with) ATF6 pathway homeostasis by regulating *XIST* [12]. Furthermore, in a cadmium-induced kidney injury model, m6A modification showed a significant correlation with the expression of UPR signaling molecules (including ATF6). This correlation likely represents the role of m6A modification as a potential regulator of UPR signal initiation or response, although the specific molecular mechanisms remain to be fully elucidated [9].

Additionally, various m6A regulatory enzymes maintain ER homeostasis through metabolic reprogramming, exhibiting a dualistic nature characterized by both "protective" and "damaging" effects. Regarding the buffering or alleviation of ERS, ALKBH5 regulates ER lipid raft-associated 1 (*ERLIN1*) to control ER calcium flux [5], while METTL3 prevents hepatocyte ERS by inhibiting ceramide accumulation [13]. FUS RNA-binding protein (FUS) collaborates with METTL3 to suppress the UPR and promote gastric cancer progression [14]. In contrast, regarding the initiation or amplification of ERS, fat mass and obesity-associated protein (FTO) exacerbates lipotoxic injury by stabilizing acetyl-CoA carboxylase 1 (*ACC1*) mRNA [15]; Vir-like m6A methyltransferase associated (VIRMA) overexpression increases cellular sensitivity to death under stress [16]; while YTH do-

main family protein 2 (YTHDF2) affects ER homeostasis in bladder cancer by degrading lipoyltransferase 1 (*LIPT1*) mRNA, thereby exacerbating ERS-induced injury in bladder cancer [17].

3. Feedback Regulation of m6A Modifier Enzymes by Endoplasmic Reticulum Stress

3.1. Regulation of the "Writer" Complex by Endoplasmic Reticulum Stress

Activation of the UPR signaling pathways modulates the expression profile of the m6A "writer" complex. Within the IRE1/XBP1 branch, XBP1s participate in the transcriptional upregulation of *METTL3* and *METTL14*. Studies have demonstrated that ERS upregulates *METTL3/14* expression via XBP1s, thereby elevating global m6A levels and promoting ER-phagy to alleviate stress, suggesting a direct regulatory effect of the UPR on methyltransferases [10]. Furthermore, the PERK/ATF4 pathway is also involved in regulating the m6A methyltransferase complex. In a myocardial ischemia-reperfusion model, Wilms' tumor 1-associated protein (WTAP) expression was upregulated and modulated by the PERK/ATF4 pathway, subsequently influencing the assembly and activity of the m6A methyltransferase complex, thereby exacerbating myocardial ischemia-reperfusion injury [18].

3.2. Regulation of "Erasers" and "Readers" by Endoplasmic Reticulum Stress

The expression abundance of the demethylases FTO and ALKBH5 exhibits significant context-dependent patterns under ERS. In a diabetic nephropathy model, ERS induced FTO upregulation, promoting lipid accumulation and exacerbating injury [15]; conversely, in an ischemic stroke model, FTO exerted neuroprotective effects by inhibiting neuronal apoptosis through regulation of the microRNA-503-5p/ubiquitin-specific peptidase 10 (*miR-503-5p/USP10*) axis [19]. The function of ALKBH5 similarly displays duality: in renal cell carcinoma, it alleviates stress by stabilizing mesencephalic astrocyte-derived neurotrophic factor (*MANF*) mRNA [6]; however, in keloids, ALKBH5 activates the IRE1α-XBP1 pathway to promote ERS by upregulating reticulocalbin 1 (*RCN1*) [20].

Regarding reader proteins, the YTHDF family finely regulates the metabolic fate of ERS-related genes by recognizing m6A modifications. YTHDF2 plays a central role across multiple models: it participates in FTO-mediated regulation of *ACC1* mRNA stability [15], mediates *RCN1* mRNA degradation in keloids [20], and disrupts ER homeostasis in bladder cancer by degrading lipoyltransferase 1 (*LIPT1*) mRNA [17]. Additionally, YTHDF1 has also been confirmed to promote the translation of ERS-related genes [21].

4. The Role of m6A Modification and Endoplasmic Reticulum Stress Interplay in Cell Fate Decisions

Under conditions of ERS, m6A modification exhibits a stress intensity-dependent

regulatory effect, influencing the choice between the restoration of cellular homeostasis and the mode of cell death. Under conditions of mild or short-term ERS, m6A modification facilitates the restoration of homeostasis by promoting the clearance of unfolded proteins and inhibiting apoptotic signaling. For instance, XBP1s transcriptionally upregulates *METTL3/METTL14*, enhancing the stability of *CALCOCO1* and *p62* mRNAs to promote ER-phagy; concurrently, ALKBH5 maintains ER-associated degradation (ERAD)-mediated calcium homeostasis by regulating *ERLIN1* [5] [10]. Furthermore, m6A modification prevents the premature initiation of apoptotic programs: FTO upregulates the anti-apoptotic factor ubiquitin-specific peptidase 10 (*USP10*) by inhibiting *miR-503-5p* maturation, thereby reducing neuronal apoptosis [19]; similarly, the normal function of METTL3 in gastric cancer participates in suppressing excessive stress responses [14]. This regulatory network confers stress tolerance to cells; in renal cell carcinoma, ALKBH5-mediated demethylation of mesencephalic astrocyte-derived neurotrophic factor (*MANF*) mRNA enhances cellular resistance to stress by inhibiting IRE1*α* phosphorylation [6]. The regulation of stanniocalcin 2 (*STC2*) and ER protein 29 (*ERP29*) by m6A further corroborates its critical role in tumor adaptation and drug resistance [22] [23]. However, the dynamic alterations in m6A modification profoundly influence the induction and resolution of ERS. The modification levels, in conjunction with stress intensity and duration, collectively determine cell fate outcomes, oscillating between survival adaptation and death. In pathological contexts, dysregulation of m6A modification often exacerbates stress injury and drives disease progression. In gastric cancer, loss of METTL3 or FUS function can induce severe ERS and promote apoptosis, thereby effectively restraining tumor progression [14]; conversely, in an ischemic stroke model, ALKBH5 exerts a protective effect by reducing *STAT5* mRNA stability, effectively alleviating neuroinflammation and neuronal apoptosis to assist cells in resisting stress-induced injury [24].

5. Pathophysiological Significance and Disease Associations

5.1. Cancer

Tumor cells frequently reside in a microenvironment characterized by hypoxia, acidosis, and nutrient deprivation, conditions that readily induce ERS [10] [16] [25]. M6A modification plays a facilitating role in the process by which tumor cells hijack UPR signaling to gain a survival advantage; however, its regulatory direction is highly context-dependent [10]. In breast cancer, XBP1s-mediated upregulation of *METTL3/METTL14* facilitates cellular stress adaptation by enhancing ER-phagy and influences chemosensitivity [10]. Conversely, in colorectal cancer, YTHDC2 mediates chemoresistance by stabilizing *LIMK1* mRNA, thereby activating eIF2*α* phosphorylation and promoting stress granule formation [8]. In contrast, m6A modification can also promote tumor progression by alleviating stress. In renal cell carcinoma, ALKBH5 upregulates *MANF* expression via demethylation, inhibiting IRE1*α* phosphorylation to mitigate ERS, thereby sustain-

ing cancer cell survival [6]. Furthermore, m6A modification exhibits stage-specific dual roles in tumorigenesis. For instance, in early-stage hepatocellular carcinoma, METTL3 may exert tumor-suppressive functions by maintaining moderate levels of ERS, and its loss paradoxically accelerates tumorigenesis due to an impaired stress response [26].

5.2. Neurodegenerative Diseases

Neurodegenerative diseases represent not merely a linear trajectory of protein accumulation but a multidimensional collapse of biological organization, involving the loss of intracellular signaling, transcriptional identity, and proteostasis integrity [27]. In this context, ERS and aberrant m6A modification constitute critical pathological hubs. ERS is a core feature of diseases such as Alzheimer's disease (AD). The presence of the toxic peptide β-amyloid 1-42 (Aβ1-42) impairs ER function, preventing the effective clearance of misfolded proteins via the UPR, thereby exacerbating apoptosis and oxidative stress [28]. M6A modification serves as a crucial link between proteostasis and ERS. Studies have revealed that in Aβ1-42-treated cells, downregulation of *METTL14* reduces the stability of cerebellin 4 (*CBLN4*) mRNA, releasing the inhibition on ERS and consequently aggravating neuronal injury [28]. Moreover, widespread dysregulation of m6A modifiers (e.g., METTL3, YTHDF1) disrupts translational fidelity and proteostasis, playing a central role in the pathogenesis of diseases such as AD and amyotrophic lateral sclerosis (ALS) [27].

5.3. Metabolic Diseases

Metabolic diseases, including obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD), are closely associated with ERS. M6A modifiers exhibit complex bidirectional roles in the regulation of metabolic homeostasis. The m6A demethylase FTO often acts as a pathogenic mediator. In diabetic nephropathy, FTO overexpression stabilizes *ACC1* mRNA in an m6A-dependent manner, promoting fatty acid metabolism and exacerbating podocyte lipotoxic injury and ERS [15]. However, its function exhibits tissue specificity; within the nervous system, FTO exerts neuroprotective effects by regulating the *miR-503-5p/USP10* axis [19], and its regulation of cellular stress responses may operate independently of its demethylase activity [29]. Conversely, the m6A methyltransferase METTL3 serves as a critical protective factor in maintaining ER homeostasis. Beyond the consensus that its deficiency in pancreatic β-cells leads to severe ERS and diabetes onset, studies indicate that METTL3 alleviates intestinal ERS by upregulating the m6A methylation level of heat shock protein 70 (*HSP70*) [30]. These findings underscore the critical importance of the dynamic balance within the m6A modification network for the maintenance of metabolic organ function.

5.4. Cardiovascular Diseases

As terminally differentiated cells, cardiomyocytes are exquisitely sensitive to ERS.

M6A modification plays a pivotal role in pathological processes such as heart failure, ischemic heart disease, and pulmonary hypertension, and is closely associated with ERS [19] [21] [24] [31]. By regulating mRNA translation and stability, m6A modification influences the PERK/eIF2*α*/CHOP pathway and the *miR-503-5p/USP10* axis, thereby mediating the progression of ERS and determining cell fate [19] [21] [24].

5.5. Commonalities and Disease Specificity of Cross-Disease Mechanistic Nodes

A cross-sectional analysis of the m6A modification-mediated regulation of ERS mechanisms across the aforementioned diseases reveals key molecular regulatory nodes. Among these, the *METTL3/14*-XBP1s axis represents a prominent node shared across diseases, yet its function exhibits distinct "context-dependence." In breast cancer, this axis enhances ER-phagy by upregulating METTL3/METTL14 to promote cell survival [10]; conversely, in early-stage tumors (e.g., hepatocellular carcinoma) or normal metabolic organs (e.g., pancreatic *β*-cells, intestine), METTL3 acts as a protective factor maintaining ERS homeostasis, and its deficiency directly leads to stress dysregulation and pathological injury [25] [29]. In contrast, the ALKBH5-*MANF* axis and the FTO-*ACC1* axis demonstrate stronger disease specificity. In renal cell carcinoma, ALKBH5 suppresses IRE1*α* phosphorylation by upregulating MANF via demethylation, representing a unique survival strategy for tumor cells to evade ERS-induced lethality [6]; meanwhile, the FTO-*ACC1* axis specifically mediates lipotoxic injury in metabolic diseases (e.g., diabetic nephropathy) [15]. Furthermore, the roles of downstream effector molecules, such as YTHDC2 and YTHDF1, are diametrically different: the former activates pro-survival stress granules by stabilizing *LIMK1* mRNA in colorectal cancer [8], whereas the loss of the latter in neurodegenerative diseases leads to the collapse of protein homeostasis [26]. In summary, within the interaction network between m6A modification enzymes and ERS signaling pathways, METTL3-mediated methylation primarily functions as a "buffer" for ERS intensity, varying with cellular survival demands, whereas demethylases such as ALKBH5 and FTO predominantly serve as disease-specific "pathogenic" or "protective" switches.

6. Conclusions and Perspectives

An intricate molecular interaction network exists between m6A modification and ERS. As an upstream regulator, m6A modification determines the trajectory of ERS by dynamically regulating the translation and degradation of key molecules within the UPR pathways. Conversely, ERS, acting as a downstream effector and feedback signal, acts upon m6A modifier enzymes to reshape the cellular post-transcriptional modification landscape. The interplay between these two components constitutes a core mechanism by which cells sense environmental stress and make fate decisions; dysregulation of this interplay is extensively involved in the pathogenesis and progression of major diseases, including tumors, neurodegen-

erative diseases, and metabolic disorders.

Despite significant progress in this field, numerous challenges and opportunities remain. First, the precise elucidation of underlying mechanisms requires further in-depth investigation. The specific mechanisms by which m6A modification selectively regulates the three UPR branches (IRE1, PERK, and ATF6) under varying spatiotemporal conditions remain incompletely understood. In particular, the conformational changes of reader proteins under different stress intensities and the differential recruitment of their downstream effector molecules warrant further clarification. Second, research regarding dynamic processes and organelle interactions remains limited. Current studies have largely focused on static descriptions or observations at specific time points, lacking real-time dynamic monitoring of the interplay between m6A modification and ERS. Future research should integrate techniques such as live-cell imaging and single-molecule tracking to uncover the details of their interaction within subcellular structures, such as endoplasmic reticulum-mitochondria contact sites (MAMs). Finally, while the prospect of clinical translation is promising, progress must be pursued with prudence. Intervention strategies based on the m6A-ERS interaction network have demonstrated tangible potential. First, targeting m6A demethylases represents a pivotal strategy for reversing drug resistance. In colorectal cancer, inhibiting the activity of FTO or YTHDC2 can block *LIMK1*-mediated eIF2α phosphorylation and stress granule formation, thereby abrogating the protective mechanisms underlying chemoresistance in tumor cells [8] [15]. Second, developing blockers for the m6A modification of UPR sensors holds promise for precision therapy. In renal cell carcinoma, targeted inhibition of ALKBH5 abrogates its upregulation of *MANF*, thereby restoring IRE1α phosphorylation activity and forcing tumor cells into apoptosis due to ERS overload [6]. However, drug development must confront a core safety concern: the risk of context-dependent switching between "pro-survival" and "pro-apoptotic" outcomes. Taking METTL3 as an example, it mediates pro-survival signals via *XBP1s* in breast cancer, suggesting inhibition as a therapeutic approach; conversely, in metabolic diseases, METTL3 serves as a protective factor maintaining pancreatic β-cell homeostasis, indicating that its activation might constitute a viable strategy [10] [29]. This "identity reversal" of the same target across different diseases, or even different stages of the same disease, necessitates that future drug designs strictly define the therapeutic window and develop tissue-specific delivery systems. Such measures are essential to avoid the collapse of homeostasis in normal tissues or the unintended acceleration of tumor progression resulting from systemic intervention.

In summary, an in-depth dissection of the interaction mechanisms between m6A modification and ERS not only advances the understanding of cellular stress biology from an epitranscriptomic perspective but also provides potential targets and a theoretical basis for the precise diagnosis and treatment of related diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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