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RNA Modifications Regulating Early Cancer Development

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Abstract

RNA modifications including adenosine-to-inosine (A-to-I) editing and N6-methyladenosine (m6A) play important roles in post-transcriptional gene regulation and have been identified as major factors in the initiation and spread of cancer. The most prevalent internal alteration in eukaryotic mRNA, m6A, is dynamically controlled by "writers" (METTL3/METTL14), "erasers" (FTO/ALKBH5), and "readers" (YTH domain proteins), which collectively affect RNA stability, splicing, translation, and destruction. Studies have shown that dysregulation of m6A plays a role in cancers such leukemia, breast cancer, and clear cell renal cell carcinoma through pathways involving METTL3 and SETD2 mutations. This dysregulation has been closely linked to tumor growth, metastasis, and therapeutic resistance. Similar to this, A-to-I RNA editing, which is mostly mediated by ADAR1, modifies RNA transcripts without altering DNA sequences and promotes protein variety and immune control. By modifying endogenous double-stranded RNA, blocking immune identification by sensors like MDA5 and PKR, and facilitating immune evasion in interferon-rich environments, ADAR1 enhances tumor survival in cancer. Through changed transcripts like AZIN1 and GLI1, overexpression of ADAR1 has also been connected to the development of tumors. These results collectively show that A-to-I RNA editing and m6A alteration are both attractive therapeutic targets for precision cancer therapy approaches in addition to being biomarkers of disease progression.

Introduction

Traditional molecular biology research typically largely focuses on DNA mutations and protein dysregulation as the primary drivers of cellular function and disease. However, a growing body of research indicates that post-transcriptional processes are essential for adjusting tumor-suppressive and oncogenic pathways before irreversible genetic alterations take over. Among these processes, RNA chemical changes have become important regulators that can quickly alter cellular function in response to both internal and external stimuli. Even though there has been a lot of research showing that RNA editing causes changes in cancer, most studies look at advanced or metastatic tumors. That makes it harder to decipher whether RNA editing helped start the cancer or if it changed later as the tumor progressed. Another issue is that many studies focus on overall editing levels instead of specific editing events in important genes like oncogenes or tumor suppressor genes.

Among these modifications, N6-methyladenosine (m6A) methylation is one of the most abundant and functionally significant marks in eukaryotic RNA. Changes in m6A recognition or deposition can destabilize tumor-suppressor mRNAs or increase the translation of oncogenic transcripts, altering cellular signaling networks to support the progression of cancer. Early transformation enables the selective amplification of cancer-promoting pathways because m6A alterations have gene-specific effects rather than uniform effects across the transcriptome. These findings position RNA methylation not merely as a downstream consequence of transformation, but as an active regulatory layer capable of driving tumorigenic processes, especially in the early stages of development.

Another major epitranscriptomic mechanism with profound implications in cancer is adenosine-to-inosine (A-to-I) RNA editing, catalyzed primarily by the enzyme ADAR1. A-to-I

editing is a process where certain adenosine bases in RNA are changed into inosine by enzymes called ADARs (adenosine deaminases acting on RNA). Since inosine is read like guanosine by the cell, this can change how proteins are made or how RNA behaves. Hyperactivation of ADAR1 increases editing within double-stranded RNA regions, allowing tumor cells to evade innate immune sensing pathways and enhance their survival. Given its frequent upregulation across diverse cancer types, ADAR1 has emerged as a promising target for cancer immunotherapy. Over the course of this paper, we will be discussing the correlation between aberrant RNA modifications, such as in m6A methylation and A-to-I editing, and early tumor initiation, progression, and therapeutic resistance, suggesting that RNA-level regulation represents an additional layer of complexity in cancer biology that has historically been underexplored.

Methodology

This study will utilize a systematic review and meta-analysis, under PRISMA, to identify and evaluate the primary research examining the role of m6A methylation and A-to-I RNA editing in cancer development, specifically looking at mechanisms influencing oncogene activation and tumor-suppressor silencing. We will use a series of findings from studies conducted from a wide range of methodologies. To gather these studies, we collected peer-reviewed articles from PubMed, Nature, JSTOR, (other sources we end up gathering), using keyword combinations which included: “m6A methylation AND cancer,” “A-to-I RNA editing AND cancer,” “RNA modification AND tumor suppressor,” (other key terms others may have used). Our inclusion criteria for these sources included the sources relevance to our topic: study focuses on early-stage tumors or early cancer development, study examined m6A methylation or A-to-I RNA editing, studies included high-quality RNA sequencing or included sample patients who had not received treatment for cancer, and outcomes from research studies examined include RNA editing or methylation frequency or effects on oncogenes, tumor suppressors, or immune pathways. We excluded any studies if they were not primary data, had a reasonable sample size and replicability, looked at other RNA modifications that were not related to m6A or A-to-I editing, or only focused on late stage cancer. We chose these criteria to make sure we are actually studying RNA editing changes related to early cancer development and not changes caused by treatment, advanced disease, or poor data quality. Additionally, using the selection criteria for the outcomes from these studies will better help us to compare expression levels of RNA modification regulators between tumor and normal tissues across multiple cancer types for m6A and A-to-I editing. From each study, we took the following variables to use in our analysis: Cancer type, stage of disease, presence of matched normal tissue, RNA modification type, RNA

editing frequency, and changes in oncogene expression. To synthesize our data, we used a computational analysis approach to examine the role of RNA modifications in cancer progression, focusing on m6A methylation and ADAR1-mediated A-to-I RNA editing. This will be done by assigning binary values to our variables in order to compare and measure each variable’s prevalence across papers to measure a variable's consistency or prevalence across studies. In addition to our quantitative analysis, we will be utilizing qualitative data to identify key themes and recurring biological patterns. The findings we gather from these studies will be classed under what mechanisms they discuss, and what mechanistic effects they have on oncogene activation, tumor-suppressing silencing, RNA processes, and immune-related pathways.

M6A

Background

N6-methyladenosine, a reversible chemical modification in which a methyl group is added to the nitrogen at the sixth position of adenosine in RNA, is referred to as m6A RNA modification (Qu et al., 2024; Shi et al., 2025). It is found in numerous non-coding RNAs and is the most prevalent internal alteration in eukaryotic mRNA (Qu et al., 2024; Shi et al., 2025). m6A is regarded as a key layer of epitranscriptomic regulation since it may quickly modify RNA activity without altering the nucleotide sequence (Qu et al., 2024; Shi et al., 2025).

Three classes of regulators, commonly referred to as writers, erasers, and readers, govern m6A (Qu et al., 2024; Shi et al., 2025). The primary writers of the methyl mark on RNA are the methyltransferase complex, which is concentrated on METTL3, METTL14, and related proteins including WTAP (Qu et al., 2024; Shi et al., 2025). The primary erasers, FTO and ALKBH5, eliminate the alteration, demonstrating the dynamic and reversible nature of m6A (Qu et al., 2024; Shi et al., 2025). The YTH domain family, IGF2BP proteins, and other proteins that bind m6A-marked RNA and decide what happens to that transcript next are the readers (Qu et al., 2024; Shi et al., 2025).

Functionally, m6A influences a number of important facets of RNA metabolism (Shen et al., 2025; Shi et al., 2025). RNA splicing, nuclear export, translation efficiency, localization, and degradation can all be affected by m6A, depending on the transcript and the reader that binds it (Shen et al., 2025; Shi et al., 2025). In certain situations, m6A accelerates RNA degradation; in other situations, it improves translation or transcript stability (Shen et al., 2025; Shi et al., 2025). m6A aids cells in regulating gene expression throughout development, stress reactions, and illness due to these context-dependent effects (Shen et al., 2025; Shi et al., 2025).

When the expression, mutation status, location, or activity of its regulators are changed in cancer, m6A becomes dysregulated (Shen et al., 2025; Shi et al., 2025). Writers, erasers, and readers may exhibit aberrant overexpression or downregulation in tumors, altering the methylation landscape across extensive sets of RNAs (Shen et al., 2025; Shi et al., 2025). This does not result in the same outcome for every cancer; in some cases, malignancy is driven by increased m6A, whereas in others, loss of m6A control is the issue (Shen et al., 2025; Shi et al., 2025). Which oncogenic or tumor-suppressive transcripts are impacted in that particular tumor type is most important (Shen et al., 2025; Shi et al., 2025).

This imbalance has wide-ranging physiologic effects (Mu et al., 2024; Shen et al., 2025). In addition to supporting invasion and metastasis, aberrant m6A signaling can aid cancer cells in avoiding apoptosis, increase cell proliferation, and increase resistance to treatment (Mu et al., 2024; Shen et al., 2025). Because m6A can stabilize oncogenic RNAs or decrease the expression of tumor suppressor pathways, many studies now associate changed m6A regulator expression with aggressive tumor behavior and poor prognosis (Mu et al., 2024; Shen et al., 2025).

Additionally, m6A interacts with important cancer signaling pathways (Mu et al., 2024; Shen et al., 2025). It has been demonstrated that m6A-regulated transcripts affect pathways like PI3K/AKT, MAPK, Wnt/β-catenin, NF-κB, and other growth and survival programs in a variety of tumor types (Mu et al., 2024; Shen et al., 2025). Mechanistically, m6A can alter the translation or abundance of important signaling elements, enabling tumors to rewire networks related to proliferation, metabolism, EMT, and stress response (Mu et al., 2024; Shen et al., 2025).

The involvement of m6A in the tumor microenvironment and tumor-immune interactions is a particularly significant topic of recent research (Mu et al., 2024; Pan et al., 2023). T-cell responses, immune-cell differentiation, antigen presentation, cytokine signaling, and macrophage

polarization are all regulated by m6A (Mu et al., 2024; Pan et al., 2023). For instance, altered METTL3-dependent m6A signaling in macrophages and myeloid cells might change the immunological milieu in ways that promote tumor growth, metastasis, and reduced immunotherapy responses (Mu et al., 2024; Pan et al., 2023). More generally, immune evasion and the control of checkpoint-related pathways in malignancies have been associated with m6A (Mu et al., 2024; Pan et al., 2023).

Because it links chromatin regulation to m6A deposition, SETD2 is crucial in this situation (Shaikh et al., 2025; Wu et al., 2025). H3K36 trimethylation (H3K36me3) is caused by the histone methyltransferase SETD2 (Shaikh et al., 2025). Because METTL14 binds H3K36me3-marked chromatin and aids in recruiting the methyltransferase machinery to nascent RNA, foundational work shown that H3K36me3 helps direct m6A deposition co-transcriptionally (Shaikh et al., 2025) . Loss or mutation of SETD2 can interfere with proper m6A patterning since it is a significant source of H3K36me3 (Shaikh et al., 2025; Wu et al., 2025). This is important for cancer because, in addition to its known chromatin effects, SETD2 is often changed in a variety of malignancies, and its malfunction may contribute to aberrant epitranscriptomic control (Shaikh et al., 2025; Wu et al., 2025).

Ultimately, m6A is a key regulator of RNA metabolism, oncogenic signaling, and tumor immunity, it is generally significant in cancer research (Pan et al., 2023; Qu et al., 2024; Shen et al., 2025). Its regulators are being investigated more and more as potential therapeutic targets, including in conjunction with immunotherapy or targeted therapy, biomarkers, and reasons for variations in tumor behavior (Pan et al., 2023; Qu et al., 2024; Shen et al., 2025). m6A has emerged as one of the most significant epitranscriptomic processes for comprehending how

tumors develop, disseminate, and react to therapy, even if the field is still figuring out context-specific effects in various cancers (Pan et al., 2023; Qu et al., 2024; Shen et al., 2025).

Dysregulation of M6A in cancer

The source of most m6A dysregulation comes from mistaken expressions of the methyltransferase complex (METTL3), an important enzyme involved in RNA modification that performs the methylation. This is the most abundant messenger of internal modification found in eukaryotic mRNA (Yuan et. al, 2025). The incorrect expression of METTL3 can contribute to tumor progression, metastasis, and resistance to chemotherapy and targeted therapies, but this can largely depend on the location of these malignant tumors and the pathways and environments it has targeted (Yuan et. al, 2025). In colorectal cancer, specifically, METTL3 is upregulated in cancer lines and tissues as well as positively correlated with poorer overall survival (Uddin et. al, 2021). The m6A erasers FTO and ALKBH5 are also prone to dysregulation in cancer, meaning that they can contribute to tumor development or progression. In cervical cancer, m6A levels correlate significantly with FIGO stage, tumor size, degree of differentiation, lymph invasion, and recurrence; The mRNA levels of methyltransferases METTL3 and Methyltransferase-like 14 (METTL14), an important protein-coding gene in m6A methyltransferases complex, were found reduced while the dimethylases FTO and ALKBH5 were increased in cancer tissue compared to paired adjacent non-cancerous tissue. (Wang et. al, 2017) In renal cell carcinoma (RCC), however, lower FTO expression is associated with poor survival rate of RCC patients. This shows how m6A dysregulation depends from patient to patient and the type of cancer that is impacted. m6A dysregulation in cancer not only occurs due to the cell's molecular machinery, but it can also be caused by environmental or infectious stimuli. Specifically, METTL3 and

METTL14 can be upregulated through enterovirus infections, which can cause impact m6A methylations. (Sebastian-delaCruz et. al, 2026)

Functional Consequences of m6A dysregulation

Across cancer types, the dysregulation of m6A is most usually coupled to the promotion of unchecked cellular proliferation. Differences in m6A methylation patterns throughout different cancer types has made m6A a potential biomarker, with different methylation levels correlating with tumor progression and clinical outcomes. In cervical cancer, suppressing both METTL3 and METTL14 promoted cancer proliferation. Additionally, overexpressing dimethylases FTO and ALKBH5, m6A "erasers," increased proliferative activities, showing that less m6A deposition can drive cellular proliferation (Wang et. al, 2017). M6A dysregulation can also contribute to the evasion of apoptosis. This was shown through reducing the expression of METTL3 and METTL14 to result in a reduced m6A modification of MDM2 RNA, which lessened the expression and stability of MDM2 and increased p53 expression levels, allowing of the restoration of apoptotic pressures on leukemia cells. (Shoemaker et. al, 2024).

Defects in the N6-methyladenosine (m6A) methylation RNA modification have been linked in the onset of various cancers, one of which has been shown to be clear cell renal carcinoma (ccRCC). Known to be the most prominent form of kidney cancer, affecting roughly 80% of cases, ccRCC arises when cells in the kidney tubules that typically appear clear or pale under a microscope transform to a cancerous state (National Cancer Institute, 2020). Studies have characterized this cancer by vascular tumors linked to chromosome 3p alterations and VHL gene inactivation. While both contribute to ccRCC pathogenesis, this paper will specifically focus on the chromosome 3p alterations to demonstrate how they intersect with m6A-mediated regulatory mechanisms.

One key regulator connecting chromatin state to m6A deposition is SETD2, a histone methyltransferase located on the 3p locus responsible for generating H3K36me3 marks during transcription elongation (Nezami & MacLennan, n.d.). These histone marks serve as signals that recruit the m6A "writer" complex (METTL3/METTL14) to newly formed RNA transcripts, enabling proper co-transcriptional methylation. Studies show that m6A modification is amplified in the event that H3K36me3 is peaked, typically during the S phase of DNA replication, and is reduced when H3K36me3 levels are depleted/lowered. In cancers such as ccRCC, loss or mutation of SETD2 disrupts H3K36me3 patterns, leading to altered m6A deposition across transcripts and, consequently, widespread changes in RNA processing and gene expression that promote oncogenic signalling and tumor progression (Kumari & Muthusamy, 2020). Since H3K36me3 is recognized and bound directly to METTL14, which is a big part of m6A methyltransferase complex (MTC). It is evidenced that in later stages of ccRCC, dysfunctional SETD2, results in reduced H3K36me3 levels which contributes to tumor progression (Chiang et al., 2018). As a result, this established SETD2 as a vital tumor suppressor chromatin remodeling gene associated with ccRCC.

This relationship highlights why m6A RNA modification is a powerful reference point for studying cancer. Unlike DNA mutations, which are relatively static, m6A modifications are dynamic and reversible (Zong et al., 2020), allowing them to rapidly fine-tune gene expression in response to cellular conditions. Through regulating mRNA stability, splicing, and translation, m6A directly influences key oncogenic pathways and cellular behaviors such as proliferation, differentiation, and immune evasion. Disruptions in m6A regulation, whether through altered expression of writers, erasers, readers, or upstream regulators like SETD2, can therefore reprogram cellular signaling networks in ways that promote tumor initiation and progression.

Importantly, because m6A sits at the intersection of transcriptional control and post-transcriptional regulation, it provides a systems-level view of how cancer cells adapt and survive. m6A modifications are also advantageous for tumor–immune interactions, as they regulate the stability and translation of transcripts related to immune signaling and immune checkpoint pathways (Ding et al., 2025). This regulation affects immune recognition and facilitates tumor immune evasion. Its dynamic nature and widespread impact on gene expression make it not only a useful biomarker for disease states but also a promising therapeutic target. Studying m6A and its regulators, such as SETD2, allows researchers to better understand how epitranscriptomic dysregulation contributes to cancer and opens new avenues for targeted interventions.

Discussion

Based on the findings in this research study, m6A methylation becomes dysregulated in cancer through irregular expression of regulators like protein writers METTL3 and METTL14 and protein erasers like FTO and ALKBH5. In several cancers, like colorectal cancer, the irregular expression of METTL3 is positively associated with tumor progression, metastasis, and poorer survival. However, m6A dysregulation does not affect all cancer types equally. For example, in cervical cancer, METTL3 and METTL14 that add the m6A RNA modification were found in lower levels while FTO and ALKBH5 that remove m6A RNA modifiers were found at higher levels, implying that lower m6A modification can still be associated with the support of cancer progression. Additionally, m6A dysregulation affects how certain chancers behave. As shown in multiple research studies, the change of m6A patterns showed increased cell proliferation, tumor progression, and apoptosis resistance.

These findings suggest that m6A methylation's impact on cancer development can be largely context-dependent. Different regulators can have different effects depending on what cancer is involved in the individual's body. Because of m6A's impact and variation in levels depending on what cancer is involved in the individual, it has presented itself as a potential biomarker with different methylation levels correlating with tumor progression and clinical outcomes.

In the same vein, upstream epigenetic regulation helps explain this context dependence. The relationship between SETD2 loss and altered m6A deposition in ccRCC illustrates how chromatin state can directly influence RNA methylation patterns during early tumor development. SETD2, a histone methyltransferase located on chromosome 3p, generates H3K36me3 marks that help recruit the m6A writer complex (METTL3/METTL14) during transcription. SETD2 loss, a chromatin (histone) modification defect, directly disrupts this

process and reshapes m6A patterns on RNA processing and gene expression, positioning it as a driver of cancer initiation rather than a downstream consequence. This connection is important because it shows that early chromatin alterations, such as loss of SETD2, can initiate cascading changes in m6A RNA methylation that reprogram gene expression during the earliest stages of tumor development.

Future studies should focus on the role of m6A regulations in different cancers. As shown in our studies, since METTL3, METTL14, FTO, and ALKBH5 can have different effects dependent on the cancer type, there should be greater study on each regulator and its impact on certain cancers to better understand m6A methylation levels as a potential biomarker for cancer. Through this research, we may be able to better understand which m6A changes are true-cancer driving factors. This may also help us develop personalized therapies for targeting m6A dysregulation in different types of cancer.

Adenosine to Inosine

Background

A-to-I RNA editing is a post-transcriptional modification in which adenosine (A) residues in RNA are converted into inosine (I). This process is catalyzed by enzymes in the adenosine deaminase acting on the RNA family, primarily ADAR1 and ADAR2 (Nishikura, 2010). These enzymes bind to double-stranded RNA (dsRNA) regions and deaminate adenosine, changing its chemical structure into inosine. Because cellular machinery interprets inosine as guanosine (G), this modification effectively results in an A-to-G substitution at the RNA level without altering the underlying DNA sequence. ADAR1 plays a particularly important role in both RNA editing and innate immune regulation. It is highly active in long dsRNA structures, many of which are formed by repetitive elements such as Alu sequences that are abundant in the human genome. ADAR1 prevents the immune system from mistakenly recognizing endogenous dsRNA as viral RNA. It does this by editing these dsRNA regions, thereby disrupting perfect base pairing and reducing activation of cytosolic RNA sensors such as MDA5 (Liddicoat & Hartner, 2015). Without ADAR1, cells can trigger inappropriate interferon responses, highlighting its critical role in maintaining immune homeostasis (Eisenberg & Levanon, 2018).

A-to-I editing occurs in several regions of RNA transcripts. In coding regions, editing can lead to amino acid substitutions, directly altering protein sequence and function. In untranslated regions (UTRs), editing can influence RNA stability, localization, and translation efficiency. Editing is also highly prevalent in intronic regions and Alu repetitive elements, where it contributes to the regulation of RNA structure and processing. These edits often occur within double-stranded RNA structures formed by complementary sequences (Nishikura, 2010; Eisenberg & Levanon, 2018).

Functionally, A-to-I editing can impact RNA behavior in multiple ways. It can change codons and therefore protein structure, alter splice sites and influence alternative splicing, modify RNA secondary structure, which affects stability, and regulate translation efficiency. Through these mechanisms, RNA editing serves as a dynamic layer of gene regulation that expands transcriptomic and proteomic diversity beyond what is encoded in the genome (Nishikura, 2010).

Dysregulation of ADAR1 in Cancer

In cancer, the tightly regulated process of A-to-I RNA editing becomes disrupted, most often through the overexpression and hyperactivation of ADAR1. Numerous studies have shown that ADAR1 is upregulated across a wide range of cancers, including lung cancer, hepatocellular carcinoma, breast cancer, and various leukemias (Chan et al., 2014). This overexpression leads to a global increase in RNA editing levels, which can be detected through RNA sequencing analyses.

Large-scale datasets such as those generated by The Cancer Genome Atlas (TCGA) have revealed that A-to-I editing is not randomly altered in tumors but instead follows consistent, cancer-specific patterns (Han et al., 2015). Pan-cancer analyses demonstrate that tumors often exhibit increased editing at specific sites, suggesting that RNA editing contributes to oncogenic processes rather than being a passive byproduct of cellular dysregulation. In many cases, ADAR1 gene amplification or increased transcription is linked to oncogenic signaling pathways, further reinforcing its role in tumor biology (Paz-Yaacov et al., 2015).

One critical aspect of ADAR1 dysregulation is its interaction with the immune system. By editing endogenous dsRNA, ADAR1 suppresses activation of innate immune pathways that would otherwise detect abnormal RNA structures. In cancer cells, elevated ADAR1 activity

helps tumors evade immune surveillance by preventing activation of interferon responses (Liddicoat & Hartner, 2015). This creates a more permissive environment for tumor growth and survival.

Additionally, increased editing activity can reshape the transcriptome in ways that favor cancer progression (Paz-Yaacov et al., 2015). Altered editing patterns can lead to the production of protein variants that enhance proliferation, resist apoptosis, or promote metastasis. The consistency of these editing changes across tumor types supports the idea that A-to-I RNA editing is systematically rewired in cancer and plays an active role in disease development (Han et al., 2015).

A-to-I Editing of Oncogenes and Tumor-Suppressor Transcripts

Beyond global changes in editing levels, A-to-I RNA editing has been shown to directly modify specific transcripts that are critical for cancer development. One of the most well-studied examples is the editing of AZIN1 (antizyme inhibitor 1). In this case, ADAR1-mediated editing results in a serine-to-glycine substitution that alters the protein's conformation and increases its stability. The edited form of AZIN1 has enhanced activity in promoting cell proliferation and is strongly associated with liver cancer progression (Chen et al., 2013).

Another important target is GLI1, a transcription factor in the Hedgehog signaling pathway. Editing of GLI1 can alter its transcriptional activity, leading to increased expression of genes involved in cell growth and survival. This modification enhances oncogenic signaling and contributes to tumor development (Han et al., 2015).

BLCAP (bladder cancer-associated protein) is another transcript affected by A-to-I editing. Editing of BLCAP has been linked to reduced tumor-suppressive function, allowing cancer cells to evade growth inhibition. Similarly, NEIL1, a DNA repair enzyme, undergoes

editing that changes its substrate specificity. The edited form of NEIL1 may impair normal DNA repair processes, contributing to genomic instability, which is a hallmark of cancer (Han et al., 2015).

These examples illustrate how RNA editing can produce functionally distinct protein isoforms with direct consequences for tumor biology. Edited transcripts can promote proliferation by enhancing growth signaling pathways, support survival by preventing apoptosis, and facilitate invasion by altering cellular behavior and interactions with the surrounding environment. Together, these mechanistic links demonstrate that A-to-I RNA editing is not only correlated with cancer but actively drives tumorigenic processes through precise molecular changes in key genes.

Discussion

The findings of this study demonstrate that A-to-I RNA editing, particularly mediated by ADAR1, functions as a critical regulatory mechanism in early cancer development. Across multiple cancer types, ADAR1 is consistently overexpressed, leading to increased global RNA editing activity and reproducible, site-specific editing patterns. These patterns indicate that RNA editing is not a random byproduct of cellular dysfunction, but rather a systematically altered process that contributes to tumorigenesis. Additionally, editing events in key transcripts such as AZIN1, GLI1, BLCAP, and NEIL1 show that single-nucleotide changes at the RNA level can significantly alter protein function, promoting proliferation, survival, and genomic instability. Together, these findings establish A-to-I RNA editing as an active driver of cancer rather than a secondary consequence of DNA mutations.

The significance of these findings lies in their expansion of the traditional understanding of cancer biology. While cancer has historically been viewed as a disease driven primarily by genetic mutations, this study highlights the importance of post-transcriptional regulation as an additional and critical layer of control. A-to-I RNA editing introduces functional diversity without altering the genome, allowing cancer cells to rapidly adapt and modify gene expression. Furthermore, the role of ADAR1 in suppressing innate immune responses underscores its importance in maintaining tumor survival. By editing endogenous double-stranded RNA, ADAR1 prevents activation of immune pathways that would otherwise target cancer cells. This positions RNA editing at the intersection of gene regulation and immune evasion, two fundamental processes in cancer progression.

The dysregulation of ADAR1 and A-to-I RNA editing presents several promising opportunities for clinical application. One major implication is the potential to target ADAR1 as

a therapeutic strategy. Inhibiting ADAR1 activity could restore immune recognition of tumor cells by allowing endogenous double-stranded RNA to activate interferon signaling pathways, thereby enhancing the effectiveness of immunotherapies such as immune checkpoint inhibitors. In addition, specific RNA editing events, such as those observed in AZIN1, could serve as biomarkers for cancer diagnosis, prognosis, or treatment response. Incorporating RNA editing profiles into precision medicine approaches may allow clinicians to better stratify patients and tailor therapies based on the molecular characteristics of their tumors. However, given ADAR1's essential role in normal immune regulation, therapeutic strategies will need to be carefully designed to minimize unintended immune-related side effects.

Future research should focus on further elucidating the role of A-to-I RNA editing in cancer and developing strategies to translate these findings into clinical practice. A key priority is the identification of functionally relevant editing sites across different cancer types to distinguish driver events from background editing. Advances in RNA sequencing and computational analysis will be essential for achieving this goal. Additionally, the development of targeted RNA-editing technologies, such as engineered ADAR systems or CRISPR-based tools, may enable precise manipulation of pathogenic editing events. Further investigation into the interaction between RNA editing and the tumor microenvironment, particularly immune cells, will also be critical for understanding how editing contributes to cancer progression in vivo. Ultimately, these efforts could lead to the development of novel therapeutic approaches that target RNA-level regulation as a means of combating cancer.

Conclusion

This paper examined how two of the most common RNA modifications, m6A methylation and A-to-I editing, contribute to early cancer development. Across the studies we reviewed, both modifications appear to actively drive cancer rather than serve as side effects of it. Because they change how RNA behaves without altering the DNA itself, they give cancer cells a fast way to rewire gene expression, which helps them grow, avoid apoptosis, and resist treatment.

The findings on m6A show that its role in cancer depends heavily on context. The same regulator can push cancer in opposite directions depending on the tissue type. For example, METTL3 overexpression is associated with worse survival in colorectal cancer, but in cervical cancer the pattern is reversed. Lower METTL3 and METTL14 paired with higher FTO and ALKBH5 is what promotes cancer growth. SETD2 adds another layer to this by linking chromatin regulation to m6A. It produces H3K36me3, which helps recruit METTL14 to RNA as it is being transcribed. When SETD2 is mutated, as it often is in clear cell renal cell carcinoma, m6A patterns shift in ways that contribute to tumor progression. This connection also helps explain why m6A behaves so differently across cancer types.

The findings on A-to-I editing show a more consistent pattern. ADAR1 is overexpressed in most of the cancers we reviewed, and its editing activity changes transcripts like AZIN1, GLI1, BLCAP, and NEIL1 in ways that alter protein function. These edits can promote tumor growth, enhance survival, and disrupt DNA repair. ADAR1 also helps cancer cells evade the immune system. By editing endogenous double-stranded RNA, it prevents sensors like MDA5 from recognizing that RNA as foreign and triggering an interferon response. Because ADAR1

plays both of these roles at once, it is a strong therapeutic target, since blocking it could weaken the tumor while also restoring immune detection.

This review has a few limitations. Much of the existing literature focuses on tumors that have already developed, which makes it difficult to tell which RNA changes initiate cancer versus which ones appear later during progression. Many studies also report editing or methylation broadly across the transcriptome rather than focusing on specific sites, which can obscure which changes actually matter. The variety of cancer types and methodologies across the included studies also makes direct comparison difficult, even within a PRISMA-based framework.

Future research should focus on early-stage or pre-cancerous samples, ideally using matched healthy tissue and untreated patients. Tools like single-cell RNA sequencing and CRISPR-based RNA editing could help separate the edits that actually drive cancer from background modifications. Clinically, both m6A regulators and ADAR1 show promise as biomarkers and therapeutic targets, especially when paired with immunotherapy. Recognizing RNA modifications as active drivers of cancer rather than passive markers expands how we understand the disease and opens up new options for diagnosis and treatment that DNA-focused approaches alone cannot offer.

References

Chan, T. H. M., Qamra, A., Tan, K. T., Guo, J., Yang, H., Qi, L., … Ng, I. O. L. (2014). ADAR-mediated RNA editing predicts progression and prognosis of hepatocellular carcinoma. *Gastroenterology, 146*(2), 556–567. https://www.gastrojournal.org/article/S0016-5085(13)01517-5/fulltext

Chen, L., Li, Y., Lin, C. H., Chan, T. H. M., Chow, R. K. K., Song, Y., … Ng, I. O. L. (2013). Recoding RNA editing of AZIN1 predisposes to hepatocellular carcinoma. *Nature Medicine, 19*(2), 209–216. https://www.nature.com/articles/nm.3043

Chiang, Y. C., Park, I. Y., Terzo, E. A., Tripathi, D. N., Mason, F. M., Fahey, C. C., Karki, M., Shuster, C. B., Sohn, B. H., Chowdhury, P., Powell, R. T., Ohi, R., Tsai, Y.-H., de Cubas, A. A., Khan, A., Davis, I. J., Strahl, B. D., Parker, J. S., Dere, R., & Walker, C. L. (2018). SETD2 haploinsufficiency for microtubule methylation is an early driver of genomic instability in renal cell carcinoma. *Cancer Research, 78*(12), 3135–3146. https://doi.org/10.1158/0008-5472.CAN-17-3460

Ding, Y. P., Liu, C. C., & Yu, K. D. (2025). RNA modifications in the tumor microenvironment: insights into the cancer-immunity cycle and beyond. Experimental hematology & oncology, 14(1), 48. https://doi.org/10.1186/s40164-025-00648-1

Eisenberg, E., & Levanon, E. Y. (2018). A-to-I RNA editing—Immune protector and transcriptome diversifier. *Nature Reviews Genetics, 19*(8), 473–490. https://www.nature.com/articles/s41576-018-0006-1

Han, L., Diao, L., Yu, S., Xu, X., Li, J., Zhang, R., … Liang, H. (2015). The genomic landscape and clinical relevance of A-to-I RNA editing in human cancers. *Cancer Cell, 28*(4), 515–528. linkinghub.elsevier.com/retrieve/pii/S1535610815003049

Kumari, S., & Muthusamy, S. (2020). SETD2 as a regulator of N6-methyladenosine RNA methylation and modifiers in cancer. *European Journal of Cancer Prevention, 29*(6), 556–564. https://doi.org/10.1097/CEJ.0000000000000587

Liddicoat, B. J., & Hartner, J. C. (2015). ADAR1 and innate immunity. *Current Topics in Microbiology and Immunology, 391*, 163–178. https://link.springer.com/chapter/10.1007/82_2015_442

Mu, S., Li, Y., Zhang, X., et al. (2024). The role of m6A methylation in tumor immunity and cancer progression. *Biomolecules, 14*(8), 1042. https://www.mdpi.com/2218-273X/14/8/1042

National Cancer Institute. (2020). *Clear cell renal cell carcinoma*. U.S. Department of Health and Human Services. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-kidney-tumors/clear-cell-renal-cell-carcinoma

Nezami, B. G., & MacLennan, G. T. (n.d.). *Clear cell renal cell carcinoma*. PathologyOutlines.com. https://www.pathologyoutlines.com/topic/kidneytumormalignantrccclear.html

Nishikura, K. (2010). Functions and regulation of RNA editing by ADAR deaminases. *Annual Review of Biochemistry, 79*, 321–349. https://www.annualreviews.org/content/journals/10.1146/annurev-biochem-060208-105251

Pan, J., Zhang, Y., Wang, Z., et al. (2023). Roles and therapeutic implications of m6A modification in tumor immune evasion. *Frontiers in Immunology, 14*, 1132601. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1132601/f

ull

Paz-Yaacov, N., Bazak, L., Buchumenski, I., Porath, H. T., Danan-Gotthold, M., Knisbacher, B. A., … Levanon, E. Y. (2015). Elevated RNA editing activity is a major contributor to transcriptomic diversity in tumors. *Cell Reports, 13*(2), 267–276. linkinghub.elsevier.com/retrieve/pii/S2211124715009936

Qu, Y., Zhao, Y., Wang, H., et al. (2024). Role of N6-methyladenosine RNA modification in cancer. *Cell Death Discovery, 10*, 415. https://www.nature.com/articles/s41420-024-02266-y

Sebastian-delaCruz, Maialen, Ane Olazagoitia-Garmendia, Izei Pascual-Gonzalez, Luis Manuel Mendoza, Maria Legarda, Carlos Tutau, Luis Bujanda, et al. "m6A RNA Methylation Modulates Antiviral Response in Celiac Disease." *Genes and Immunity* 27, no. 1 (January 10, 2026): 130–39. https://doi.org/10.1038/s41435-025-00373-z.

Shaikh, S., et al. (2025). Deciphering the interplay between SETD2-mediated H3K36me3 and RNA N6-methyladenosine in clear cell renal cell carcinoma. *Epigenetics, 20*(1). https://www.tandfonline.com/doi/full/10.1080/15592294.2025.2456418

Shen, R., Jiang, Z., Wang, H., Zheng, Z., & Jiang, X. (2025). Molecular mechanisms of m6A modifications regulating tumor progression and radiosensitivity. *Molecular Medicine, 31*, 64. https://link.springer.com/article/10.1186/s10020-025-01121-9

Shi, T., Zhang, H., & Chen, Y. (2025). The m6A revolution: Transforming tumor immunity and enhancing immunotherapy outcomes. *Cell & Bioscience, 15*(1), 27. https://pubmed.ncbi.nlm.nih.gov/39987091/

Shoemaker, R., Huang, M.-F., Wu, Y.-S., Huang, C.-S., & Lee, D.-F. (2024). Decoding the molecular symphony: interactions between the m6A and p53 signaling pathways in cancer. NAR Cancer, 6(3), zcae037. https://doi.org/10.1093/narcan/zcae037

Tabnak, Peyman, Yaser Ghasemi, Mohammad Natami, Roya Khorram, and Mohammad Ebrahimnezhad. "Role of m6A Modification in Dysregulation of Wnt/B-catenin Pathway in Cancer." *Biomedicine & Pharmacotherapy* 157 (November 17, 2022): 114023. https://doi.org/10.1016/j.biopha.2022.114023.

Uddin, Mohammad Burhan, Zhishan Wang, and Chengfeng Yang. "The m6A RNA Methylation Regulates Oncogenic Signaling Pathways Driving Cell Malignant Transformation and Carcinogenesis." *Molecular Cancer* 20, no. 1 (April 4, 2021): 61. https://doi.org/10.1186/s12943-021-01356-0.

Wang, Xiuli, Zenghui Li, Beihua Kong, Chen Song, Jianglin Cong, Jianqing Hou, and Shaoguang Wang. "Reduced m6A mRNA Methylation Is Correlated With the Progression of Human Cervical Cancer." *Oncotarget* 8, no. 58 (October 24, 2017): 98918–30. https://doi.org/10.18632/oncotarget.22041.

Wei, Yuyao, Yang Wu, Chun Zhang, Mengling Yuan, Yuqi Sun, Mengran Li, Zili Zhang, and Mei Guo. "The m6A Modification in Cancer: Roles, Implications, and Its Potential in Therapy." *Molecular Biomedicine* 6, no. 1 (September 23, 2025): 67. https://doi.org/10.1186/s43556-025-00314-2.

Wu, P.-F., Yuan, H., & Chen, Q. (2025). Editorial: m6A methylation and cancer immunity. *Frontiers in Immunology, 16*, 1726760. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2025.1726760/full

Yuan, Fang, Wenjuan Zhang, Yuxuan Xia, Xiangqin Zhou, and Huihui Gao. “The Role and Mechanism of METTL3 in Cancer: Emerging Insights Into m6A Methylation and Therapeutic Potential.” *European Journal of Medical Research* 30, no. 1 (October 27, 2025): 1017. https://doi.org/10.1186/s40001-025-03351-3.

Zong, L., Mo, S., Yu, S., Zhou, Y., Zhang, M., Chen, J., & Xiang, Y. (2020). Expression of the immune checkpoint VISTA in breast cancer. *International Journal of Clinical Oncology, 25*(5), 820–830. https://doi.org/10.1007/s10147-020-01629-2