RNA Modifications in Cancer: Functions, Mechanisms, and Therapeutic Implications

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Abstract
Over 170 chemical modifications have been identified in protein-coding and noncoding RNAs and shown to exhibit broad impacts on gene expression. Dysregulation of RNA modifications caused by aberrant expression of or mutations in RNA modifiers aberrantly reprograms the epitranscriptome and skews global gene expression, which in turn leads to tumorigenesis and drug resistance. Here we review current knowledge of the functions and underlying mechanisms of aberrant RNA modifications in human cancers, particularly several common RNA modifications, including N⁶-methyladenosine (m⁶A), A-to-I editing, pseudouridine (ψ), 5-methylcytosine (m⁵C), 5-hydroxymethylcytosine (hm⁵C), N⁰-methyladenosine (m¹A), and N⁴-acetylcytidine (ac⁴C), providing insights into therapeutic implications of targeting RNA modifications and the associated machineries for cancer therapy.
1. INTRODUCTION

The research on RNA modifications began in the 1950s with the discovery of pseudouridine (ψ, also known as the fifth RNA nucleotide) (Davis & Allen 1957). So far, over 170 types of modified nucleotides have been identified from three kingdoms of life, expanding the diversity of RNA (Boccaletto et al. 2018, Frye et al. 2018, Xuan et al. 2018). However, the study on RNA modifications was limited in past decades owing to the lack of high-throughput techniques for RNA modification mapping and the misconception that RNA modifications are static and likely not functionally important. This field was revived by the discovery of FTO as the first RNA demethylase (Jia et al. 2011), which suggests that RNA modification is reversible, dynamic, and thereby very likely functionally essential. Since 2012, numerous next-generation sequencing (NGS) methods have been developed for the transcriptome-wide detection of widespread and conserved RNA modifications in messenger RNAs (mRNAs), including N^6-methyladenosine (m^6A) (Dominissini et al. 2012, Linder et al. 2015, Meyer et al. 2012), N^6,2′-O-dimethyladenosine (m^6Am^0) (Linder et al. 2015), 5-methylcytosine (m^5C) (Hussain et al. 2013, Khoddami & Cairns 2013, Squires et al. 2012), 5-hydroxymethylcytosine (hm^5C) (Delatte et al. 2016), N^4-methyladenosine (m^4A) (Dominissini et al. 2016, Li et al. 2016), inosine (Suzuki et al. 2015), N^4-acetylcytidine (ac4C) (Arango et al. 2018), and ψ (Carlile et al. 2014, Schwartz et al. 2014a) (Figure 1). Such profiling studies showed that RNA modifications could be cell context specific and dynamically fine-tuned during physiological processes, while many modifications sites are evolutionarily conserved. Thus far, accumulating evidences indicate that RNA modifications play important roles in virtually all normal bioprocesses and tissue development as well as in disease progression. Exploration of the links between RNA modifications and human cancer in the hope of developing effective epigenetic therapies represents one of the new frontiers in cancer research.

2. ABERRANT M^6A MODIFICATIONS IN HUMAN CANCERS

As the most pervasive internal modification on mRNAs and long noncoding RNAs (lncRNAs) first identified in the 1970s (Desrosiers et al. 1974, Perry & Kelley 1974), m^6A represents one of the best studied RNA modifications. NGS methods, including MeRIP-seq (methylated RNA immunoprecipitation sequencing, also known as m^6A-seq) and the single-nucleotide-resolution miCLIP-seq (m^6A individual-nucleotide-resolution cross-linking and immunoprecipitation sequencing), have been widely used for transcriptome-wide m^6A mapping, which characterized 10,000–30,000 m^6A modification sites/peaks in the transcripts of more than 7,000 human or mouse genes. Such transcriptome-wide profiling enables the identification of the DRACH (D = G, A, or U; R = G or A; H = A, C, or U) consensus sequence of m^6A modification and reveals the enrichment of these modifications in the coding region [or coding sequence (CDS)] and 3′ untranslated region (3′UTR), particularly around stop codons (Dominissini et al. 2012, Meyer et al. 2012). It is now known that m^6A methylation is mainly catalyzed by the methyltransferase complex (MTC, also known as writers) in which METTL3 is the catalytic unit while METTL14 is essential for stabilizing the complex, binding RNA substrates, and deciding the methylation site (H. Huang et al. 2019, Liu et al. 2014, Sledz & Jinek 2016, P. Wang et al. 2016, X. Wang et al. 2016). Additional regulatory components of MTC, including WTAP and its cofactors KIAA1429, ZC3H13, and RBM15/RBM15B, contribute to anchoring MTC in nucleus speckles and U-rich regions adjacent to m^6A sites in mRNAs (Knuckles et al. 2018, Patil et al. 2016, Ping et al. 2014, Schwartz et al. 2014b, Wen et al. 2018, Yue et al. 2018). It is also reported that METTL16 alone could catalyze m^6A in U6 small nuclear RNA (snRNA) and U6-like hairpins in MAT2A mRNA (Pendleton et al. 2017). The methyl group can be selectively removed from m^6A-modified RNAs by demethylases (also known as erasers) FTO and ALKBH5 (Jia et al. 2011, Zheng et al. 2013), which enables the
Figure 1

Existence, regulation, and detection of common chemical modifications found across eukaryotic mRNA transcripts. The chemical structures are shown on top, and the reported writers, erasers, and readers, as well as the NGS methods for mapping the epitranscriptome, are summarized below the corresponding modifications. Abbreviations: ac4C, N⁴-acetylcytidine; hm⁵C, 5-hydroxymethylcytosine; I, inosine; m⁶A, N⁶-methyladenosine; m⁵C, 5-methylcytosine; m⁶A, N⁶-methyladenosine; m⁶Am, N⁶, 2′-O-dimethyladenosine; m⁷G, 7-methylguanosine; mRNA, messenger RNA; NGS, next-generation sequencing; ψ, pseudouridine.

The reversible regulation of m⁶A under certain physiological or pathological conditions. The impacts of m⁶A on mRNA fate determination are broad and rely on the existence of specific m⁶A-binding proteins (also known as m⁶A readers). Members of the YT521-B homology (YTH) domain family of proteins, including YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2, are among the earliest-identified m⁶A readers, which exhibit different functions in mediating mRNA splicing (by YTHDC1), decay (by YTHDF2, YTHDF3, and YTHDC2), translation (by YTHDF1, YTHDF3, and YTHDC2), or modulating RNA structures (by YTHDC2) (Hsu et al. 2017; A. Li et al. 2017; Shi et al. 2017; Wang et al. 2014, 2015; Wojtas et al. 2017; Xiao et al. 2016). In contrast to the function of YTH family proteins in mRNA decay, a recently identified family of m⁶A-binding proteins, including IGF2BP1 (IGF2 mRNA-binding protein 1), IGF2BP2, and IGF2BP3, protects m⁶A-modified transcripts from degradation and facilitates their translation (Huang et al. 2018). hnRNPC and hnRNPA2B1 were considered as comprising another type of m⁶A readers that bind to unfolded RNA via an m⁶A structural switch mechanism, in which the presence of m⁶A reduces the ability of RNA to form secondary structures due to the weaker base pairing of
Aberrant m^6_A RNA modifications in human cancers. Aberrant m^6_A methylations caused by overexpression (red) or downregulation (blue) of m^6_A modifiers in different types of human cancers exert various functions in cancer development and progression. Although the influence seems to be transcriptome wide, the regulation of critical m^6_A-containing transcripts (italics) with oncogenic or tumor-suppressive functions plays a major role in tumorigenesis. Abbreviations: AML, acute myeloid leukemia; CSC, cancer stem cell; EMT, epithelial-mesenchymal transition; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; LSC, leukemia stem cell.

m^6_A-U than of A-U, thus allowing for greater access of these RNA-binding proteins to RNA (Alarcon et al. 2015, Liu et al. 2015, Wu et al. 2018). Additionally, m^6_A modification of mRNA promotes cap-dependent or -independent translation through METTL3-eIF3 or eIF3a (Choe et al. 2018, Lin et al. 2016, Meyer et al. 2015). Numerous data have shown that m^6_A modification in mRNAs or IncRNAs plays important roles in virtually all normal bioprocesses (see the review by Roundtree et al. 2017). More recently, evidence is emerging that aberrant deposition, removal, and recognition of m^6_A modification are closely associated with diverse human cancers (Figure 2).

2.1. Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a common hematopoietic malignancy in adults and children characterized by abnormal accumulation of immature blast cells in the bone marrow and peripheral blood, owing to the gain of stem cell–like renewal capacity and the blockage of normal differentiation (Thomas & Majeti 2017). More than 70% of AML patients cannot survive over five years...
with contemporary treatment. Tightly controlled m^6A modification is important for hematopoietic homeostasis (Vu et al. 2017, Weng et al. 2018, C. Zhang et al. 2017), and dysregulation of m^6A by aberrant expression of either demethylase or methyltransferase can lead to differentiation blockage and leukemogenesis (see the review by Deng et al. 2018a). The first link between m^6A modification and leukemia pathogenesis came from the study of FTO. We found that FTO was highly expressed in certain subtypes of AML, including those carrying t(11q23)/MLL rearrangements, t(15;17)/PML-RARA, FLT3-ITD (internal tandem duplication), or NPM1 mutations and played an oncogenic role in these AML subtypes as an m^6A demethylase by posttranscriptionally regulating expression of important transcripts such as ASB2 and RARA (Z. Li et al. 2017).

Subsequently, FTO was identified as a direct target of R-2-hydroxyglutarate (R-2HG) and mediated the intrinsic and broad antileukemia activity of R-2HG through an FTO/m^6A/MYC-CEBPA axis, which further demonstrated the critical oncogenic role of FTO in leukemia (Su et al. 2018).

Meanwhile, the association of the m^6A installing machinery with leukemia was also established. METTL3 and METTL14, two major components of m^6A MTC, are important for the self-renewal of hematopoietic stem cells (HSCs). Depletion of METTL3 or METTL14 in human cord blood CD34^+ hematopoietic stem/progenitor cells promoted myeloid differentiation (Vu et al. 2017, Weng et al. 2018). Consistently, conditional deletion of Mettl3 or Mettl14 impaired HSC self-renewal activity in vitro and in mice (Weng et al. 2018, Yao et al. 2018). Given that abnormal myeloid differentiation is closely associated with AML, the general high expression of METTL3 and METTL14 in AML suggests their potential oncogenic function (Vu et al. 2017, Weng et al. 2018). Indeed, we found that METTL14 was critical for AML initiation and maintenance, as well as for the self-renewal of leukemia stem cells (LSCs) and drug response of AML cells, by regulating its important target transcripts such as MYB and MYC in an m^6A-dependent manner (Weng et al. 2018). The oncogenic role of METTL3 in AML was demonstrated by two groups independently. Vu et al. (2017) showed that METTL3 promoted cell growth and suppressed apoptosis and differentiation in vitro, as well as affected the survival of bone marrow–transplanted mice, by promoting translation of its RNA targets such as MYC, BCL-2, and PTEN. Barbieri et al. (2017) found that both METTL3 and METTL14 could bind to certain regions in chromatin, with around 120 peaks/binding sites identified for each protein. They further showed that METTL3 was recruited by CEBPZ to the transcriptional start sites of SPI and SP2 to introduce m^6A modifications to their coding regions; the resulting enhanced translation efficiency of SPI1 and SPI2 in turn led to enhanced MYC signaling and leukemia progression (Barbieri et al. 2017).

In addition to METTL3 and METTL14, other components of MTC such as WTAP, RBM15, and ZC3H13 have been implicated in leukemogenesis (Bansal et al. 2014, Duhoux et al. 2012, Ma et al. 2001). METTL16 was also potentially implicated in AML by a genome-wide screening (Barbieri et al. 2017). It is reasonable to speculate that roles of these proteins in leukemogenesis are possibly related to m^6A modification, for which further studies are warranted.

It is interesting that elevated expression of either an MTC component (e.g., METTL3 or METTL14) or a demethylase (e.g., FTO) contributes to the development of AML. They may regulate distinct cohorts of target genes with similar biological functions and thereby display oncogenic roles in the same cancer cell context; nonetheless, they may also target some shared genes (e.g., MYC) and cause similar biological consequences through different mechanisms (Deng et al. 2018b). Analogous to RNA m^6A modification, imbalance of DNA methylation caused by loss-of-function mutations of either DNMT3A, a DNA methyltransferase, or TET2, a DNA demethylase, is also associated with AML development and progression, highlighting the impact of epigenetic imbalance in the pathogenesis of leukemia (Deng et al. 2018a,b).
2.2. Glioblastoma

Glioblastoma (GBM) is the most aggressive cancer that occurs in the brain and spinal cord, with an average survival time of 12–18 months. The cause of GBM is largely unknown and thus results in a lack of prevention methods and satisfied treatment. Recently, several studies indicated that m^6A RNA methylation is important for tumorigenesis, maintenance of self-renewal, and therapy resistance in GBM. As a poor clinical outcome factor, ALKBH5 is highly expressed in patient-derived GBM cells and enriched at the GBM stem cell (GSC) niches of patient samples (S. Zhang et al. 2017). Silencing of ALKBH5 in GSC inhibited proliferation and tumorigenesis and induced astrocytic or neuronal commitment by impairing self-renewal. FOXM1 mRNA was identified as a direct target of ALKBH5 and became unstable upon m^6A removal, while FOXM1-AS facilitates the interaction between ALKBH5 and FOXM1 precursor mRNA. Similarly, FTO also displayed an oncogenic role in GMB (Cui et al. 2017, Su et al. 2018), and pharmacological inhibition of FTO by a chemical inhibitor, MA2, suppressed tumor progression in GSC-grafted mice (Cui et al. 2017).

Cui et al. (2017) also found that METTL3 and METTL14 function as tumor suppressors in GBM by regulating m^6A modification and the mRNA level of target genes (e.g., ADAM19). In contrast, Visvanathan et al. (2018) reported that METTL3 was upregulated in GBM and played a critical oncogenic role by positively regulating the stability and expression of SOX2. The different roles of METTL3 reported in GBM could be owing to the distinct cell types used and the genetic heterogeneity in GBM. Other m^6A regulators such as WTAP and IGF2 mRNA-binding proteins (IGF2BPs) are highly expressed in GBM and play a role during GBM development and progression (Bell et al. 2013, Jin et al. 2012).

2.3. Lung Cancer

Lung cancer, also known as lung carcinoma, is the leading cause of cancer-related death worldwide. The expression of METTL3 is significantly increased in lung adenocarcinoma and colon adenocarcinoma compared to normal tissues (Lin et al. 2016). Consistently, the level of METTL3 was also elevated in a panel of lung adenocarcinoma cancer cell lines and correlates with tumor stages in primary lung adenocarcinoma samples (Choe et al. 2018, Lin et al. 2016). Surprisingly, although circulating tumor cells from lung cancer patients were characterized with a higher level of RNA m^6A modification (Huang et al. 2016), recent studies have suggested that the oncogenic role of METTL3 is independent of its catalytic activity but rather relies on its translation-promoting ability (Choe et al. 2018, Lin et al. 2016). In these studies, METTL3 recognized m^6A-modified mRNA and enhanced mRNA translation by recruiting eIF3 to the translation-initiation machinery. A follow-up study showed that circularization of mRNA was mediated by interaction between the eIF3h subunit at the 5’ cap of the mRNA and METTL3 at the 3’ UTR near the stop codon, and that hundreds of genes, enriched for oncogenes associated with tumor progression and apoptosis (e.g., EGFR, TAZ, MAPK2, DNMT3A, and BRD4), were regulated by METTL3-mediated translation control (Choe et al. 2018). As a result, METTL3 plays an oncogenic role in promoting lung cancer cell growth, survival, invasion, and transformation.

Besides METTL3, FTO also functions as an oncogene in lung cancer. High FTO expression was significantly associated with poor prognosis in 488 lung squamous cell carcinoma patients in a TCGA (The Cancer Genome Atlas) cohort (Liu et al. 2018b). Modulation of FTO expression affected cell proliferation, apoptosis, and invasion by regulating MZF1 in an m^6A-dependent manner.

In addition, IGF2BP1, IGF2BP2, and IGF2BP3 were found to be highly expressed and acted as oncogenes in lung cancer, especially in non-small-cell lung cancer (NSCLC), likely through their
interactions with KRAS, TP53, and EIF4E-BP2 mRNAs and LIN28B-AS1 lncRNA (Bell et al. 2013). However, whether these interactions are regulated by m⁶A modification remains unclear.

2.4. Hepatocellular Carcinoma

The most common type of primary liver cancer, hepatocellular carcinoma (HCC), occurs predominantly in patients with chronic liver diseases, such as cirrhosis caused by hepatitis B or C virus infection. Aberrant expression and function of m⁶A regulators were observed in the development and progression of HCC. Ma et al. (2017) found that m⁶A levels of poly(A) RNAs were decreased in HCC tissues largely due to downregulation of METTL14, which was associated with metastasis and prognosis in HCC; METTL14-dependent m⁶A methylation modulated the processing of primary miR126 to produce mature miR126 with a metastasis-suppressive function. In contrast, METTL3 was shown to be significantly upregulated in HCC and associated with poor prognosis, and it played a critical oncogenic role in HCC by negatively regulating expression of SOCS2 through a YTHDF2-dependent mechanism (Chen et al. 2018).

Nonetheless, controversial functions have been reported in HCC for YTHDF2 itself. Zhong et al. (2019) reported that YTHDF2 was specifically inhibited by the hypoxia environment of HCC, and its forced expression suppressed cell proliferation and tumor growth by destabilizing EGFR mRNA. In contrast, Z. Yang et al. (2017) found that the expression of YTHDF2 was negatively regulated by miR145 in HCC, in which YTHDF2 plays an oncogenic role. Similarly, YTHDF1 was significantly upregulated in HCC and positively correlated with pathological stages and poor survival in HCC patients (Zhao et al. 2018).

IGF2BPs are highly expressed in HCC cells and patient samples, are positively correlated with prognosis, and play oncogenic roles in HCC (Gutschner et al. 2014, Huang et al. 2018). Although it was not realized in early studies that IGF2BPs recognize most of their target mRNAs in an m⁶A-dependent manner, the transcripts of some well-known oncogenes (e.g., MYC and Ki67) had been identified as canonical targets of IGF2BPs (Gutschner et al. 2014). We recently identified IGF2BPs as m⁶A readers and showed that they could recognize and bind to the coding region instability determinant of MYC mRNA in an m⁶A-dependent manner, leading to the increased expression of MYC (Huang et al. 2018). SRF (serum response factor) is another well-studied functional target of IGF2BP1 in HCC (Muller et al. 2019).

2.5. Breast Cancer

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among women. Exposure of breast cancer cells to hypoxia, a critical feature of the tumor microenvironment, induced m⁶A hypomethylation and increased stabilization of NANOG and KLF4 mRNAs, which led to the enhanced breast cancer stem cell phenotype (Zhang et al. 2016a); at the same time, the deposition of m⁶A on mRNAs was suppressed by ZNF217 (Zhang et al. 2016b), which interacted with METTL3 and abrogated METTL3-mediated m⁶A methylation (Aguilo et al. 2015). The expression of both ALKBH5 and ZNF217 was induced by HIF-1α or HIF-2α under hypoxia (Zhang et al. 2016a,b). Another study showed that ALKBH5 and METTL14 constituted a positive feedback loop with RNA stability factor HuR to regulate the stability of key epithelial-mesenchymal transition (EMT) and angiogenesis-associated transcripts in breast cancer cells (Panneerdoss et al. 2018).

As obesity is strongly associated with higher incidence and worse disease outcome of breast cancer, the upregulation or single-nucleotide polymorphisms of FTO, a genetic factor of obesity, were frequently found in breast cancer patients (Kaklamani et al. 2011, Tan et al. 2015). It was
also reported that FTO influences the energy metabolism of breast cancer via the PI3K/AKT signaling pathway (Liu et al. 2017); however, whether this is related to its demethylase activity has yet to be investigated.

### 2.6. Other Cancers

Endometrial cancer and cervical cancer are two common gynecologic cancers in which aberrant m^6^A modification also plays a role. It has been reported that 70% of endometrial tumors exhibit a reduction in m^6^A methylation, probably due to the R298P mutation of METTL14 or reduced expression of METTL3 (Liu et al. 2018a). Arg 298 in METTL14 is critical for RNA substrate recognition of the MTC (P. Wang et al. 2016, X. Wang et al. 2016) and is frequently mutated in endometrial tumors (Kandoth et al. 2013). Reduced m^6^A methylation promoted proliferation and tumorigenicity of endometrial cancer cells through activation of the AKT pathway by controlling the expression of two key AKT regulators, PHLPP2 and mTORC2 (Liu et al. 2018a). In cervical squamous cell carcinoma (CSCC), the mRNA level of FTO was more elevated in tumor tissues than in adjacent normal tissues, and FTO enhances the resistance of CSCC to chemo-radiotherapy via demethylation of the β-catenin mRNA (Zhou et al. 2018). IGF2BP were also shown by our group to play oncogenic roles in cervical cancer cells by stabilizing MYC mRNA (Huang et al. 2018).

Bladder cancer (BCa) is the fourth-most common malignancy in men, for which most cases are diagnosed in advanced stages and cannot get curative surgery or satisfied chemotherapy. METTL3 was significantly upregulated in human BCa and promoted BCa cell proliferation, invasion, and survival in vitro and tumorigenicity in vivo, likely by regulating the expression of AFF4, IKBKB, RELA, MYC, and CDCP1 in an m^6^A-dependent manner (Cheng et al. 2019, Yang et al. 2019).

As one of the most aggressive types of cancer, pancreatic cancer develops with local invasiveness or metastases to distant sites in its early stages. ALKBH5 was downregulated in pancreatic cancer cells and mediated the m^6^A demethylation and downregulation of an lncRNA, KCNK15-AS1; their forced expression could inhibit cell migration and invasion by affecting EMT (He et al. 2018).

Overall, the m^6^A machinery is deregulated in various human cancers and functions as either oncogenes or tumor suppressors, suggesting a widespread interaction between m^6^A modification and human cancers. Nonetheless, in many reports, a direct link has yet to be fully established between these oncogenic or tumor-suppressive functions and the changes of m^6^A modification, especially in critical cancer-associated transcripts.

### 3. ABERRANT A-TO-I EDITING IN HUMAN CANCERS

RNA editing of adenosine into inosine (A-to-I) by the family of adenosine deaminases acting on RNA (ADARs) (Figure 1) is a common posttranscriptional gene regulatory mechanism for both coding and noncoding RNAs that contributes to RNA and protein diversity by affecting Watson-Crick and wobble base pairing. ADAR1 induces malignant reprogramming of myeloid progenitors and LSC self-renewal in chronic myeloid leukemia by regulating the expression of hematopoietic transcription factor PU.1 and GATA1 (Jiang et al. 2013). In contrast, a global hypoediting by ADAR1 downregulation has been observed in solid tumors (Paz et al. 2007), reflecting the complicated roles of ADAR1 in different types of cancers.

Inosine, which is usually interpreted as guanosine and sometimes as adenosine or uracil, could induce context-dependent recoding and translation stalling when present in the codon (Licht et al. 2019). Editing-caused protein recoding could introduce missense mutations in proto-oncogenes.
In liver cancer, A-to-I editing of *AZIN* was more frequently found in HCC tissues than in normal liver tissues, leading to a serine-to-glycine substitution at residue 367 and a cytoplasm-to-nuclear translocation of *AZIN* (Chen et al. 2013). Edited *AZIN* augments its tumor-initiating potential by increasing its affinity to antizyme and reducing antizyme-mediated degradation of ornithine-decarboxylase and cyclin D1 (Chen et al. 2013). In pancreatic, esophageal, and colon cancers, RNA editing of *PROX1* caused tumor-associated missense mutations including E328G, R334G, and H536R (Takahashi et al. 2006). RNA editing–mediated N136S amino acid substitution of RHOQ increases RHOQ activity and the invasion potential of colorectal cancer (Han et al. 2014). In familial esophageal squamous cell carcinoma (ESCC), A-to-I RNA editing–mediated downregulation of SLC22A3 is almost exclusively present in cancer tissues and may serve as a potential biomarker for familial ESCC patients (Fu et al. 2017).

In contrast, recoding RNA editing can also make a negative contribution via suppression of tumorigenesis and metastasis. For instance, an A-to-I-edited form of GABRA3 could only be detected in noninvasive breast cancers and suppressed breast cancer cell invasion and metastasis via inhibition of the AKT signaling pathway (Gumireddy et al. 2016). ADAR2-mediated Q/R site editing of *GluR-B* is essential for the normal development of mice but is markedly reduced in malignant gliomas (Maas et al. 2001).

As inosine is converted to guanosine by reverse transcription, comparison of deep sequencing results generated from cDNA with the corresponding genomic sequence enables mapping of A-to-I editing sites throughout the transcriptome. The first transcriptome-wide RNA editing analysis in cancer identified a significant reduction of A-to-I editing of Alu repetitive elements in brain, prostate, lung, kidney, and testis tumors, which was linked to the reduced expression of ADAR1 or ADAR2 (Paz et al. 2007). Later on, a transcriptome-wide landscape of A-to-I RNA editing was revealed by systematic analysis of 6,236 patient samples in 17 cancer types from TCGA (Han et al. 2015). Although the editing levels at most sites remained similar, the RNA editing pattern was diverse across cancer types: Overediting patterns were observed in head and neck squamous cell carcinoma, breast cancer, thyroid carcinoma, and lung adenocarcinoma tumors, while underediting patterns were common in kidney chromophobe and kidney renal papillary cell carcinoma tumors (Han et al. 2015). More recently, an integrated study of TCGA genomic data and CPTAC (Clinical Proteomic Tumor Analysis Consortium) proteomic data showed that A-to-I editing events are manifested at proteomic levels and are a source of cancer protein heterogeneity (Peng et al. 2018). Interestingly, in addition to affecting the coding function of mRNA, RNA editing occurring in 3′ UTR regions perturbed microRNA (miRNA)-mediated regulation of oncogenes and tumor suppressors (L. Zhang et al. 2016).

A-to-I editing also occurs in noncoding RNAs, such as miRNAs. When editing takes place in primary transcript miRNA (pri-miRNA) or precursor miRNA (pre-miRNA), especially at the recognition or cleavage sites of processing enzymes, the biogenesis of miRNA could be affected (Yang et al. 2006). RNA editing of pri-miR455 and pre-miR222/221 impaired the biogenesis of miR455 and miR222/221, respectively, the wild-type forms of which promoted cell growth and metastasis in melanoma and GBM (Shoshan et al. 2015, Tomaselli et al. 2015). ADAR1-mediated miRNA editing could also regulate let-7 biogenesis and enhance self-renewal of LSCs, which could be antagonized by a small inhibitor of ADAR1, 8-AZA (Zipeto et al. 2016). If the editing takes place in the mature miRNA, especially at the seed region of position 2–8, the interaction between miRNA and the 3′ UTR of target mRNAs could be disrupted and therefore relieve miRNA-mediated inhibition. Such editing events impaired the inhibition of *PAP2A* mRNA by mir376a, of *CPEB1* by miR-455–5p, and of *ZEB1/ZEB2* by mir200b in different cancers (Choudhury et al. 2012, Shoshan et al. 2015, Wang et al. 2017). A systematic analysis characterized numerous A-to-I RNA editing events in miRNAs across 20 cancer types, with 15 editing hotspots (Wang et al. 2017).
Together, these results indicate that dysregulation of A-to-I RNA editing on either mRNAs or miRNAs could make a notable contribution to the malignant phenotype.

4. ABERRANT PSEUDOURIDINE MODIFICATIONS IN HUMAN CANCERS

As the first discovered and a pervasive modified nucleotide, \( \Psi \) was identified as the so-called fifth RNA nucleotide (Figure 1). The presence of \( \Psi \) was first reported in ribosomal RNA (rRNA) and transfer RNA (tRNA) (Davis & Allen 1957) and subsequently in snRNAs (Reddy et al. 1972). More recently, a series of NGS methods, including Pseudo-seq, \( \Psi \)-seq, PSI-seq, and CeU-seq, have been developed and identified a tremendous amount of \( \Psi \) modifications in most classes of coding and noncoding RNAs from yeast to human, including rRNAs, tRNAs, snRNAs, small nucleolar RNAs (snoRNAs), small Cajal body–specific RNAs, miRNAs, mitochondrial RNAs, lncRNAs, and mRNAs (Carlile et al. 2014, Li et al. 2015, Lovejoy et al. 2014, Schwartz et al. 2014a).

\( \Psi \) is derived from the C-N to C-C glycosidic isomerization of uridine, which brings an extra hydrogen bond donor at its non-Watson-Crick edge and can therefore change RNA secondary structure, facilitate translation, or mediate recoding when present in RNAs (Karijolich et al. 2015). The incorporation of \( \Psi \) is catalyzed by either stand-alone \( \Psi \) synthases (PUS1–9) or snoRNA-guided \( \Psi \) synthases (Dyskerin/DKC1) (Figure 1). Although the conversion of U to \( \Psi \) is considered irreversible, cellular \( \Psi \) modification could be induced by stress (Wu et al. 2011).

It is believed that the urinary and plasma \( \Psi \) levels can reflect the physiological and pathological state of the organism. Indeed, \( \Psi \) level in urinary excretion is often higher in patients with leukemia or solid tumors (Gehrke et al. 1979, Nielsen et al. 1974, Weissman et al. 1963) and is eliminated after effective chemotherapy (Gehrke et al. 1979). The overproduction of \( \Psi \) could also be detected from the blood of mice or humans with malignant proliferative diseases. In inbred mice with high incidence of spontaneous lymphoma (AKR mice), \( \Psi \) in serum is significantly increased in the period preceding the development of lymphoma (Russo et al. 1984). Elevated \( \Psi \) could also be detected in the blood plasma of human patients with chronic lymphocytic leukemia, multiple myeloma, adenocarcinomas of the large intestine, and advanced-stage lung cancer (Motyl et al. 1993). With these findings, the evaluation of \( \Psi \) in biological fluids has been proposed as a potential tumor marker but has not yet been included in routine diagnostics (Penzo et al. 2017).

DKC1 binds to the box H/ACA snoRNAs and the RNA component of telomerase. Defects of DKC1 could cause the dysregulation of snoRNA and telomerase function, as well as related diseases. Dyskeratosis congenita (DC) is a rare progressive congenital disorder with increased tumor susceptibility caused by mutations of DKC1. DKC1-mediated \( \Psi \) sites in rRNA are important for rRNA and mRNA binding; therefore, the reduction in rRNA \( \Psi \) modification could result in inefficient translation of tumor suppressors, such as BCL-XL, XIAP, p27, and p53 (Bellodi et al. 2010, Yoon et al. 2006). In contrast to the defects of DKC1 and \( \Psi \) modification in DC patients, the expression of DCK1 and \( \Psi \) levels was frequently elevated in human cancers, such as breast and prostate cancers, and correlated with tumor progression and poor prognosis (Montanaro et al. 2006, Sieron et al. 2009). Notably, DCK1 is a direct and conserved transcriptional target of c-MYC (Alawi & Lee 2007). Nevertheless, the underlying mechanisms of DCK1 overexpression in cancers have yet to be elucidated.

Box H/ACA snoRNAs are associated with DKC1 and core proteins NOP10, NHP2, and GAR1 to guide \( \Psi \) modification at specific sites on rRNA and target molecules. Recent studies have indicated that the expression of a subset of H/ACA snoRNAs is altered in human cancers, particularly in hematological malignancies, such as leukemia, lymphoma, and multiple myeloma (Gong...
et al. 2017; Ronchetti et al. 2012; Valleron et al. 2012a,b). For instance, SNORA31, SNORA6, SNORA62, and SNORA71C are downregulated in chronic lymphocytic leukemia (Ronchetti et al. 2013). Noticeably, although most of the H/ACA snoRNAs appear to be decreased in diseases, high expression of SNORA42 was found in NSCLC and colorectal cancer and correlated with poor survival (Mei et al. 2012, Okugawa et al. 2017).

5. OTHER RNA MODIFICATIONS AND HUMAN CANCERS

Two of the best-studied epigenetic marks on DNA, m$^5$C and hm$^5$C, have been identified in RNA as well (Figure 1). m$^5$C was detected in rRNA and tRNA and recently was found to be prevalent in mRNA by multiple NGS methods, including biosulfite-seq, MeRIP-seq, miCLIP-seq, and Azaseq. In HeLa and mouse cells, m$^5$C modifications were found to be enriched in 5′ and 3′UTRs in a GC-rich context, particularly around the translational start codon (Amort et al. 2017, Squires et al. 2012, X.Yanget al. 2017). Methylated cytosine could recruit nuclear factor ALYREF and facilitate the exportation of m$^5$C-modified mRNA (X.Yanget al. 2017). An elevated RNA m$^5$C level could be detected in the circulating tumor cells from lung cancer patients compared to whole blood cells (Huang et al. 2016). There are some links between the RNA cytosine methyltransferases NSUN and DNMT2 and tumorigenesis; however their exact roles remain not fully understood. NSUN2 (also known as Misu) was first found as a direct target of MYC that mediated MYC-induced proliferation and was upregulated in benign and malignant skin tumors (Frye & Watt 2006). Knockdown of NSUN2 inhibits growth of human squamous cell carcinoma xenografts in nude mice. NSUN2 was also overexpressed in ovarian cancer and breast cancer and was associated with tumor prognosis and metastasis (J.C.Yanget al. 2017, Yi et al. 2017). With variable expression in human cancer cell lines, the association between DNMT2 and human cancers remains unknown (Schafer et al. 2009). Treatment of human cancer cells with methylation inhibitor azacytidine could specifically inhibit RNA methylation at DNMT2 target sites, but not at the target sites of other RNA methyltransferases, linking the drug effect of azacytidine to DNMT2-regulated RNA metabolism (Schafer et al. 2009).

m$^1$A involves the methylation of adenosine at the N1 site (Figure 1), which for decades was thought to mainly occur in noncoding RNAs but now has been identified in thousands of mRNA transcripts (Dominissini et al. 2016). In human and mouse transcriptomes, m$^1$A is enriched around the start codon upstream of the first splice site and correlates positively with protein production. m$^1$A is a dynamic modification in response to physiological conditions (i.e., glucose or amino acid starvation, heat shock, or serum starvation) with a well-identified demethylase, ALKBH3. As a clinical marker of prostate cancer, ALKBH3 showed oncogenic roles in many human cancers, including prostate cancer, renal cell carcinoma, NSCLC, breast cancer, and HCC (Chen et al. 2019, Hotta et al. 2015, Konishi et al. 2005, Tasaki et al. 2011). Recent research has revealed that the mRNA stability of CSF-1 was regulated by ALKBH3-induced m$^1$A demethylation in the 5′UTR of CSF-1, which contributed to the invasion of breast and ovarian cancers, providing the first link between the oncogenic function of ALKBH3 and m$^1$A demethylation of mRNA (Woo & Chambers 2019). However, the global function of m$^1$A and its regulation during tumorigenesis are currently unknown.

Most recently, the profiling of ac4C was pinpointed in the human transcriptome, leading to the finding that ac4C is widely distributed in the transcriptome with a majority of sites occurring within the CDS of mRNAs (Arango et al. 2018). Acetylation of cytidine in wobble sites promotes translation efficiency. As the only known RNA acetyltransferase, NAT10 catalyzes ac4C in a broad range of mRNAs (Figure 1) (Arango et al. 2018). The expression of NAT10 is enhanced in several cancers, such as HCC, colon cancer, and lung cancer (Xu et al. 2012, Zhang et al. 2015). Notably,
RNA epigenetic markers, including the abundance of RNA modifications (e.g., m^6^A, m^5^C, and ψ) in cell-free RNA and the expression or mutation of their regulators, are useful diagnostic or prognostic markers for cancer screening and could also be used to predict drug response for therapy selection. Small inhibitors of FTO showed potent inhibitory effects in leukemia and GBM, shedding light on the promising prospects of epigenetic therapies targeting oncogenic RNA-modification writers, erasers, or readers in different cancer types. RNA epigenetic therapies could also synergize with chemotherapy or immune therapy. Abbreviations: HCC, hepatocellular carcinoma; GBM, glioblastoma; m^5^C, 5-methylcytosine; m^6^A, N^6^-methyladenosine; MA, meclofenamic acid; R-2HG, R-2-hydroxyglutarate; TKI, tyrosine kinase inhibitor; ψ, pseudouridine.

while NAT10 mainly localizes in the nucleus in normal tissues, it is aberrantly exported from the nucleus to the cytoplasm or membrane in HCC and colorectal cancer (Tan et al. 2018, Zhang et al. 2014). The potential oncogenic function of NAT10 in cancers suggests that RNA acetylation may also play a role in tumorigenesis.

6. INSIGHT OF CANCER DIAGNOSIS AND THERAPEUTICS

6.1. Epigenetic Markers for Diagnosis and Prognosis

Specific genetic and epigenetic alterations could be detected in plasma, serum, and urine cell–free DNA and RNA as valuable biomarkers for noninvasive diagnosis for human diseases. Epigenetic markers are innovative and effective cancer screening tools because of their stability, frequency, reversibility, and accessibility. For instance, m^5^C and hm^5^C in cell-free DNA could serve as parallel biomarkers for human cancers (W. Li et al. 2017, Song et al. 2017). As described above, the level of certain RNA modification (e.g., m^6^A, m^5^C, and ψ) is also accessible in biological fluids (e.g., blood and urine) and displayed a specific elevating pattern in certain types of cancers, which makes them promising diagnostic biomarkers for human cancers (Figure 3) (Gehrke et al. 1979, Huang et al. 2016, Motyl et al. 1993, Nielsen et al. 1974, Weissman et al. 1963).

Furthermore, it has been indicated that RNA modifications are associated with drug response and chemoresistance. Both 5-AZA-resistant leukemia cell lines and primary specimens have a significant increase in RNA m^5^C methylation and NSUN1-/BRD4-associated active chromatin, suggesting a link between RNA m^5^C and drug resistance (Cheng et al. 2018). An association has also been found between tyrosine kinase inhibitor (TKI) resistance and m^6^A modification. Leukemia cells with hypomethylation of m^6^A demonstrated more TKI tolerance and growth
advantage owing to enhanced mRNA stability and protein production of proliferation-and-survival-related transcripts (Yan et al. 2018). These findings suggest that RNA modification signatures may serve as predictive markers for personalized leukemia treatment.

6.2. Epigenetic Therapy

Unlike genetic changes, epigenetic modifications are reversible, making them druggable for targeted therapies (Figure 3). Since the discovery of FTO as an m^6^A RNA demethylase (Jia et al. 2011), efforts have been made to identify selective small-molecule inhibitors targeting the enzymatic activity of FTO. FTO belongs to the family of Fe^2+^- and 2-oxoglutarate-dependent AlkB dioxygenases, whose demethylase activity largely relies on the presence of Fe^2+^ and 2-oxoglutarate. Natural compounds with structures similar to 2-oxoglutarate, such as Rhein, were identified as the competitive inhibitor of FTO and could significantly inhibit the activity of FTO in vitro and inside cells (Chen et al. 2012). However, the lack of selectivity among members of the AlkB family limited its application in cancer therapy. Compared to Rhein, meclofenamic acid (MA), an FDA (US Food and Drug Administration)-approved nonsteroidal anti-inflammatory drug, exhibited better selectivity for FTO over ALKBH5 (Huang et al. 2015) and showed significant therapeutic efficacy in treating GSC-induced tumors in mice (Cui et al. 2017). Our group found that R-2HG, an analog of 2-oxoglutarate, exhibited broad antitumor effects in vitro and in vivo by targeting FTO (Su et al. 2018). Most recently, Y. Huang et al. (2019) developed a more effective FTO-specific inhibitor, FB23-2, on the basis of MA, which showed improved therapeutic efficacy over MA in treating AML.

Priming T cells against tumor neoantigens is crucial for spontaneous antitumor immune responses and the clinical efficacy of immunotherapies. However, the mechanisms by which tumors evade neoantigen recognition remain elusive. Very recently, Han et al. (2019) showed that durable neoantigen-specific immunity is regulated by mRNA m^6^A methylation through the m^6^A-binding protein YTHDF1. Ythdf1-deficient mouse dendritic cells augmented the cross-presentation of tumor antigens and the priming of CD8+ T cells in vivo. These findings identified epigenetic regulators as key mediators of tumor immune evasion and potential therapeutic targets to synergize with the immune checkpoint blockade to drive a potent antitumor response (Figure 3).

7. SUMMARY AND FUTURE PERSPECTIVES

Evidence is emerging that RNA modifications play important oncogenic or tumor-suppressor roles in the initiation, progression, metastasis, or drug resistance of various types of cancers. However, we are just beginning to understand the functions and underlying molecular mechanisms of RNA modifications in cancers. There are numerous questions to be answered. For instance, why do some writer and eraser genes play similar functions in the same cancer types? How do different components of a given RNA modification machinery orchestrate the regulation of the epitranscriptome in cancers? Moreover, current knowledge of RNA modification is mainly restricted to a few of the most common modifications, while the vast majority of RNA modifications remain hard to detect and thus their functional study has been scarce. More advanced novel sequencing methodologies with high resolution, precision, and sensitivity will lead to rapid and sustainable developments in this field, which is important for fully understanding the roles of RNA modifications in cancers and identifying novel targets for cancer therapy. The development of effective and selective inhibitors targeting cancer-associated RNA modification machinery components holds great potential in cancer therapy. Such inhibitors can be applied alone or in combination with
chemotherapy, targeted therapy (e.g., TKIs), or immune therapy (e.g., anti-PD-1/PD-L1 agents), which may transform our treatments of various types of cancers.

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LITERATURE CITED
Aguilo F, Zhang F, Sancho A, Fidalgo M, Di Cecilia S, et al. 2015. Coordination of m^6A mRNA methylation and gene transcription by ZFP217 regulates pluripotency and reprogramming. *Cell Stem Cell* 17:689–704
Alarcon CR, Goodarzi H, Lee H, Liu X, Tavazoie S, Tavazoie SF. 2015. HNRNPA2B1 is a mediator of m^6A-dependent nuclear RNA processing events. *Cell* 162:1299–308
Alawi F, Lee MN. 2007. DKC1 is a direct and conserved transcriptional target of c-MYC. *Biochem. Biophys. Res. Commun.* 362:893–98
Amort T, Rieder D, Wille A, Khokhlova-Cubberley D, Riml C, et al. 2017. Distinct 5-methylcytosine profiles in poly(A) RNA from mouse embryonic stem cells and brain. *Genome Biol.* 18:1
Arango D, Sturgill D, Alhusaini N, Dillman AA, Sweet TJ, et al. 2018. Acetylation of cytidine in mRNA promotes translation efficiency. *Cell* 175:1872–86.e24
Bansal H, Yihua Q, Iyer SP, Ganapathy S, Proia DA, et al. 2014. WTAP is a novel oncogenic protein in acute myeloid leukemia. *Leukemia* 28:1171–74
Barbieri I, Tzelepis K, Pandolfi L, Shi J, Millan-Zambrano G, et al. 2017. Promoter-bound METTL3 maintains myeloid leukaemia by m^6A-dependent translation control. *Nature* 552:126–31
Bell JL, Wachter K, Muhleck B, Pazaitis N, Kohn M, et al. 2013. Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): post-transcriptional drivers of cancer progression? *Cell. Mol. Life Sci.* 70:2657–75
Bellodi C, Kopmar N, Ruggero D. 2010. Deregulation of oncogene-induced senescence and p53 translational control in X-linked dyskeratosis congenita. *EMBO J.* 29:1865–76
Boccaletto P, Machnicka MA, Purta E, Piatkowski P, Baginski B, et al. 2018. MDMOMICS: a database of RNA modification pathways. 2017 update. *Nucleic Acids Res.* 46: D303–7
Carlile TM, Rojas-Duran MF, Zinshteyn B, Shih H, Bartoli KM, Gilbert WV. 2014. Pseudouridine profiling reveals regulated mRNA pseudouridylation in yeast and human cells. *Nature* 515:143–46
Chen B, Ye F, Yu L, Jia G, Huang X, et al. 2012. Development of cell-active N^6-methyladenosine RNA demethylase FTO inhibitor. *J. Am. Chem. Soc.* 134:17963–71
Chen L, Li Y, Lin CH, Chan TH, Chow RK, et al. 2013. Recoding RNA editing of AZIN1 predisposes to hepatocellular carcinoma. *Nat. Med.* 19:209–16
Chen M, Wei L, Law CT, Tsang FH, Shen J, et al. 2018. RNA N^6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2. *Hepatology* 67:2254–70
Chen Z, Qi M, Shen B, Luo G, Wu Y, et al. 2019. Transfer RNA demethylase ALKBH3 promotes cancer progression via induction of rRNA-derived small RNAs. *Nucleic Acids Res.* 47:2533–45
Cheng JX, Chen L, Li Y, Cloe A, Yue M, et al. 2018. RNA cytosine methylation and methyltransferases mediate chromatin organization and 5-azacytidine response and resistance in leukaemia. *Nat. Commun.* 9:1163
Cheng M, Sheng L, Gao Q, Xiong Q, Zhang H, et al. 2019. The m^6^A methyltransferase METTL3 promotes bladder cancer progression via AFF4/NF-kB/MYC signaling network. *Oncogene* 38:3667–80

Choe J, Lin S, Zhang W, Liu Q, Wang L, et al. 2018. mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. *Nature* 561:55–60

Choudhury Y, Tay FC, Lam DH, Sandanaraj E, Tang C, et al. 2012. Attenuated adenosine-to-inosine editing of microRNA-376a^∗^ promotes invasiveness of glioblastoma cells. *J. Clin. Investig.* 122:4059–76

Cui Q, Shi H, Ye P, Li L, Qu Q, et al. 2017. m^6^A RNA methylation regulates the self-renewal and tumorigenesis of glioblastoma stem cells. *Cell Rep.* 18:2622–34

Davis FF, Allen FW. 1957. Ribonucleic acids from yeast which contain a fifth nucleotide. *J. Biol. Chem.* 227:907–15

Delatte B, Wang F, Ngoc LV, Collignon E, Bonvin E, et al. 2016. Transcriptome-wide distribution and function of RNA hydroxymethylcytosine. *Science* 351:282–85

Deng X, Su R, Feng X, Wei M, Chen J. 2018a. Role of N^6^-methyladenosine modification in cancer. *Curr. Opin. Genet. Dev.* 48:1–7

Deng X, Su R, Wang H, Huang H, Li Z, Chen J. 2018b. RNA N^6^-methyladenosine modification in cancers: current status and perspectives. *Cell Res.* 28:507–30

Dominissini D, Moshitch-Moshkovitz S, Schwartz S, Salmon-Divon M, Ungar L, et al. 2012. Topology of the human and mouse m^6^A RNA methyleomes revealed by m^6^A-seq. *Nature* 485:201–6

Dominissini D, Nachtergaele S, Moshitch-Moshkovitz S, Peer E, Kol N, et al. 2016. The dynamic N^4^-methyladenosine methyleome in eukaryotic messenger RNA. *Nature* 530:441–46

Duhoux FP, Ameye G, Lambert C, Herman M, Iossifidis S, et al. 2012. Novel head-to-head gene fusion of MLL with ZC3H13 in a JAK2 V617F-positive patient with essential thrombocythemia without blast cells. *Leuk. Res.* 36:e27–30

Frye M, Harada BT, Behm M, He C. 2018. RNA modifications modulate gene expression during development. *Science* 361:1346–49

Frye M, Watt FM. 2006. The RNA methyltransferase Misu (NSun2) mediates Myc-induced proliferation and is upregulated in tumors. *Curr. Biol.* 16:971–81

Fu L, Qin YR, Ming XY, Zuo XB, Diao YW, et al. 2017. RNA editing of SLC22A3 drives early tumor invasion and metastasis in familial esophageal cancer. *PNAS* 114:E4631–40

Gebhrke CW, Kuo KC, Waalkes TP, Borek E. 1979. Patterns of urinary excretion of modified nucleosides. *Cancer Res.* 39:1150–53

Gong J, Li Y, Liu CQ, Xiang Y, Li C, et al. 2017. A pan-cancer analysis of the expression and clinical relevance of small nucleolar RNAs in human cancer. *Cell Rep.* 21:1968–81

Gumireddy K, Li A, Kossenkov AV, Sakurai M, Yan J, et al. 2016. The mRNA-edited form of GABRA3 suppresses GABRA3-mediated Akt activation and breast cancer metastasis. *Nat. Commun.* 7:10715

Gutschner T, Hammerle M, Pazaitis N, Bley N, Fiskin E, et al. 2014. Insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) is an important protumorigenic factor in hepatocellular carcinoma. *Hepatology* 59:1900–11

Han D, Liu J, Chen C, Dong L, Liu Y, et al. 2019. Anti-tumour immunity controlled through mRNA m^6^A methylation and YTHDF1 in dendritic cells. *Nature* 566:270–74

Han L, Diao L, Yu S, Xu X, Li J, et al. 2015. The genomic landscape and clinical relevance of A-to-I RNA editing in human cancers. *Cancer Cell* 28:515–28

Han SW, Kim HP, Shin JY, Jeong EG, Lee WC, et al. 2014. RNA editing in *RHOQ* promotes invasion potential in colorectal cancer. *J. Exp. Med.* 211:613–21

He Y, Hu H, Wang Y, Yuan H, Lu Z, et al. 2018. ALKBH5 inhibits pancreatic cancer motility by decreasing long non-coding RNA KCNK15-A51 methylation. *Cell Physiol. Biochem.* 48:838–46

Hotta K, Sho M, Fujimoto K, Shimada K, Yamato I, et al. 2015. Clinical significance and therapeutic potential of prostate cancer antigen-1/ALKBH3 in human renal cell carcinoma. *Onco. Rep.* 34:648–54

Hsu PJ, Zhu Y, Ma H, Guo Y, Shi X, et al. 2017. Ythdc2 is an N^6^-methyladenosine binding protein that regulates mammalian spermatogenesis. *Cell Res.* 27:1115–27
Huang H, Weng H, Sun W, Qin X, Shi H, et al. 2018. Recognition of RNA N6-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. Nat. Cell Biol. 20:285–95

Huang H, Weng H, Zhou K, Wu T, Zhao BS, et al. 2019. Histone H3 trimethylation at lysine 36 guides m^6A RNA modification co-transcriptionally. Nature 567:414–19

Huang W, Qi CB, Lv SW, Xie M, Feng YQ, et al. 2016. Determination of DNA and RNA methylation in circulating tumor cells by mass spectrometry. Anal. Chem. 88:1378–84

Huang Y, Su R, Sheng Y, Dong L, Dong Z, et al. 2019. Small-molecule targeting of oncogenic FTO demethylase in acute myeloid leukemia. Cancer Cell 35:677–91.e10

Huang Y, Yan J, Li Q, Li J, Gong S, et al. 2015. Meflofenamic acid selectively inhibits FTO demethylation of m^6A over ALKBH5. Nucleic Acids Res. 43:373–84

Hussain S, Sajini AA, Blanco S, Dietmann S, Lombard P, et al. 2013. NSun2-mediated cytosine-5 methylation of vault noncoding RNA determines its processing into regulatory small RNAs. Cell Rep. 4:255–61

Jia G, Fu Y, Zhao X, Dai Q, Zheng G, et al. 2011. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat. Chem. Biol. 7:885–87

Jiang Q, Crews LA, Barrett CL, Chun HJ, Court AC, et al. 2013. ADAR1 promotes malignant progenitor reprogramming in chronic myeloid leukemia. Proc. Natl. Acad. Sci. 110:1041–46

Jin DI, Lee SW, Han ME, Kim HJ, Seo SA, et al. 2012. Expression and roles of Wilms' tumor 1-associating protein in glioblastoma. Cancer Sci. 103:2102–9

Kaklamani V, Yi N, Siziopekou K, Zhang K, et al. 2011. The role of the fat mass and obesity associated gene (FTO) in breast cancer risk. BMC Med. Genet. 12:52

Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. 2013. Integrated genomic characterization of endometrial carcinoma. Nature 497:67–73

Karijolich J, Yi C, Yu YT. 2015. Transcriptome-wide dynamics of RNA pseudouridylation. Nat. Rev. Mol. Cell Biol. 16:581–85

Khoddami V, Cairns BR. 2013. Identification of direct targets and modified bases of RNA cytosine methyltransferases. Nat. Biotechnol. 31:458–64

Knuckles P, Lence T, Haussmann IU, Jacob D, Kreim N, et al. 2018. Zc3h13/Flacc is required for adenosine methylation by bridging the mRNA-binding factor Rbm15/Spenito to the m^6A machinery component Wtap/Fl(2)d. Genes Dev. 32:415–29

Kasamichi N, Nakamura M, Ishida E, Shimada K, Mitsui E, et al. 2005. High expression of a new marker PCA-1 in human prostate carcinoma. Clin. Cancer Res. 11:5090–97

Li A, Chen YS, Ping XL, Yang X, Xiao W, et al. 2017. Cytoplasmic m^6A reader YTHDF3 promotes mRNA translation. Cell Res. 27:444–47

Li W, Zhang X, Lu X, You L, Song Y, et al. 2017. 5-hydroxymethylcytosine signatures in circulating cell-free DNA as diagnostic biomarkers for human cancers. Cell Res. 27:1243–57

Li X, Xiong X, Wang K, Wang L, Shu X, et al. 2016. Transcriptome-wide mapping reveals reversible and dynamic N6-methyladenosine methylome. Nat. Chem. Biol. 12:311–16

Li X, Zhu P, Ma S, Song J, Bai J, et al. 2015. Chemical pulldown reveals dynamic pseudouridylation of the mammalian transcriptome. Nat. Chem. Biol. 11:592–97

Li Z, Weng H, Su R, Weng X, Zuo Z, et al. 2017. FTO plays an oncogenic role in acute myeloid leukemia as a N^6-methyladenosine RNA demethylase. Cancer Cell 31:127–41

Licht K, Hartl M, Amman F, Anrather D, Janiszew MP, Jantsch MF. 2019. Inosine induces context-dependent recoding and translational stalling. Nucleic Acids Res. 47:3–14

Lin S, Choe J, Du P, Triboulet R, Gregory RI. 2016. The m^6A methyltransferase METTL3 promotes translation in human cancer cells. Mol. Cell 62:335–45

Linder B, Grozhik AV, Olarerin-George AO, Meydan C, Mason CE, Jaffrey SR. 2015. Single-nucleotide-resolution mapping of m^6A and m^6Am throughout the transcriptome. Nat. Methods 12:767–72

Liu J, Eckert MA, Harada BT, Liu SM, Lu Z, et al. 2018a. m^6A mRNA methylation regulates AKT activity to promote the proliferation and tumorigenicity of endometrial cancer. Nat. Cell Biol. 20:1074–83

Liu J, Ren D, Du Z, Wang H, Zhang H, Jin Y. 2018b. m^6A demethylase FTO facilitates tumor progression in lung squamous cell carcinoma by regulating MZF1 expression. Biochem. Biophys. Res. Commun. 502:456–64
Liu J, Yue Y, Han D, Wang X, Fu Y, et al. 2014. A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. Nat. Chem. Biol. 10:93–95
Liu N, Dai Q, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. 2017. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. Oncol. Lett. 13:4685–90
Lovejoy AF, Riordan DP, Brown PO. 2014. Transcriptome-wide mapping of pseudouridines: pseudouridine synthases modify specific mRNAs in S. cerevisiae. PLOS ONE 9:e110799
Ma JZ, Yang F, Zheng G, He C, Parisien M, Pan T. 2015. N6-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. Nature 518:560–64
Ronchetti D, Todoerti K, Tiana G, Agnelli L, Mosca L, et al. 2012. The expression pattern of small nucleolar and small Cajal body–specific RNAs characterizes distinct molecular subtypes of multiple myeloma. Blood Cancer J. 2:e296

Roundtree IA, Evans ME, Pan T, He C. 2017. Dynamic RNA modifications in gene expression regulation. Cell 169:1187–200

Russo T, Colonna A, Salvatore F, Cimino F, Bridges S, Gurgio C. 1984. Serum pseudouridine as a biochemical marker in the development of AKR mouse lymphoma. Cancer Res. 44:2567–70

Schaefer M, Hagemann S, Hanna K, Lyko F. 2009. Azacytidine inhibits RNA methylation at DNMT2 target sites in human cancer cell lines. Cancer Res. 69:8127–32

Schwartz S, Bernstein DA, Mumbach MR, Jovanovic M, Herbst RH, et al. 2014a. Transcriptome-wide mapping reveals widespread dynamic-pseudouridylation of ncRNA and mRNA. Cell 159:148–62

Schwartz S, Mumbach MR, Jovanovic M, Wang T, Maciag K, et al. 2014b. Perturbation of m6A writers reveals two distinct classes of mRNA methylation at internal and 5’ sites. Cell Rep. 8:284–96

Shi H, Wang X, Lu Z, Zhao BS, Ma H, et al. 2017. YTHDF3 facilitates translation and decay of N6-methyladenosine-modified RNA. Cell Res. 27:315–28

Shoshan E, Mobley AK, Braeuer RR, Kamiya T, Huang L, et al. 2015. Reduced adenosine-to-inosine miR-455-5p editing promotes melanoma growth and metastasis. Nat. Cell Biol. 17:311–21

Sieron P, Hader C, Hatina J, Engers R, Wlazlinski A, et al. 2009. DKC1 overexpression associated with prostate cancer progression. Br. J. Cancer 101:1410–16

Sledz P, Jinek M. 2016. Structural insights into the molecular mechanism of the m6A writer complex. eLife 5:e18434

Song CX, Yin S, Ma L, Wheeler A, Chen Y, et al. 2017. 5-Hydroxymethylcytosine signatures in cell-free DNA provide information about tumor types and stages. Cell Res. 27:1231–42

Squires JE, Patel HR, Nousch M, Sibbritt T, Humphreys DT, et al. 2012. Widespread occurrence of 5-methylcytosine in human coding and non-coding RNA. Nucleic Acids Res. 40:5023–33

Su R, Dong L, Li C, Nachtergaele S, Wunderlich M, et al. 2018. R-2HG exhibits anti-tumor activity by targeting FTO/m6A/MYC/CEBPA signaling. Cell 172:90–105.e23

Suzuki T, Ueda H, Okada S, Sakurai M. 2015. Transcriptome-wide identification of adenosine-to-inosine editing using the ICE-seq method. Nat. Protoc. 10:715–32

Takahashi M, Yoshimoto T, Shimoda M, Kono T, Koizumi M, et al. 2006. Loss of function of the candidate tumor suppressor prox1 by RNA mutation in human cancer cells. Neoplasia 8:1003–10

Tan A, Dang Y, Chen G, Mo Z. 2015. Overexpression of the fat mass and obesity associated gene (FTO) in breast cancer and its clinical implications. Int. J. Clin. Exp. Pathol. 8:13405–10

Tan Y, Zheng J, Liu X, Lu M, Zhang C, et al. 2018. Loss of nucleolar localization of NAT10 promotes cell migration and invasion in hepatocellular carcinoma. Biochem. Biophys. Res. Commun. 499:1032–38

Tasaki M, Shimada K, Kimura H, Tsujikawa K, Konishi N. 2011. ALKBH3, a human AlkB homologue, contributes to cell survival in human non-small-cell lung cancer. Br. J. Cancer 104:700–6

Thomas D, Majeti R. 2017. Biology and relevance of human acute myeloid leukemia stem cells. Blood 129:1577–85

Tomaselli S, Galeano F, Alon S, Raho S, Galardi S, et al. 2015. Modulation of microRNA editing, expression and processing by ADAR2 deaminase in glioblastoma. Genome Biol. 16: 5

Valleron W, Laprevotte E, Gautier EF, Quelen C, Demur C, et al. 2012a. Specific small nucleolar RNA expression profiles in acute leukemia. Leukemia 26:2052–60

Valleron W, Ysbaert L, Berquet L, Fataccioli V, Quelen C, et al. 2012b. Small nucleolar RNA expression profiling identifies potential prognostic markers in peripheral T-cell lymphoma. Blood 120:3997–4005

Visvanathan A, Patil V, Arivazhagan A, et al. 2018. Essential role of METTL3-mediated m6A modification in glioma stem-like cells maintenance and radioresistance. Oncogene 37:522–33

Vu LP, Pickering BF, Cheng Y, Zaccara S, Nguyen D, et al. 2017. The N6-methyladenosine (m6A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells. Nat. Med. 23:1369–76

Wang P, Dostater KA, Nam Y. 2016. Structural basis for cooperative function of Mettl3 and Mettl14 methyltransferases. Mol. Cell 63:306–17
Wang X, Feng J, Xue Y, Guan Z, Zhang D, et al. 2016. Structural basis of N6-adenosine methylation by the METTL3–METTL14 complex. Nature 534:575–78

Wang X, Lu Z, Gomez A, Hon GC, Yue Y, et al. 2014. N6-methyladenosine-dependent regulation of messenger RNA stability. Nature 505:117–20

Wang X, Zhao BS, Roundtree IA, Lu Z, Han D, et al. 2015. N6-methyladenosine modulates messenger RNA translation efficiency. Cell 161:1388–99

Wang Y, Xu X, Yu S, Jeong KJ, Zhou Z, et al. 2017. Systematic characterization of A-to-I RNA editing hotspots in microRNAs across human cancers. Genome Res. 27:1112–25

Weissman SM, Lewis M, Karon M. 1963. Pseudouridin metabolism. IV. Excretion of pseudouridine and other metabolites in chronic leukemia. Blood 22:657–63

Wen J, Lv R, Ma H, Shen H, He C, et al. 2018. Zc3h13 regulates nuclear RNA m6A methylation and mouse embryonic stem cell self-renewal. Mol. Cell 69:1028–38.e6

Weng H, Huang H, Wu H, Qin X, Zhao BS, et al. 2018. METTL14 inhibits hematopoietic stem/progenitor differentiation and promotes leukemogenesis via mRNA m6A modification. Cell Stem Cell 22:191–205.e

Wojtas MN, Pandey RR, Mendel M, Homolka D, Sachidanandam R, Pillai RS. 2017. Regulation of m6A transcripts by the 3′→5′ RNA helicase YTHDC2 is essential for a successful meiotic program in the mammalian germline. Mol. Cell 68:374–87.e12

Woo HH, Chambers SK. 2019. Human ALKBH3-induced m1A demethylation increases the CSF-1 mRNA stability in breast and ovarian cancer cells. Biochim. Biophys. Acta Gene Regul. Mech. 1862:35–46

Wu B, Su S, Patil DP, Liu H, Gan J, et al. 2018. Molecular basis for the specific and multivariant recognitions of RNA substrates by human hnRNP A2/B1. Nat. Commun. 9:420

Wu G, Xiao M, Yang C, Yu YT. 2011. U2 snRNA is inducibly pseudouridylated at novel sites by Pus7p and snR81 RNP. EMBO J. 30:79–89

Xiao W, Adhikari S, Dahal U, Chen YS, Hao YJ, et al. 2016. Nuclear m6A reader YTHDC1 regulates mRNA splicing. Mol. Cell 61:507–19

Xu H, Jiang B, Meng L, Ren T, Zeng Y, et al. 2012. Nα-acetyltransferase 10 protein inhibits apoptosis through RhoA/Rho-related MCL1 expression. Carcinogenesis 33:1193–202

Xuan JJ, Sun WJ, Lin PH, Zhou KR, Liu S, et al. 2018. RMBase v2.0: deciphering the map of RNA modifications from epitranscriptome sequencing data. Nucleic Acids Res. 46:D327–34

Yang F, Jin H, Que B, Chao Y, Zhang H, et al. 2019. Dynamic m6A mRNA methylation reveals the role of METTL3–m6A–CDCP1 signaling axis in chemical carcinogenesis. Oncogene 38:6755–72

Yang JC, Risch E, Zhang M, Huang C, Huang H, Lu L. 2017. Association of tRNA methyltransferase NSUN2/IGF-II molecular signature with ovarian cancer survival. Future Oncol. 13:1981–90

Yang W, Chendrimada TP, Wang Q, Higuchi M, Seeburg PH, et al. 2006. Modulation of microRNA processing and expression through RNA editing by ADAR deaminases. Nat. Struct. Mol. Biol. 13:13–21

Yang X, Yang Y, Sun BF, Chen YS, Xu JW, et al. 2017. 5-methylcytosine promotes mRNA export—NSUN2 as the methyltransferase and ALYREF as an m6A reader. Cell Res. 27:606–25

Yang Z, Li J, Feng G, Gao S, Wang Y, et al. 2017. MicroRNA-145 modulates N6-methyladenosine levels by targeting the 3′-untranslated mRNA region of the N6-methyladenosine binding YTH domain family 2 protein. J. Biol. Chem. 292:3614–23

Yao QJ, Sang L, Lin M, Yin X, Dong W, et al. 2018. Mettl3–Mett14 methyltransferase complex regulates the quiescence of adult hematopoietic stem cells. Cell Res. 28:952–54

Yi J, Gao R, Chen Y, Yang Z, Han P, et al. 2017. Overexpression of NSUN2 by DNA hypomethylation is associated with metastatic progression in human breast cancer. OncoTargets Ther. 8:20751–65

Yoon A, Peng G, Brandenburger Y, Zollo O, Xu W, et al. 2006. Impaired control of IRES-mediated translation in X-linked dyskeratosis congenita. Science 312:902–6

Yue Y, Liu J, Cui X, Cao J, Luo G, et al. 2018. VIRMA mediates preferential m6A mRNA methylation in 3′UTR and near stop codon and associates with alternative polyadenylation. Cell Discov. 4:10

Zhang C, Chen Y, Sun B, Wang L, Yang Y, et al. 2017. m6A modulates hematopoietic stem and progenitor cell specification. Nature 549:273–76
Zhang C, Samanta D, Lu H, Bullen JW, Zhang H, et al. 2016a. Hypoxia induces the breast cancer stem cell phenotype by HIF-dependent and ALKBH5-mediated m^6A-demethylation of NANOG mRNA. *PNAS* 113:E2047–56

Zhang C, Zhi WI, Lu H, Samanta D, Chen I, et al. 2016b. Hypoxia-inducible factors regulate pluripotency factor expression by ZNF217- and ALKBH5-mediated modulation of RNA methylation in breast cancer cells. *Oncotarget* 7:64527–42

Zhang H, Hou W, Wang HL, Liu HJ, Jia XY, et al. 2014. GSK-3β-regulated N-acetyltransferase 10 is involved in colorectal cancer invasion. *Clin. Cancer Res.* 20:4717–29

Zhang L, Yang CS, Varelas X, Monti S. 2016. Altered RNA editing in 3′ UTR perturbs microRNA-mediated regulation of oncogenes and tumor-suppressors. *Sci. Rep.* 6:23226

Zhao X, Chen Y, Mao Q, Jiang X, Jiang W, et al. 2018. Overexpression of YTHDF1 is associated with poor prognosis in patients with hepatocellular carcinoma. *Int. J. Clin. Exp. Pathol.* 8:14765–71

Zheng G, Dahl JA, Niu Y, Fedoresac P, Huang CM, et al. 2013. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol. Cell* 49:18–29

Zhong L, Liao D, Zhang M, Zeng C, Li X, et al. 2019. YTHDF2 suppresses cell proliferation and growth via destabilizing the EGFR mRNA in hepatocellular carcinoma. *Cancer Lett.* 442:252–61

Zhou S, Bai ZL, Xia D, Zhao ZJ, Zhao R, et al. 2018. FTO regulates the chemo-radiotherapy resistance of cervical squamous cell carcinoma (CSCC) by targeting β-catenin through mRNA demethylation. *Mol. Carcinog.* 57:590–97

Zipeto MA, Court AC, Sadarangani A, Delos Santos NP, Balaian L, et al. 2016. ADAR1 activation drives leukemia stem cell self-renewal by impairing let-7 biogenesis. *Cell Stem Cell* 19:177–91
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