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COMMENTARY

The YTHDC1-m6A-MEG3 Regulatory Axis in Radiation-Induced Liver Injury: Deciphering Early-Stage Epitranscriptomic Alterations and Molecular Dynamics

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Abstract: Radiation-induced liver injury (RILI) remains one of the most severe complications encountered during radiotherapy for hepatocellular carcinoma (HCC), cholangiocarcinoma, and tumors of the right lower lung. Although clinically significant, the molecular mechanisms that drive RILI are still incompletely understood. In our recent study published in *Cell Death and Disease*, entitled "The YTHDC1 Reader Protein Recognizes and Regulates the lncRNA MEG3 Following Its METTL3-Mediated m6A Methylation: A Novel Mechanism Early During RILI", we investigated in depth the epitranscriptomic regulation of RILI pathogenesis. Post-irradiation, the disease progresses in a staged manner: an early phase characterized by hepatocyte apoptosis and inflammatory activation, a subsequent stage dominated by fibrotic remodeling, and ultimately leading to liver failure. The absence of reliable early biomarkers severely limits timely diagnosis and therapeutic intervention. Among potential candidates, RNA modifications such as N6-methyladenosine (m6A) have emerged as key modulators of cellular stress responses and early pathogenic mechanisms, holding promise as novel diagnostic or therapeutic targets. As a major regulator of RNA metabolism, m6A influences transcript splicing, stability, and translation through the orchestrated actions of classes of proteins known as writers, erasers, and readers. This regulatory layer not only contributes to fundamental processes including DNA repair and inflammatory signaling but also shapes pathological changes via the modulation of lncRNA-chromatin interactions, highlighting its promise for therapeutic exploitation in cancer and RILI. In our study, we identified the long non-coding RNA MEG3 as a pivotal player in RILI, where it promotes apoptosis, drives inflammatory response, and accelerates fibrosis. We further demonstrated that MEG3 expression is tightly controlled by the METTL3-YTHDC1 axis, and YTHDC1-mediated recognition of m6A-modified MEG3 is essential for the progression of RILI. These insights establish the YTHDC1-MEG3 pathway as a key molecular driver of RILI and provide a framework for the design of targeted therapies to mitigate RILI.

Keywords: m6A methylation, lncRNA MEG3, RILI, METTL3-YTHDC1 axis, miR-20b/BNIP2

In recent years, epigenetic regulation has emerged as a central focus in medical research, offering critical insights into the mechanisms driving diverse pathological conditions. In February 2025, we reported a study in *Cell Death & Disease* entitled "The YTHDC1 Reader Protein Recognizes and Regulates the lncRNA MEG3 Following Its METTL3-Mediated m6A Methylation: A Novel Mechanism Early During RILI". This study provides an in-depth analysis of how m6A RNA modifications contribute to RILI. Specifically, we demonstrated that the reader protein YTHDC1 recognizes m6A-modified MEG3 and thereby modulates the miR-20b/BNIP2 signaling axis. These findings offer new perspectives on the molecular basis for early RILI and suggest potential avenues for therapeutic intervention through targeted epigenetic modulation. Below, we summarize and expand upon the implications of this research.

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Introduction to RILI

Currently, radiotherapy is used for various cancers, including hepatocellular carcinoma. However, the treatment dose is limited by the liver's inherent radiosensitivity. Targeted irradiation of the liver can also lead to cell damage and liver dysfunction, leading to radiation-induced liver disease (RILD) that occurs two weeks to six months after radiation therapy (RT).[1]

RILD is one of the significant complications in RT. It serves as a major limiting factor for escalating the radiation dose and re-irradiating tumors located in close proximity to the liver. Clinically, RILD is classified into two types: classical RILD (occurring in patients without underlying liver disease) and non-classical RILD (occurring in patients with underlying liver disease). Patients with classical RILD typically manifest symptoms such as fatigue, abdominal pain, an increase in abdominal girth, hepatomegaly, anicteric ascites, and an isolated elevation of alkaline phosphatase that is disproportionate to other liver enzymes. In contrast, patients with non-classical RILD present with jaundice and significantly elevated serum transaminase levels. Efforts should be made to keep the average dose below the tolerance threshold.[2]

Although considerable progress has been made in delineating the pathophysiology of RILI, the contribution of epitranscriptomic regulation in general, and m6A modifications in particular, remains largely unexplored. The m6A modification of non-coding RNAs regulates the cleavage, transport, stability, and degradation of non-coding RNAs themselves. It also regulates cell proliferation and metastasis in cancer, as well as stem cell differentiation and homeostasis by influencing the biological functions of cells.[3] Radiation has the potential to perturb the hepatic epitranscriptome in ways that disturb RNA-protein interactions essential for genome integrity and cellular defense. Human hepatic stellate cells (HSC) exhibit significant differences in methylation patterns after exposure to 8 Gy of X-ray irradiation. Irradiation recruits AlkB homolog 5 (ALKBH5) to demethylate the m6A residues in the 3′ untranslated region of high-mobility group box 1 (HMGB1), thereby activating the STING-interferon regulatory factor 3 signaling pathway and promoting liver inflammation.[4] Evidence from other hepatic disorders demonstrates that m6A modifications modulate critical disease pathways. The expression of ALKBH5 in HSC is induced by radiation. Subsequently, the m6A demethylation of toll-interleukin 1 receptor domain-containing adaptor protein (TIRAP) mRNA is mediated by this radiation-induced ALKBH5. As a result, the downstream NF-κB and JNK/Smad2 pathways of TIRAP are activated, which further promote the activation of HSC.[5] However, whether similar mechanisms contribute to the onset and progression of RILI has not been clarified. Much of the current literature on RILI has focused on histopathological features or proteomic signatures, often neglecting the upstream epitranscriptomic modifications that precede overt tissue damage. The discovery of m6A-dependent biomarkers has the potential to transform early diagnosis and to open therapeutic avenues, for example, by employing METTL3 or FTO activators to modulate RNA methylation and thereby limit liver injury.[6,7]

Clinically, RILI poses a persistent challenge in oncologic treatment, requiring clinicians to strike a careful balance between effective tumor control and preservation of hepatic function. Investigating m6A modifications and related RNA regulatory events could alleviate this damage, enabling earlier recognition of subclinical damage and facilitating timely intervention. Addressing this unmet need is critical for improving radiotherapy outcomes and long-term survival in patients.

m6A Methylation: A Master Regulator of RNA Fate

m6A has emerged as the most prevalent internal RNA modification, acting as a highly dynamic post-transcriptional regulator that influences nearly every step of RNA metabolism. This reversible mark is deposited by methyltransferases ("writers"), removed by demethylases ("erasers"), and interpreted by specialized binding proteins ("readers"). Together, these components function as a molecular coding system that dictates RNA splicing, export, stability, translation, and localization.[8] Beyond their housekeeping roles, m6A modifications play critical parts in cellular adaptation to stress, safeguarding genomic integrity, and driving disease processes.

The methyltransferase complex is mainly composed of METTL3 and METTL14, and preferentially places m6A marks around the stop codon, in the 5′ and 3′ untranslated regions, and within long internal exons.[9,10] These

modifications can be erased by the demethylases FTO and ALKBH5, enabling rapid transcriptome remodeling in response to environmental changes. Their functions are recognized and mediated by relevant readers, such as YTHDC1.[11,12] Nuclear reader YTHDC1 regulates splicing decisions by recruiting splicing factor serine/arginine rich splicing factor 3 (SRSF3) to m6A-marked pre-mRNAs.[13] YTHDF1 is a well-characterized m6A reader protein that is crucial for protein translation, stem cell self-renewal, and YTHDF2 exhibits selective recognition of m6A-modified RNAs, playing a regulatory role in their degradation.[14,15] This tripartite system provides a mechanism for rapid and reversible gene-expression reprogramming without altering DNA sequences.

Upon phosphorylation, METTL3 localizes to DNA damage sites. At these sites, it catalyzes m6A within the RNAs associated with DNA damage. This m6A modification serves as a molecular signal that attracts the m6A reader protein YTHDC1, which then safeguards these RNAs. Subsequently, this process further recruits RAD51 and BRCA1, facilitating the homologous recombination (HR)-mediated repair of damaged DNA.[16] Thus, m6A acts as a dual safeguard, coordinating RNA fate and reinforcing DNA repair. In addition, in terms of inflammation, METTL3 promotes the oxidized low-density lipoprotein (oxLDL)-induced inflammatory response in macrophages by regulating the m6A modification of signal transducer and activator of transcription 1 (STAT1) mRNA, thereby affecting the expression and activation of STAT1.[17]

The nuclear reader YTHDC1 exhibits remarkable specificity for lncRNAs and their associated proteins. For instance, during the progression of HCC, YTHDC1 exerts an epigenetic regulatory effect on the long non-coding RNA NEAT1. This regulatory process activates the lipid metabolic processes associated with stearoyl-CoA desaturase (SCD).[18] A study reveals that methylated substrate's capacity to repel bulk water molecules contributes to the preference of the YTH domain (eg, YTHDC1) for m6A.[19] YTHDC1 recognizes the m6A-modified lnc668 and enhances the METTL3-mediated modification of lnc668. Subsequently, the phase-separated YTHDC1 promotes the nuclear export of the m6A-modified lnc668. After the nuclear export of lnc668, it promotes the translation and stability of its host gene, phosphatidylinositol-binding clathrin assembly protein, activates the differentiation of fibroblasts into myofibroblasts, and leads to the exacerbation of pulmonary fibrosis.[20] YTHDC1 recognizes m6A on LINE1 RNA in the nucleus and regulates the formation of the LINE1-NCL partnership and the chromatin recruitment of KAP1.[21]

Collectively, the m6A epitranscriptome functions as a dynamic regulatory interface that couples external signals with transcript fate, orchestrated by the interplay of writers, erasers, and readers. Its roles in DNA repair, inflammatory signaling, and nuclear organization highlight its versatility in both physiological and pathological settings. Future studies focusing on isoform-specific readers and single-cell m6A profiling promise to refine our understanding of this RNA code and may accelerate the development of RNA-based therapeutics in cancer, neurodegenerative disease, and immune disorders. Far from being a passive marker, m6A serves as a master regulator of cellular identity, plasticity, and stress adaptation.

MEG3 Acts as A Tumor-Suppressive lncRNA with Dual Roles

MEG3 and Apoptosis

The long non-coding RNA Maternally Expressed Gene 3 (MEG3) has emerged as a pivotal regulator in liver pathology, displaying context-dependent functions that range from tumor suppression to the mediation of acute tissue injury. These roles reflect its ability to integrate multiple stress-response pathways, with distinct outcomes depending on the cellular environment. MEG3 regulates key processes, including p53 signaling, mitochondrial apoptosis, and profibrotic remodeling, effectively acting as a molecular "switch" that calibrates the balance between repair and malignant transformation. Its context-specific activity makes MEG3 a central determinant in the trajectory of liver disease progression.[22] The tumor-suppressive activity of MEG3 is largely mediated through its modulation of the p53 pathway. By binding directly to p53, MEG3 stabilizes its association with chromatin, thereby potentiating the transcription of pro-apoptotic genes such as BAX and PUMA. This cascade effectively limits HCC proliferation.[23] Chemotherapy resistance stands as a pivotal factor influencing the prognosis of patients diagnosed with lung neoplasms. MEG3 has been found to up-regulate the sensitivity of lung tumor cells to chemotherapy drugs. Moreover, a recent report indicated that MEG3 potentiates the anti-tumor activity of curcumin in gemcitabine-resistant non-small cell lung cancer (NSCLC) cells via the PTEN

pathway.[24] MEG3 acts as a promoter of cell death during ischemia. It engages in both physical and functional interactions with p53 to mediate the damage caused by ischemia.[25] Acute liver injury often induces a marked increase in MEG3 expression, which exacerbates damage by amplifying oxidative stress and necroptotic cell death. For instance, in acetaminophen-induced hepatotoxicity, MEG3 enhances RIPK1/MLKL-mediated necroptosis by impairing cytoprotective autophagy.[26,27] Thus, MEG3 exhibits a dual-edged function as it is suppressed in the context of malignancy yet overactivated in settings of acute damage, underscoring its complex role in liver pathogenesis.

The ultimate consequences of MEG3 activation depend on the nature of the hepatic insult. During RILI, MEG3 exhibits a pro-apoptotic effect, facilitating p21-dependent cell cycle arrest. MEG3 overexpression suppresses ^{131}I-resistant thyroid carcinoma cell viability, promotes apoptosis, and induces DNA damage.[28–30] MEG3 also promotes mitochondrial apoptosis by suppressing anti-apoptotic members of the Bcl-2 protein family, thereby facilitating cytochrome c release, a mechanism particularly relevant in chemoresistant HCC cells.[31,32] On the contrary, overexpression of MEG3 also inhibits the NF-κB signaling pathway and increases the Bcl-2/Bax ratio by downregulating miR-34a. This increased Bcl-2/Bax ratio slows down cell apoptosis.[33,34]

MEG3 and Inflammation

Knocking down MEG3 not only partially eliminated the activation effect of cisplatin (DDP) on NLRP3/caspase-1/GSDMD pathway-mediated pyroptosis, but also reversed the inhibitory effect of DDP on the tumor growth and metastasis ability in vitro and in vivo, further confirming that MEG3 may partially mediate the pyroptosis signaling during DDP treatment.[35] MEG3 functioned as a competing endogenous RNA (ceRNA) for miR-7a-5p, thereby modulating the expression of NlRP3 and subsequently inducing inflammation in microglial cells.[36] A study corroborated the upregulated expression of long non-coding RNA MEG3 during cerebral ischemia-reperfusion injury (CIRI). This upregulation contributes to pyroptosis through the modulation of the miR-145-5p/TLR4 axis. Specifically, silencing MEG3 led to a decrease in the expression of NLRP3, consequently preventing pyroptosis. Conversely, the inhibition of miR-145-5p counteracted the effect of MEG3 knockdown and promoted pyroptosis.[37] MEG3 functioned as an endogenous competitive sponge through sequence complementarity with miR-223, effectively suppressing the activity of miR-223. This suppression led to an upregulation of NLRP3 expression, ultimately promoting pyroptosis in endothelial cells.[38] Under certain specific conditions, MEG3 inhibits NLRP3 inflammasome pyroptosis by recruiting EZH2/YTHDC1.[39]

MEG3 can target the miR-34a/ silent information regulator factor 2-related enzyme 1(SIRT1) axis, inhibit the NF-κB signaling pathway, and alleviate high glucose (HG)-induced cell apoptosis and inflammation.[33] Melatonin enhances the activity of SIRT1 through the MEG3/miR-204 axis, leading to the deacetylation of SIRT1 target genes forkhead box O1 (FoxO1) and the NF-κB subunit p65, and ultimately contributing to the alleviation of oxidative stress and inflammation.[40] Besides, transfection of si-MEG3 can reverse the inflammatory injury and insulin resistance in mature 3T3-L1 adipocytes induced by TNF-α.[41]

MEG3 and Fibrosis

In chemically induced liver injury triggered by carbon tetrachloride (CCl_4) or ethanol, MEG3 levels were remarkably decreased in CCl4-induced human fibrotic livers, and MEG3 inhibited the activation of HSC and the process of liver fibrosis.[42] MEG3 has the potential to halt the pulmonary fibrosis induced by nickel oxide nanoparticles (NiO NPs) through the inhibition of the TGF-β1-mediated PI3K/AKT pathway.[43]

Overall, MEG3 represents the intricate duality of lncRNA biology, functioning both as a suppressor of tumorigenesis and as an amplifier of acute injury. Its effects are dictated by epigenetic status, microenvironmental context, and the source of cellular stress. This makes MEG3 both an attractive and challenging therapeutic target. Reactivating MEG3 in HCC using demethylating compounds or lncRNA delivery vectors could restore tumor-suppressive signaling,[44] while transient inhibition during acute injury might mitigate hepatotoxicity. MEG3 also causes cell death, exacerbates inflammation, and slows down fibrosis. Future directions should focus on clarifying upstream regulatory networks, including competing endogenous RNAs and chromatin modifiers, and applying single-cell technologies to map the

spatiotemporal activity of MEG3 across disease states. Dissecting these regulatory mechanisms will be essential for harnessing MEG3 in therapeutic strategies for liver disease.

The METTL3-YTHDC1-MEG3 Axis: An Emerging Core Mechanism in Early Radiation-Induced Liver Injury

RILI remains a dose-limiting complication of abdominal radiotherapy. Recent studies highlight the interaction between the m6A modification and the lncRNA MEG3 as a central determinant in the early pathogenesis of RILI. The METTL3-YTHDC1-MEG3 signaling axis orchestrates pro-apoptotic, inflammatory, and metabolic abnormalities, providing mechanistic insight into radiation toxicity and revealing potential targets for therapeutic intervention. METTL3, the catalytic subunit of the m6A methyltransferase complex, deposits m6A marks on MEG3 transcripts. Radiation exposure induces METTL3 upregulation in hepatocytes, which reinforces the formation of the m6A-MEG3-YTHDC1 complex, leading to MEG3's nuclear export and degradation, and thus reducing its bioavailability. This dynamic highlights METTL3 as a pivotal regulator of MEG3 in irradiated livers.[45]

In the current study, after METTL3 knockdown, the m6A modification level of MEG3 decreased significantly. Meanwhile, the expression level of MEG3 protein increased significantly. After YTHDC1 knockdown, the MEG3 level was significantly higher than that in the control group, which proved that YTHDC1 could promote the degradation of MEG3. METTL3 mediated m6A methylation can promote MEG3 degradation in a YTHDC1 dependent manner after radioactive hepatocyte injury in a YTHDC1-dependent fashion, thereby explaining the role of the METTL3-YTHDC1-MEG3 axis in RILI.

MEG3, a well-studied tumor-suppressor lncRNA, has been associated with apoptosis regulation in multiple cell types. In the context of irradiated hepatocytes, increased MEG3 stability can potentially tip the balance towards apoptosis. Although the exact molecular mechanisms by which MEG3 exerts its pro-apoptotic effects in this scenario are still being investigated, studies in other systems have shown that MEG3 can interact with various proteins and signaling pathways related to apoptosis.[45,46] Research has shown that METTL3, as a key component of the m6A methyltransferase complex, can influence the m6A modification levels of various RNAs, including lncRNAs like MEG3. In irradiated hepatocytes, inhibition of METTL3 can promote radiation-induced apoptosis by enhancing the stability of MEG3, which underscores the critical role of this axis in regulating hepatocyte survival.[45] MEG3 triggered an up-regulation of miR-493-5p, which specifically targeted METTL3. In the context of experimental models, overexpression of MEG3 or knockdown of METTL3 led to significant suppression of cell proliferation and a notable promotion of apoptosis in cells.[47] YTHDF2 expedited the decay of MEG3 through the recognition of METTL3-mediated m6A modification. In a mouse model, when compared to the group of mice injected with cells transfected with a vector control, the group injected with MEG3-knockdown cells exhibited significantly larger tumor volumes and more rapid tumor growth rates.[48]

Taken together, these studies highlight the METTL3-YTHDC1-MEG3 axis as a promising therapeutic target for RILI. Inhibition of METTL3 or blockade of YTHDC1 function could promote MEG3-dependent apoptosis.

Key Unresolved Questions

There are several key outstanding questions in this research space that warrant consideration.

5.1 How does radiation spatially and temporally influence METTL3 expression in cells?

5.2 How does radiation spatially and temporally influence MEG3 expression in cells?

5.3 How does this regulatory METTL3-YTHDC1 axis interact with NEAT1 and other RNAs in the context of RILI?

Collectively, these questions underscore the complexity of MEG3 regulation during the early phases of RILI. Radiation-induced METTL3 activity modifies MEG3 through m6A deposition, transforming it from a tumor-suppressive lncRNA into a pro-death mediator stabilized by YTHDC1. In this altered state, MEG3 drives apoptosis, amplifies inflammation, and disrupts metabolic homeostasis, thereby exacerbating radiation toxicity (Figure 1). A deeper understanding of the interactions among m6A writers, readers, and lncRNAs has the potential to guide the development of highly targeted radioprotective interventions. Such precision approaches could ultimately improve the therapeutic index of radiotherapy by protecting normal tissue without diminishing antitumor efficacy.

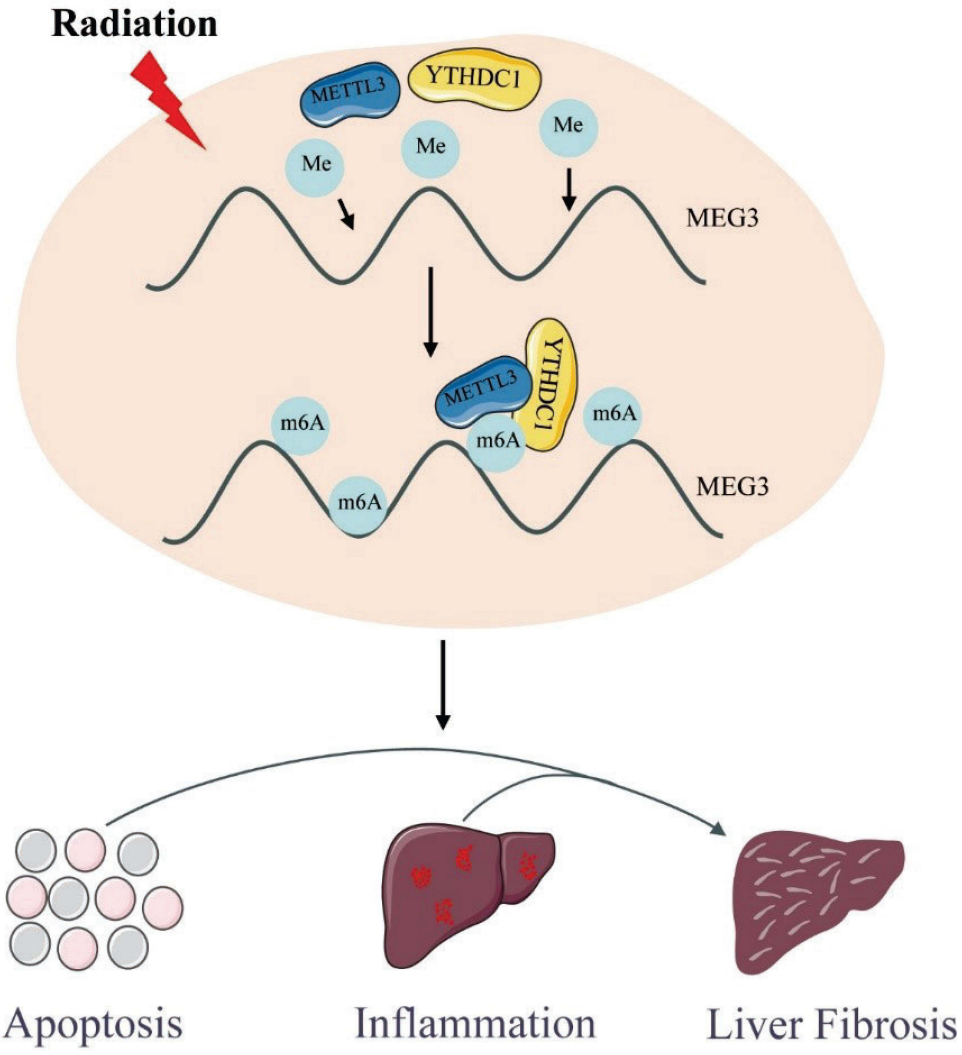

Figure 1 METTL3 mediates m6A modification of MEG3 in a YTHDC1-dependent manner in the context of RILI.

Ethical Approval

This commentary does not involve any ethical content.

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Author Contributions

Cun-yang Guo: writing, editing and original draft preparation; Yi-fei Du: data curation, writing; Hui-cong Yan: validation, writing; Xin-ming Fan: software; Fang-qi Tian: consult the literature and summarize; Ping Xu: writing, reviewing and supervision. All authors contributed to the article and approved the submitted version.

Disclosure

The authors declare that there are no conflicts of interest in this work.

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