

MiRNA Epitranscriptomic Modifications in Cancer

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MicroRNAs are small non-coding RNAs, acting as post-transcriptional regulators of gene expression. In the last two decades, their role in cancer as oncogenes (oncomir), as well as tumor suppressors, has been extensively demonstrated. Recently, epitranscriptomics, namely the study of RNA modifications, has emerged as a new field of great interest, being an additional layer in the regulation of gene expression. Almost all classes of eukaryotic RNAs, including miRNAs, undergo epitranscriptomic modifications. Alterations of RNA modification pathways have been described for many diseases—in particular, in the context of malignancies.

microRNA

cancer

epitranscriptomics

m6A

m5C

A-to-I editing

m7G

1. Introduction

MicroRNAs (miRNAs) are a class of short, non-coding RNAs that control gene expression at the post-transcriptional level via either translational repression or mRNA degradation.

Since miRNAs act as pervasive regulators of gene expression, it is not surprising that they were involved in normal animal development and in a variety of biological processes [\[1\]\[2\]](#). The aberrant expression of miRNAs is also associated with many human diseases [\[3\]\[4\]](#).

One hundred and seventy-two post-transcriptional modifications of RNAs have been reported thus far [\[5\]](#), collectively known as the “epitranscriptome” [\[6\]](#). Some of these epitranscriptomic modifications have been thoroughly investigated, unraveling their contribution to RNA stability and/or activity [\[7\]\[8\]\[9\]](#). The most common and best-characterized epitranscriptomic modifications include N6-methyl-Adenosine (m6A) [\[10\]](#), pseudoUridine (Ψ) [\[11\]](#), Adenosine-to-Inosine (A-to-I) editing [\[12\]](#) and 5-methyl-Cytidine (m5C) [\[13\]](#).

In epigenetics, a widely exploited paradigm postulates that DNA methylation and histone modifications are installed by “writer” enzymes, recruit “reader” proteins and are removed by “eraser” enzymes [\[14\]](#). Although it has been proposed that the same general view may hold true for epitranscriptomic modifications, the intrinsic features of RNA imply that “readers” and “erasers” may be dispensable for some modifications [\[15\]](#). “Writer” enzymes have been identified for all major RNA modifications [\[16\]\[17\]\[18\]\[19\]\[20\]\[21\]](#). Otherwise, “reader” proteins have been described only for m6A [\[22\]](#) and m5C [\[23\]](#). Several RNA modifications directly affect the RNA structure and/or base pairing, thus requiring no “reader” proteins to exert their functions. This is obvious for A-to-I editing, which changes the identity of a base, and it has also been demonstrated for Ψ [\[24\]\[25\]](#). Furthermore, while it has been suggested that

m6A can be removed from modified RNA molecules [26][27], most epitranscriptomic modifications are apparently not dynamic. On the one hand, because of the very short half-life of most eukaryotic RNAs, specific “eraser” enzymes might be dispensable at least for some epitranscriptomic modifications that may actually be removed through the rapid turnover of modified RNA molecules. On the other hand, epitranscriptomic modifications on more stable RNA molecules (e.g., rRNAs) may lack any “eraser” enzymes simply because reverting such modifications is not beneficial to the cell. Accordingly, no “eraser” enzyme has been identified yet for m5C, Ψ, A-to-I editing and many other epitranscriptomic modifications [28][29].

2. miRNAs: Biogenesis and Functions

miRNAs are a class of small (18–24 nt) non-coding RNAs that are processed from long primary miRNAs (pri-miRNAs) generally transcribed by RNA Polymerase II [30][31][32] and harbor one or more hairpin structure [33]. Pri-miRNA processing starts in the nucleus, where the Microprocessor complex, formed by the RNase III enzyme DROSHA, the RNA-binding protein Di George Syndrome Critical Region Gene 8 (DGCR8) and other proteins [34][35] catalyzes the endonucleolytic cleavage of the pri-miRNA to yield a ~70-nt-long hairpin pre-miRNA [36].

Pre-miRNAs are then exported to the cytoplasm by Exportin-5 [37][38][39]. In the cytoplasm, pre-miRNAs undergo further cleavage by DICER, which removes the terminal loop of the hairpin to yield a duplex consisting of the mature miRNA (guide strand) base-paired to the passenger strand [40][41].

The mature miRNA within RISC recruits the complex onto target RNA molecules by base-pairing between a “seed” region (nt 2–7) at the 5′ end of the miRNA and the 3′ UTR of the target RNA [42][43][44], leading to gene silencing through translation repression and mRNA decay.

MiRNAs participate in gene regulatory networks that control diverse biological processes in multicellular organisms, such as animal development (reviewed in reference [1]), cell fate specification and differentiation [45], the immune response [46] and inflammation [47]. Changes in the miRNA expression levels have been associated with a wide range of human diseases, including diabetes, cardiovascular and kidney disease and cancer [3][4]. A huge number of miRNAs are downregulated or upregulated in human cancers, where they exert oncogenic or tumor suppressor functions, depending on the cellular context. Alterations of miRNAs in different malignancies have been linked to genetic deletion or amplification, as well as to DNA methylation of the miRNA genomic loci, to the modulation of the pri-mRNA transcription level by transcription factors or to the dysregulation of one or more steps in miRNA biogenesis (reviewed in reference [48]). Recently, epitranscriptomics is emerging as an additional layer of the regulation of the miRNA function in cancer.

3. Epitranscriptomic Modifications of miRNA in Cancer

3.1. N6-Methyl-Adenosine (m6A)

m6A was first reported in the 1970s in mammalian RNAs [49][50][51]. A full comprehension of the role of this modification took several decades. In 1997, the protein Methyltransferase-like (METTL) 3 was identified as the first

“writer” of m6A in mammalian cells [20]. Further investigations have shown that m6A is installed by a nuclear complex comprised of METTL3, METTL14 and WT1-Associated Protein (WTAP) [19]. Further components of this complex include KIAA1429, RNA Binding Motif Protein 15 (RBM15) and Zinc Finger CCCH-Type Containing 13 (ZC3H13) [52][53][54].

Several members belonging to the YTH (YT521-B homology) family, such as human YT521-B (also known as YTHDC1), YTHDC2, YTHDF1, YTHDF2 and YTHDF3, have been identified as m6A-binding or “reader” proteins [15][22]. The members belonging to the DF family likely confine m6A-modified RNAs in specific cytoplasmic liquid–liquid phase separation compartments [55].

Several other “reader” proteins have been shown to bind m6A-modified RNAs thanks to a so-called “m6A switch” [56]. Indeed, m6A installation may trigger a conformational switch that allows the binding of these “reader” proteins, which, in fact, do not directly bind to the m6A residue itself [10]. This mechanism is exploited by several members of the hnRNP (heterogeneous nuclear ribonucleoprotein) family. Finally, insulin-like growth factor 2 mRNA-binding proteins (IGF2BP) were also reported to bind m6A-modified RNAs, promoting their stability [57].

Although two enzymes able to “erase” m6A from mammalian RNAs have been reported, i.e., FTO Alpha-Ketoglutarate-Dependent Dioxygenase (FTO) and AlkB Homolog 5, RNA Demethylase (ALKBH5) [26][27], the specificity and the relevance of these enzymes in physiological conditions are still a matter of debate [58].

About 0.1–0.4% of all adenosines in global cellular RNAs are modified as m6A, and this modification accounts for ~50% of all methylated ribonucleotides [49]. m6A was found in all classes of cellular RNAs: mRNAs (in particular, in long internal exons, locations upstream of stop codons and the 3'-UTR regions) [22][59][60]; ribosomal RNAs; transfer RNAs and various non-coding RNAs [61][62][63].

In cancer, the relevancy of m6A in miRNA maturation was first unveiled for miR-126 in hepatocellular carcinoma (HCC) [64].

From that moment on, increasing evidence has disclosed the relevance of the m6A modification of miRNA in cancer progression. Most of the literature confirms that m6A mainly promotes pri-miRNA processing and that the deregulation of the enzymes involved in writing or reading m6A is correlated with tumor onset. Notably, alteration of the m6A deposition on miRNAs is not only a common feature of different tumors but also participates in tumorigenesis processes (**Figure 1** and **Table 1**).

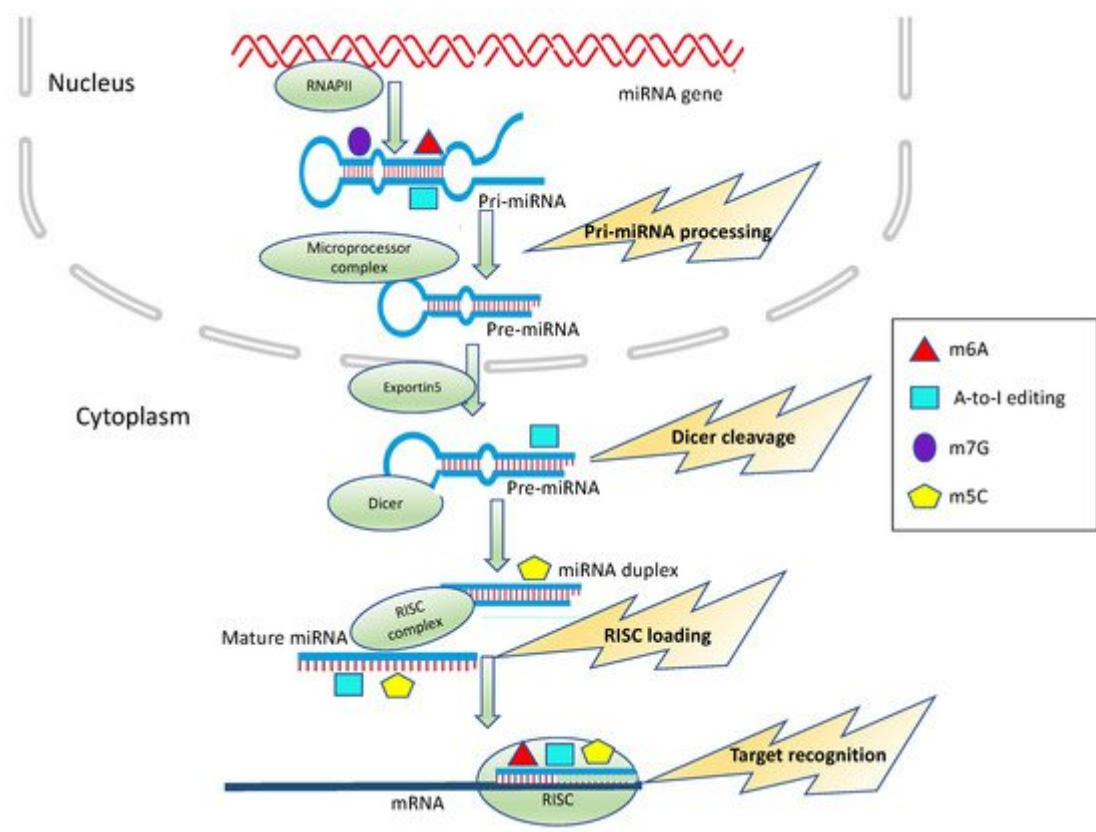


Figure 1. Epitranscriptomic modification impacts on miRNA processing and activity. m6A, A-to-I editing, m5C and m7G can affect different steps of miRNA biogenesis, including Microprocessor cleavage, Dicer cleavage and RISC loading or alter target recognition and binding.

Table 1. Effects of m6A modification of miRNAs in cancer.

Cancer Type	m6A-Modified miRNA(s)	Increase/Decrease ¹	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
Colorectal Cancer	miR-1246	↑	processing	Up-regulation of mature of miR-1246 results in the reduction of SPRED2, thus activating the RAF/MEK/ERK pathway	[65]
	miR-375	↓	processing	Down-regulation of mature miR-375 increases the expression of its targets YAP1 and SP1 thus increasing proliferation, and migration and invasion	[66]

Cancer Type	m6A-Modified miRNA(s)	Increase/ Decrease ¹	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
	miR-483, miR-676 miR-877	n.d.	processing	miR-483, miR-676 and miR-877 modulate mitochondrial metabolism by targeting electron transport chain genes	[67]
	miR-17-5p let-7a-5p	↑	Binding to targets	n.d.	[68]
Pancreatic cancer	miR-25-3p	↑	processing	Up-regulation of mature miR-25-3p results in the reduction of PHLPP2, leading to AKT activation.	[69]
	miR-17-5p let-7a-5p	↑	Binding to targets	n.d.	[68]
Hepatocellular Carcinoma	miR-126	↓	processing	Down-regulation of mature miR-126 which acts as a tumor suppressor	[64]
Bladder cancer	miR-221/222	↑	processing	Up-regulation of mature miR-221/222 results in the reduction of PTEN, leading to proliferation	[70]

Cancer Type	m6A-Modified miRNA(s)	Increase/Decrease ¹	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
Gallbladder cancer	miRNA-92	↑	processing	Up-regulation of mature miRNA-92 results in the reduction of PTEN, thus activating PI3K/AKT signaling	[71]
Ovarian cancer	miR-126	↑	processing	Up-regulation of mature miR-126-5p results in the reduction of PTEN, thus activating the PI3K/Akt/mTOR pathway	[72]
Gastric cancer	miR-17-5p let-7a-5p	↑	Binding to targets	n.d.	[68]
Lung cancer (brain metastasis)	miR-143-3p	↑	processing	Up-regulation of mature miR-143-3p promotes the metastatic potential of lung cancer [76] via regulation of angiogenesis and microtubules through VASH1	[73] [77][78][79]

Inosine is recognized by the cellular machinery as guanosine, causing a change in the RNA sequence. As a consequence, depending on the modification site, this type of RNA editing can influence the RNA stability [80][81][82], splicing [83][84][85], localization and translation, as well as redefine its interactions with specific factors [86][87]. In mRNAs, the modification of A-to-I can lead to a codon change, thus affecting the primary structure of the encoded protein [88][89].

A-to-I editing mainly targets noncoding regions of RNA, such as introns and UTRs, containing repetitive Alu elements and Long Interspersed Elements (LINEs) that fold into dsRNA structures recognized by ADARs [90].

In most types of cancer, the activity of ADAR enzymes is significantly decreased, as witnessed by the extensive hypoeediting of Alu RNAs, as well as by the reduced expression of ADAR enzymes [91].

The first evidence of the editing of a miRNA was shown in 2004 by Luciano and colleagues [92], who reported A-to-I conversion within the miR-22 precursor in *Homo sapiens* and *Mus musculus*. Soon after, it was shown that the A-

to-I editing of pri-miR-142 prevents processing by DROSHA [93]. ADAR enzymes have a degree of specificity for different miRNA precursors, depending on their secondary structure [94]. The ADAR1 interaction with DICER was associated with enhanced miRNA processing in oral squamous cells carcinoma [95] and in melanoma [96], although, in both cases, the authors did not assess the editing of the miRNA precursors. Furthermore, ADAR editing has been shown to affect the DICER-dependent processing of viral miRNAs [97]. Of note, ADARs can also alter miRNA metabolism independently from their editing activity [98][99][100].

Several examples showed that the A-to-I editing of miRNA precursors inhibits the biogenesis of mature miRNAs or alters the selection of miRNA targets (**Figure 1** and **Table 2**). The deregulation of ADAR1 and/or ADAR2 in glioblastoma and in chordoma affects the expression levels of miR-21, miR-221 and miR-222 [101] and of miR-10a and miR-125a [102], respectively. Furthermore, the impairment of let-7 biogenesis by means of ADAR1-mediated A-to-I editing drives leukemia stem cells renewal [103]. In thyroid cancer, the slight overexpression of ADAR1 corresponds to a higher expression of ZEB1, a master regulator of Epithelial–Mesenchymal Transition (EMT). It has been demonstrated that editing of the seed sequence of miR-200b by ADAR1 impairs its ability to inhibit ZEB1 expression, favoring the progression of the cancer [104][105].

Table 2. Effects of A-to-I editing of miRNAs in cancer.

Cancer	A-to-I-Modified miRNA(s)	Increase/ Decrease ¹	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
Glioma	mir-376a-5p	↓	Binding to targets	Unedited miR-376a-5p promotes aggressive glioma growth, by its ability to target RAP2A and concomitant inability to target AMFR	[106]
	miR-221/222 miR-21	↓	processing	Up-regulation of mature miR-221/222 and miR-21 results in the repression of its targets p27Kip1 and PDCD4, thus increasing proliferation and migration of glioblastoma	[101]
	miR-589-3p	↓	Binding to targets	Editing within miR-589–3p retargets the miRNA from the protocadherin PCDH9 to the metalloprotease ADAM12, which is involved in glioblastoma cell invasion.	[107]

Cancer	A-to-I-Modified miRNA(s)	Increase/Decrease ¹	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
	miR-455-5p	↓	Binding to targets	Unedited miR-455-5p but not the edited form targets the tumor suppressor gene CPEB1, thus promoting tumor growth and metastasis	[108]
Melanoma	miR-378a-3p	↓	Binding to targets	Edited miR-378a-3p but not the unedited form specifically targets the PARVA oncogene, thus preventing the progression of melanoma towards the malignant phenotype	[109]
Chordoma	miR-10a miR-125a	↑	processing	Down-regulation of miR-10a and miR-125a expression and upregulates expression of their target genes	[102]
Chronic myeloid leukemia	let-7	↑	processing	Down-regulation of mature let-7 results in increased LIN28B expression and enhanced self-renewal	[103]
Thyroid cancer	miR-200b	↑	Binding to targets	Edited miR-200b has weakened activity against its target gene ZEB1, an epithelial–mesenchymal transition (EMT) marker	[105]
Lung cancer	miR-381	↑	n.d.	Edited miR-381 enhances the growth of non-small-cell lung cancer cells as compared to the unedited form	[110]

m5C is one of the most representative post-transcriptional RNA modifications [111], and it has long been known to be present in all three kingdoms of life [112][113].

m5C was originally reported in tRNAs, rRNAs [50] and coding RNAs [114]; later, it was identified in other noncoding RNAs, thanks to technologies such as bisulfite treatment and Next-Generation Sequencing (NGS) [115][116][117].

The synthesis of m5C is catalyzed by the seven members of the NOL1/NOP2/SUN domain (NSUN) family of methyltransferases [118] or by DNA methyltransferase-2 (DNMT2) [119]. These enzymes are responsible for the methylation of rRNAs, tRNAs [120][121][122][123][124], mRNAs [125][126][127], lncRNAs [128], vault-RNAs [129], enhancer-RNAs [116], mitochondrial tRNAMet [130] and mitochondrial 12S rRNA [131].

In vitro and in vivo studies have demonstrated that aly/REF nuclear factor (ALYREF) is a putative “reader” of m5C sites on mRNAs and that, following the knockdown of NSUN2, ALYREF loses its RNA-binding ability and is retained in the nucleus, suggesting a role for m5C in mRNA exports from the nucleus [23]. A further m5C “reader” is Y-Box-Binding Protein 1 (YBX1) that recognizes and binds m5C-modified mRNAs and stabilizes their target mRNAs by recruiting ELAV-like Protein 1 (ELAVL1) [132][133].

m5C “writers” and “readers” are primarily implicated in fundamental cancer-related processes such as cell differentiation, motility [134][135], proliferation [136][137], cell cycle progression [138] and senescence [126].

In particular, NSUN2 is aberrantly expressed and plays important roles in the development and pathogenesis of different types of tumors, such as breast, colorectal, lung, skin, ovarian and bladder cancers [139].

The distribution of m5C in small RNAs is poorly understood so far; nevertheless, this modification has been recently highlighted in vault RNAs (vtRNAs) [129], piwi-associated RNAs (piRNAs) [140] and miRNAs [68][141][142]. m5C deposition regulates the processing of vault ncRNAs into small vault RNAs (svRNAs) [129][143].

m5C has been only recently characterized in miRNAs. Interestingly, methylation, but not an abundance of miR-200c-3p and miR-21-3p, was increased in pancreatic and colorectal cancer tissues, as well as in serum samples from pancreatic and colorectal cancer patients [68] (Figure 1 and Table 3).

Recently, we described that m5C is widely spread in human miRNAs in various sequence contexts by taking advantage of a novel NGS analysis of bisulfite-treated small RNAs (BS-miRNA-seq) [142]. In this context, not only the presence of m5C but, also, of hm5C on several miRNAs in human cancer cell lines was unraveled.

Table 3. Effects of m5C and m7G modifications of miRNAs in cancer.

Cancer	Modified miRNA(s)	Increase/ Decrease ¹	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
Glioma	miRNA-181a-5p	↑	Binding to targets	Cytosine-methylated miRNA-181a-5p loses its ability to target	[140]

Cancer	Modified miRNA(s)	Increase/ Decrease 1	Effects on miRNA Processing/Function	Effects on Tumor Progression	Reference
	(m5C)			the mRNA of the pro-apoptotic protein BIM	
Colorectal cancer; gastric cancer; pancreatic cancer	miR- 200c-3p miR-21- 3p (m5C)	↑	Binding to targets	n.d.	[71]
Lung cancer	let-7 family (m7G)	n.d.	processing	m7G methylation within miRNAs regulates cell migration	[144]
Colon cancer	let-7e (m7G)	↓	processing	Down-regulation of mature let-7e results in the activation of its targets HMGA2 thus stimulating colon cancer cell viability and mobility	[145]

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3.4. N7-Methylguanosine (m7G)

m7G is a positively charged modification installed cotranscriptionally at the 5' Caps of eukaryotic mRNAs [146]. This modification protects and stabilizes transcripts from exonucleolytic degradation [147] and influences all the events responsible for the processing of the mRNA molecules, from transcript elongation to translation [148][149].

Notably, the presence of internal m7G sites was found not only in tRNA and rRNA molecules [150][151][152] but also in mammalian mRNAs [152]. Internal m7G could affect mRNA translation, and this modification typically occurs near the start and stop codons in a GA-enriched motif [153].

The enzyme responsible for this internal m7G modification is METTL1, which cooperates with the cofactor WD Repeat Domain 4 (WDR4) [153][154]. Interestingly, METTL1 has been linked to tumor vascular invasion and poor prognosis in hepatocellular carcinoma [144][155].

Recently, by high-throughput screening, several miRNAs were identified as harboring internal m7G sites [156]. In particular, METTL1-dependent m7G was discovered in a subset of tumor-suppressor miRNAs involved in the inhibition of cell migration, including the let-7 family. METTL1-mediated m7G occurs on pri-miRNA within G-rich regions that display the propensity to form G-quadruplexes, i.e., structures known to be inhibitory to miRNA processing [145][157][158] (**Figure 1** and **Table 3**).

Indeed, m7G in the let-7 family affects G-quadruplex formations, thus facilitating the formation of a canonical stem-loop structure and miRNA processing [156]. In line with this study, Liu and colleagues showed that, in colon cancer, the downregulation of METTL1 leads to a decrease in the let-7e levels. The alteration of let-7e expression affects its downstream target High Mobility Group AT-hook 2 (HMGA2), thus promoting cell proliferation, invasion and EMT [159].

References

1. Alberti, C.; Cochella, L. A Framework for Understanding the Roles of MiRNAs in Animal Development. *Development* 2017, 144, 2548–2559.
2. Tüfekci, K.U.; Meuwissen, R.L.J.; Genç, Ş. The Role of MicroRNAs in Biological Processes. In *miRNomics: MicroRNA Biology and Computational Analysis*; Yousef, M., Allmer, J., Eds.; Methods in Molecular Biology; Humana Press: Totowa, NJ, USA, 2014; pp. 15–31. ISBN 978-1-62703-748-8.
3. Paul, P.; Chakraborty, A.; Sarkar, D.; Langthasa, M.; Rahman, M.; Bari, M.; Singha, R.S.; Malakar, A.K.; Chakraborty, S. Interplay between MiRNAs and Human Diseases. *J. Cell. Physiol.* 2018, 233, 2007–2018.
4. Huang, Z.; Shi, J.; Gao, Y.; Cui, C.; Zhang, S.; Li, J.; Zhou, Y.; Cui, Q. HMDD v3.0: A Database for Experimentally Supported Human MicroRNA-Disease Associations. *Nucleic Acids Res.* 2019, 47, D1013–D1017.
5. Boccaletto, P.; Machnicka, M.A.; Purta, E.; Piątkowski, P.; Bagiński, B.; Wirecki, T.K.; de Crécy-Lagard, V.; Ross, R.; Limbach, P.A.; Kotter, A.; et al. MODOMICS: A Database of RNA Modification Pathways. 2017 Update. *Nucleic Acids Res.* 2018, 46, D303–D307.
6. Saletore, Y.; Meyer, K.; Korlach, J.; Vilfan, I.D.; Jaffrey, S.; Mason, C.E. The Birth of the Epitranscriptome: Deciphering the Function of RNA Modifications. *Genome Biol.* 2012, 13, 175.
7. Peer, E.; Rechavi, G.; Dominissini, D. Epitranscriptomics: Regulation of MRNA Metabolism through Modifications. *Curr. Opin. Chem. Biol.* 2017, 41, 93–98.
8. Wiener, D.; Schwartz, S. The Epitranscriptome beyond M6A. *Nat. Rev. Genet.* 2020.
9. Nachtergaele, S.; He, C. The Emerging Biology of RNA Post-Transcriptional Modifications. *RNA Biol.* 2017, 14, 156–163.

10. Zaccara, S.; Ries, R.J.; Jaffrey, S.R. Reading, Writing and Erasing mRNA Methylation. *Nat. Rev. Mol. Cell Biol.* 2019, 20, 608–624.
11. Li, X.; Ma, S.; Yi, C. Pseudouridine: The Fifth RNA Nucleotide with Renewed Interests. *Curr. Opin. Chem. Biol.* 2016, 33, 108–116.
12. Eisenberg, E.; Levanon, E.Y. A-to-I RNA Editing—Immune Protector and Transcriptome Diversifier. *Nat. Rev. Genet.* 2018, 19, 473–490.
13. Trixl, L.; Lusser, A. The Dynamic RNA Modification 5-Methylcytosine and Its Emerging Role as an Epitranscriptomic Mark. *Wiley Interdiscip. Rev. RNA* 2019, 10, e1510.
14. Janzen, W.P.; Wigle, T.J.; Jin, J.; Frye, S.V. Epigenetics: Tools and Technologies. *Drug Discov. Today Technol.* 2010, 7, e59–e65.
15. Fu, Y.; Dominissini, D.; Rechavi, G.; He, C. Gene Expression Regulation Mediated through Reversible m6A RNA Methylation. *Nat. Rev. Genet.* 2014, 15, 293–306.
16. Cortese, R.; Kammen, H.O.; Spengler, S.J.; Ames, B.N. Biosynthesis of Pseudouridine in Transfer Ribonucleic Acid. *J. Biol. Chem.* 1974, 249, 1103–1108.
17. Koonin, E.V. Pseudouridine Synthases: Four Families of Enzymes Containing a Putative Uridine-Binding Motif Also Conserved in DUTPases and DCTP Deaminases. *Nucleic Acids Res.* 1996, 24, 2411–2415.
18. Bohnsack, K.E.; Höbartner, C.; Bohnsack, M.T. Eukaryotic 5-Methylcytosine (m5C) RNA Methyltransferases: Mechanisms, Cellular Functions, and Links to Disease. *Genes* 2019, 10, 102.
19. Liu, J.; Yue, Y.; Han, D.; Wang, X.; Fu, Y.; Zhang, L.; Jia, G.; Yu, M.; Lu, Z.; Deng, X.; et al. A METTL3–METTL14 Complex Mediates Mammalian Nuclear RNA m6A-Adenosine Methylation. *Nat. Chem. Biol.* 2014, 10, 93–95.
20. Bokar, J.A.; Shambaugh, M.E.; Polayes, D.; Matera, A.G.; Rottman, F.M. Purification and cDNA Cloning of the AdoMet-Binding Subunit of the Human mRNA (m6A-Adenosine)-Methyltransferase. *RNA* 1997, 3, 1233–1247.
21. Bass, B.L.; Weintraub, H. An Unwinding Activity That Covalently Modifies Its Double-Stranded RNA Substrate. *Cell* 1988, 55, 1089–1098.
22. Dominissini, D.; Moshitch-Moshkovitz, S.; Schwartz, S.; Salmon-Divon, M.; Ungar, L.; Osenberg, S.; Cesarkas, K.; Jacob-Hirsch, J.; Amariglio, N.; Kupiec, M.; et al. Topology of the Human and Mouse m6A RNA Methylomes Revealed by m6A-Seq. *Nature* 2012, 485, 201–206.
23. Yang, X.; Yang, Y.; Sun, B.-F.; Chen, Y.-S.; Xu, J.-W.; Lai, W.-Y.; Li, A.; Wang, X.; Bhattarai, D.P.; Xiao, W.; et al. 5-Methylcytosine Promotes mRNA Export—NSUN2 as the Methyltransferase and ALYREF as an m5C Reader. *Cell Res.* 2017, 27, 606–625.

24. Newby, M.I.; Greenbaum, N.L. Sculpting of the Spliceosomal Branch Site Recognition Motif by a Conserved Pseudouridine. *Nat. Struct. Biol.* 2002, 9, 958–965.
25. Kierzek, E.; Malgowska, M.; Lisowiec, J.; Turner, D.H.; Gdaniec, Z.; Kierzek, R. The Contribution of Pseudouridine to Stabilities and Structure of RNAs. *Nucleic Acids Res.* 2014, 42, 3492–3501.
26. Jia, G.; Fu, Y.; Zhao, X.; Dai, Q.; Zheng, G.; Yang, Y.; Yi, C.; Lindahl, T.; Pan, T.; Yang, Y.-G.; et al. N 6-Methyladenosine in Nuclear RNA Is a Major Substrate of the Obesity-Associated FTO. *Nat. Chem. Biol.* 2011, 7, 885–887.
27. Zheng, G.; Dahl, J.A.; Niu, Y.; Fedorcsak, P.; Huang, C.-M.; Li, C.J.; Vågbø, C.B.; Shi, Y.; Wang, W.-L.; Song, S.-H.; et al. ALKBH5 Is a Mammalian RNA Demethylase That Impacts RNA Metabolism and Mouse Fertility. *Mol. Cell* 2013, 49, 18–29.
28. Barbieri, I.; Kouzarides, T. Role of RNA Modifications in Cancer. *Nat. Rev. Cancer* 2020, 20, 303–322.
29. Haruehanroengra, P.; Zheng, Y.Y.; Zhou, Y.; Huang, Y.; Sheng, J. RNA Modifications and Cancer. *RNA Biol.* 2020, 17, 1560–1575.
30. Lee, Y.; Kim, M.; Han, J.; Yeom, K.-H.; Lee, S.; Baek, S.H.; Kim, V.N. MicroRNA Genes Are Transcribed by RNA Polymerase II. *EMBO J.* 2004, 23, 4051–4060.
31. Rodriguez, A.; Griffiths-Jones, S.; Ashurst, J.L.; Bradley, A. Identification of Mammalian MicroRNA Host Genes and Transcription Units. *Genome Res.* 2004, 14, 1902–1910.
32. Kim, Y.-K.; Kim, V.N. Processing of Intronic MicroRNAs. *EMBO J.* 2007, 26, 775–783.
33. Lagos-Quintana, M.; Rauhut, R.; Lendeckel, W.; Tuschl, T. Identification of Novel Genes Coding for Small Expressed RNAs. *Science* 2001, 294, 853–858.
34. Denli, A.M.; Tops, B.B.J.; Plasterk, R.H.A.; Ketting, R.F.; Hannon, G.J. Processing of Primary MicroRNAs by the Microprocessor Complex. *Nature* 2004, 432, 231–235.
35. Gregory, R.I.; Yan, K.; Amuthan, G.; Chendrimada, T.; Doratotaj, B.; Cooch, N.; Shiekhattar, R. The Microprocessor Complex Mediates the Genesis of MicroRNAs. *Nature* 2004, 432, 235–240.
36. Lee, Y.; Ahn, C.; Han, J.; Choi, H.; Kim, J.; Yim, J.; Lee, J.; Provost, P.; Rådmark, O.; Kim, S.; et al. The Nuclear RNase III Drosha Initiates MicroRNA Processing. *Nature* 2003, 425, 415–419.
37. Yi, R.; Qin, Y.; Macara, I.G.; Cullen, B.R. Exportin-5 Mediates the Nuclear Export of Pre-MicroRNAs and Short Hairpin RNAs. *Genes Dev.* 2003, 17, 3011–3016.
38. Bohnsack, M.T.; Czaplinski, K.; Görlich, D. Exportin 5 Is a RanGTP-Dependent DsRNA-Binding Protein That Mediates Nuclear Export of Pre-MiRNAs. *RNA* 2004, 10, 185–191.
39. Lund, E.; Güttinger, S.; Calado, A.; Dahlberg, J.E.; Kutay, U. Nuclear Export of MicroRNA Precursors. *Science* 2004, 303, 95–98.

40. Ketting, R.F.; Fischer, S.E.; Bernstein, E.; Sijen, T.; Hannon, G.J.; Plasterk, R.H. Dicer Functions in RNA Interference and in Synthesis of Small RNA Involved in Developmental Timing in *C. Elegans*. *Genes Dev.* 2001, 15, 2654–2659.
41. Hutvágner, G.; McLachlan, J.; Pasquinelli, A.E.; Bálint, É.; Tuschl, T.; Zamore, P.D. A Cellular Function for the RNA-Interference Enzyme Dicer in the Maturation of the Let-7 Small Temporal RNA. *Science* 2001, 293, 834–838.
42. Krek, A.; Grün, D.; Poy, M.N.; Wolf, R.; Rosenberg, L.; Epstein, E.J.; MacMenamin, P.; da Piedade, I.; Gunsalus, K.C.; Stoffel, M.; et al. Combinatorial MicroRNA Target Predictions. *Nat. Genet.* 2005, 37, 495–500.
43. Lewis, B.P.; Burge, C.B.; Bartel, D.P. Conserved Seed Pairing, Often Flanked by Adenosines, Indicates That Thousands of Human Genes Are MicroRNA Targets. *Cell* 2005, 120, 15–20.
44. Chipman, L.B.; Pasquinelli, A.E. MiRNA Targeting: Growing beyond the Seed. *Trends Genet. TIG* 2019, 35, 215–222.
45. Galagali, H.; Kim, J.K. The Multifaceted Roles of MicroRNAs in Differentiation. *Curr. Opin. Cell Biol.* 2020, 67, 118–140.
46. Mehta, A.; Baltimore, D. MicroRNAs as Regulatory Elements in Immune System Logic. *Nat. Rev. Immunol.* 2016, 16, 279–294.
47. Tahamtan, A.; Teymoori-Rad, M.; Nakstad, B.; Salimi, V. Anti-Inflammatory MicroRNAs and Their Potential for Inflammatory Diseases Treatment. *Front. Immunol.* 2018, 9.
48. Ali Syeda, Z.; Langden, S.S.S.; Munkhzul, C.; Lee, M.; Song, S.J. Regulatory Mechanism of MicroRNA Expression in Cancer. *Int. J. Mol. Sci.* 2020, 21, 1723.
49. Wei, C.M.; Gershowitz, A.; Moss, B. Methylated Nucleotides Block 5' Terminus of HeLa Cell Messenger RNA. *Cell* 1975, 4, 379–386.
50. Desrosiers, R.; Friderici, K.; Rottman, F. Identification of Methylated Nucleosides in Messenger RNA from Novikoff Hepatoma Cells. *Proc. Natl. Acad. Sci. USA* 1974, 71, 3971–3975.
51. Perry, R.P.; Kelley, D.E. Existence of Methylated Messenger RNA in Mouse L Cells. *Cell* 1974, 1, 37–42.
52. Schwartz, S.; Mumbach, M.R.; Jovanovic, M.; Wang, T.; Maciag, K.; Bushkin, G.G.; Mertins, P.; Ter-Ovanesyan, D.; Habib, N.; Cacchiarelli, D.; et al. Perturbation of M6A Writers Reveals Two Distinct Classes of mRNA Methylation at Internal and 5' Sites. *Cell Rep.* 2014, 8, 284–296.
53. Patil, D.P.; Chen, C.-K.; Pickering, B.F.; Chow, A.; Jackson, C.; Guttman, M.; Jaffrey, S.R. M(6)A RNA Methylation Promotes XIST-Mediated Transcriptional Repression. *Nature* 2016, 537, 369–373.

54. Wen, J.; Lv, R.; Ma, H.; Shen, H.; He, C.; Wang, J.; Jiao, F.; Liu, H.; Yang, P.; Tan, L.; et al. Zc3h13 Regulates Nuclear RNA M6A Methylation and Mouse Embryonic Stem Cell Self-Renewal. *Mol. Cell* 2018, 69, 1028–1038.e6.
55. Ries, R.J.; Zaccara, S.; Klein, P.; Olarerin-George, A.; Namkoong, S.; Pickering, B.F.; Patil, D.P.; Kwak, H.; Lee, J.H.; Jaffrey, S.R. M6A Enhances the Phase Separation Potential of MRNA. *Nature* 2019, 571, 424–428.
56. Wu, B.; Su, S.; Patil, D.P.; Liu, H.; Gan, J.; Jaffrey, S.R.; Ma, J. Molecular Basis for the Specific and Multivariant Recognitions of RNA Substrates by Human HnRNP A2/B1. *Nat. Commun.* 2018, 9, 420.
57. Huang, H.; Weng, H.; Sun, W.; Qin, X.; Shi, H.; Wu, H.; Zhao, B.S.; Mesquita, A.; Liu, C.; Yuan, C.L.; et al. Recognition of RNA N6-Methyladenosine by IGF2BP Proteins Enhances MRNA Stability and Translation. *Nat. Cell Biol.* 2018, 20, 285–295.
58. Mauer, J.; Jaffrey, S.R. FTO, M6 Am, and the Hypothesis of Reversible Epitranscriptomic MRNA Modifications. *FEBS Lett.* 2018, 592, 2012–2022.
59. Meyer, K.D.; Saletore, Y.; Zumbo, P.; Elemento, O.; Mason, C.E.; Jaffrey, S.R. Comprehensive Analysis of MRNA Methylation Reveals Enrichment in 3' UTRs and near Stop Codons. *Cell* 2012, 149, 1635–1646.
60. Ke, S.; Alemu, E.A.; Mertens, C.; Gantman, E.C.; Fak, J.J.; Mele, A.; Haripal, B.; Zucker-Scharff, I.; Moore, M.J.; Park, C.Y.; et al. A Majority of M6A Residues Are in the Last Exons, Allowing the Potential for 3' UTR Regulation. *Genes Dev.* 2015, 29, 2037–2053.
61. Zhou, C.; Molinie, B.; Daneshvar, K.; Pondick, J.V.; Wang, J.; Van Wittenberghe, N.; Xing, Y.; Giallourakis, C.C.; Mullen, A.C. Genome-Wide Maps of M6A CircRNAs Identify Widespread and Cell-Type-Specific Methylation Patterns That Are Distinct from MRNAs. *Cell Rep.* 2017, 20, 2262–2276.
62. Yang, Y.; Fan, X.; Mao, M.; Song, X.; Wu, P.; Zhang, Y.; Jin, Y.; Yang, Y.; Chen, L.-L.; Wang, Y.; et al. Extensive Translation of Circular RNAs Driven by N 6 -Methyladenosine. *Cell Res.* 2017, 27, 626–641.
63. Linder, B.; Grozhik, A.V.; Olarerin-George, A.O.; Meydan, C.; Mason, C.E.; Jaffrey, S.R. Single-Nucleotide-Resolution Mapping of M6A and M6Am throughout the Transcriptome. *Nat. Methods* 2015, 12, 767–772.
64. Ma, J.; Yang, F.; Zhou, C.; Liu, F.; Yuan, J.; Wang, F.; Wang, T.; Xu, Q.; Zhou, W.; Sun, S. METTL14 Suppresses the Metastatic Potential of Hepatocellular Carcinoma by Modulating N 6 -methyladenosine-dependent Primary MicroRNA Processing. *Hepatology* 2017, 65, 529–543.
65. Peng, W.; Li, J.; Chen, R.; Gu, Q.; Yang, P.; Qian, W.; Ji, D.; Wang, Q.; Zhang, Z.; Tang, J.; et al. Upregulated METTL3 Promotes Metastasis of Colorectal Cancer via MiR-1246/SPRED2/MAPK

- Signaling Pathway. *J. Exp. Clin. Cancer Res.* CR 2019, 38, 393.
66. Chen, X.; Xu, M.; Xu, X.; Zeng, K.; Liu, X.; Sun, L.; Pan, B.; He, B.; Pan, Y.; Sun, H.; et al. METTL14 Suppresses CRC Progression via Regulating N6-Methyladenosine-Dependent Primary MiR-375 Processing. *Mol. Ther.* 2020, 28, 599–612.
 67. Sun, L.; Wan, A.; Zhou, Z.; Chen, D.; Liang, H.; Liu, C.; Yan, S.; Niu, Y.; Lin, Z.; Zhan, S.; et al. RNA-Binding Protein RALY Reprogrammes Mitochondrial Metabolism via Mediating MiRNA Processing in Colorectal Cancer. *Gut* 2020.
 68. Konno, M.; Koseki, J.; Asai, A.; Yamagata, A.; Shimamura, T.; Motooka, D.; Okuzaki, D.; Kawamoto, K.; Mizushima, T.; Eguchi, H.; et al. Distinct Methylation Levels of Mature MicroRNAs in Gastrointestinal Cancers. *Nat. Commun.* 2019, 10, 3888.
 69. Zhang, J.; Bai, R.; Li, M.; Ye, H.; Wu, C.; Wang, C.; Li, S.; Tan, L.; Mai, D.; Li, G.; et al. Excessive MiR-25-3p Maturation via N6-Methyladenosine Stimulated by Cigarette Smoke Promotes Pancreatic Cancer Progression. *Nat. Commun.* 2019, 10, 1858.
 70. Han, J.; Wang, J.; Yang, X.; Yu, H.; Zhou, R.; Lu, H.-C.; Yuan, W.-B.; Lu, J.; Zhou, Z.; Lu, Q.; et al. METTL3 Promote Tumor Proliferation of Bladder Cancer by Accelerating Pri-MiR221/222 Maturation in M6A-Dependent Manner. *Mol. Cancer* 2019, 18.
 71. Lin, R.; Zhan, M.; Yang, L.; Wang, H.; Shen, H.; Huang, S.; Huang, X.; Xu, S.; Zhang, Z.; Li, W.; et al. Deoxycholic Acid Modulates the Progression of Gallbladder Cancer through N6-Methyladenosine-Dependent MicroRNA Maturation. *Oncogene* 2020, 39, 4983–5000.
 72. Bi, X.; Lv, X.; Liu, D.; Guo, H.; Yao, G.; Wang, L.; Liang, X.; Yang, Y. METTL3-Mediated Maturation of MiR-126-5p Promotes Ovarian Cancer Progression via PTEN-Mediated PI3K/Akt/MTOR Pathway. *Cancer Gene Ther.* 2020.
 73. Wang, H.; Deng, Q.; Lv, Z.; Ling, Y.; Hou, X.; Chen, Z.; Dinglin, X.; Ma, S.; Li, D.; Wu, Y.; et al. N6-Methyladenosine Induced MiR-143-3p Promotes the Brain Metastasis of Lung Cancer via Regulation of VASH1. *Mol. Cancer* 2019, 18, 181.
 74. Bass, B.L.; Nishikura, K.; Keller, W.; Seeburg, P.H.; Emeson, R.B.; O'Connell, M.A.; Samuel, C.E.; Herbert, A. A Standardized Nomenclature for Adenosine Deaminases That Act on RNA. *RNA* 1997, 3, 947–949.
 75. Barraud, P.; Allain, F.H.-T. ADAR Proteins: Double-Stranded RNA and Z-DNA Binding Domains. *Curr. Top. Microbiol. Immunol.* 2012, 353, 35–60.
 76. Wagner, R.W.; Yoo, C.; Wrabetz, L.; Kamholz, J.; Buchhalter, J.; Hassan, N.F.; Khalili, K.; Kim, S.U.; Perussia, B.; McMorris, F.A. Double-Stranded RNA Unwinding and Modifying Activity Is Detected Ubiquitously in Primary Tissues and Cell Lines. *Mol. Cell. Biol.* 1990, 10, 5586–5590.

77. Gott, J.M.; Emeson, R.B. Functions and Mechanisms of RNA Editing. *Annu. Rev. Genet.* 2000, 34, 499–531.
78. Bass, B.L. RNA Editing by Adenosine Deaminases That Act on RNA. *Annu. Rev. Biochem.* 2002, 71, 817–846.
79. Wahlstedt, H.; Ohman, M. Site-Selective versus Promiscuous A-to-I Editing. *Wiley Interdiscip. Rev. RNA* 2011, 2, 761–771.
80. Stellos, K.; Gatsiou, A.; Stamatelopoulos, K.; Perisic Matic, L.; John, D.; Lunella, F.F.; Jaé, N.; Rossbach, O.; Amrhein, C.; Sigala, F.; et al. Adenosine-to-Inosine RNA Editing Controls Cathepsin S Expression in Atherosclerosis by Enabling HuR-Mediated Post-Transcriptional Regulation. *Nat. Med.* 2016, 22, 1140–1150.
81. Levanon, E.Y.; Eisenberg, E.; Yelin, R.; Nemzer, S.; Hallegger, M.; Shemesh, R.; Fligelman, Z.Y.; Shoshan, A.; Pollock, S.R.; Sztybel, D.; et al. Systematic Identification of Abundant A-to-I Editing Sites in the Human Transcriptome. *Nat. Biotechnol.* 2004, 22, 1001–1005.
82. Amin, E.M.; Liu, Y.; Deng, S.; Tan, K.S.; Chudgar, N.; Mayo, M.W.; Sanchez-Vega, F.; Adusumilli, P.S.; Schultz, N.; Jones, D.R. The RNA-Editing Enzyme ADAR Promotes Lung Adenocarcinoma Migration and Invasion by Stabilizing FAK. *Sci. Signal.* 2017, 10, eaah3941.
83. Kapoor, U.; Licht, K.; Amman, F.; Jakobi, T.; Martin, D.; Dieterich, C.; Jantsch, M.F. ADAR-Deficiency Perturbs the Global Splicing Landscape in Mouse Tissues. *Genome Res.* 2020, 30, 1107–1118.
84. Tang, S.J.; Shen, H.; An, O.; Hong, H.; Li, J.; Song, Y.; Han, J.; Tay, D.J.T.; Ng, V.H.E.; Bellido Molias, F.; et al. Cis- and Trans-Regulations of Pre-mRNA Splicing by RNA Editing Enzymes Influence Cancer Development. *Nat. Commun.* 2020, 11.
85. Chen, Y.-T.; Chang, I.Y.-F.; Liu, H.; Ma, C.-P.; Kuo, Y.-P.; Shih, C.-T.; Shih, Y.-H.; Kang, L.; Tan, B.C.-M. Tumor-Associated Intronic Editing of HNRPLL Generates a Novel Splicing Variant Linked to Cell Proliferation. *J. Biol. Chem.* 2018, 293, 10158–10171.
86. Keegan, L.P.; Gallo, A.; O'Connell, M.A. The Many Roles of an RNA Editor. *Nat. Rev. Genet.* 2001, 2, 869–878.
87. Valente, L.; Nishikura, K. ADAR Gene Family and A-to-I RNA Editing: Diverse Roles in Posttranscriptional Gene Regulation. *Prog. Nucleic Acid Res. Mol. Biol.* 2005, 79, 299–338.
88. Sommer, B.; Köhler, M.; Sprengel, R.; Seeburg, P.H. RNA Editing in Brain Controls a Determinant of Ion Flow in Glutamate-Gated Channels. *Cell* 1991, 67, 11–19.
89. Burns, C.M.; Chu, H.; Rueter, S.M.; Hutchinson, L.K.; Canton, H.; Sanders-Bush, E.; Emeson, R.B. Regulation of Serotonin-2C Receptor G-Protein Coupling by RNA Editing. *Nature* 1997, 387, 303–308.

90. Nishikura, K. Functions and Regulation of RNA Editing by ADAR Deaminases. *Annu. Rev. Biochem.* 2010, 79, 321–349.
91. Paz, N.; Levanon, E.Y.; Amariglio, N.; Heimberger, A.B.; Ram, Z.; Constantini, S.; Barbash, Z.S.; Adamsky, K.; Safran, M.; Hirschberg, A.; et al. Altered Adenosine-to-Inosine RNA Editing in Human Cancer. *Genome Res.* 2007, 17, 1586–1595.
92. Luciano, D.J.; Mirsky, H.; Vendetti, N.J.; Maas, S. RNA Editing of a MiRNA Precursor. *RNA* 2004, 10, 1174–1177.
93. Yang, W.; Chendrimada, T.P.; Wang, Q.; Higuchi, M.; Seeburg, P.H.; Shiekhata, R.; Nishikura, K. Modulation of MicroRNA Processing and Expression through RNA Editing by ADAR Deaminases. *Nat. Struct. Mol. Biol.* 2006, 13, 13–21.
94. Ishiguro, S.; Galipon, J.; Ishii, R.; Suzuki, Y.; Kondo, S.; Okada-Hatakeyama, M.; Tomita, M.; Ui-Tei, K. Base-Pairing Probability in the MicroRNA Stem Region Affects the Binding and Editing Specificity of Human A-to-I Editing Enzymes ADAR1-P110 and ADAR2. *RNA Biol.* 2018, 15, 976–989.
95. Liu, X.; Fu, Y.; Huang, J.; Wu, M.; Zhang, Z.; Xu, R.; Zhang, P.; Zhao, S.; Liu, L.; Jiang, H. ADAR1 Promotes the Epithelial-to-Mesenchymal Transition and Stem-like Cell Phenotype of Oral Cancer by Facilitating Oncogenic MicroRNA Maturation. *J. Exp. Clin. Cancer Res.* 2019, 38, 315.
96. Yujie Ding, M.M.; Shi, X.; Ji, J.; Su, Y. ADAR1p150 Regulates the Biosynthesis and Function of MiRNA-149* in Human Melanoma. *Biochem. Biophys. Res. Commun.* 2020, 523, 900–907.
97. Iizasa, H.; Wulff, B.-E.; Alla, N.R.; Maragkakis, M.; Megraw, M.; Hatzigeorgiou, A.; Iwakiri, D.; Takada, K.; Wiedmer, A.; Showe, L.; et al. Editing of Epstein-Barr Virus-Encoded BART6 MicroRNAs Controls Their Dicer Targeting and Consequently Affects Viral Latency. *J. Biol. Chem.* 2010, 285, 33358–33370.
98. Heale, B.S.E.; Keegan, L.P.; McGurk, L.; Michlewski, G.; Brindle, J.; Stanton, C.M.; Caceres, J.F.; O’Connell, M.A. Editing Independent Effects of ADARs on the MiRNA/SiRNA Pathways. *EMBO J.* 2009, 28, 3145–3156.
99. Ota, H.; Sakurai, M.; Gupta, R.; Valente, L.; Wulff, B.-E.; Ariyoshi, K.; Iizasa, H.; Davuluri, R.V.; Nishikura, K. ADAR1 Forms a Complex with Dicer to Promote MicroRNA Processing and RNA-Induced Gene Silencing. *Cell* 2013, 153, 575–589.
100. Vesely, C.; Tauber, S.; Sedlazeck, F.J.; Tajaddod, M.; von Haeseler, A.; Jantsch, M.F. ADAR2 Induces Reproducible Changes in Sequence and Abundance of Mature MicroRNAs in the Mouse Brain. *Nucleic Acids Res.* 2014, 42, 12155–12168.
101. Tomaselli, S.; Galeano, F.; Alon, S.; Raho, S.; Galardi, S.; Polito, V.A.; Presutti, C.; Vincenti, S.; Eisenberg, E.; Locatelli, F.; et al. Modulation of MicroRNA Editing, Expression and Processing by ADAR2 Deaminase in Glioblastoma. *Genome Biol.* 2015, 16, 5.

102. Kuang, L.; Lv, G.; Wang, B.; Li, L.; Dai, Y.; Li, Y. Overexpression of Adenosine Deaminase Acting on RNA 1 in Chordoma Tissues Is Associated with Chordoma Pathogenesis by Reducing MiR-125a and MiR-10a Expression. *Mol. Med. Rep.* 2015, 12, 93–98.
103. Zipeto, M.A.; Court, A.C.; Sadarangani, A.; Delos Santos, N.P.; Balaian, L.; Chun, H.-J.; Pineda, G.; Morris, S.R.; Mason, C.N.; Geron, I.; et al. ADAR1 Activation Drives Leukemia Stem Cell Self-Renewal by Impairing Let-7 Biogenesis. *Cell Stem Cell* 2016, 19, 177–191.
104. Wang, Y.; Xu, X.; Yu, S.; Jeong, K.J.; Zhou, Z.; Han, L.; Tsang, Y.H.; Li, J.; Chen, H.; Mangala, L.S.; et al. Systematic Characterization of A-to-I RNA Editing Hotspots in MicroRNAs across Human Cancers. *Genome Res.* 2017, 27, 1112–1125.
105. Ramírez-Moya, J.; Baker, A.R.; Slack, F.J.; Santisteban, P. ADAR1-Mediated RNA Editing Is a Novel Oncogenic Process in Thyroid Cancer and Regulates MiR-200 Activity. *Oncogene* 2020, 39, 3738–3753.
106. Choudhury, Y.; Tay, F.C.; Lam, D.H.; Sandanaraj, E.; Tang, C.; Ang, B.-T.; Wang, S. Attenuated Adenosine-to-Inosine Editing of MicroRNA-376a* Promotes Invasiveness of Glioblastoma Cells. *J. Clin. Investig.* 2012, 122, 4059–4076.
107. Cesarini, V.; Silvestris, D.A.; Tassinari, V.; Tomaselli, S.; Alon, S.; Eisenberg, E.; Locatelli, F.; Gallo, A. ADAR2/MiR-589-3p Axis Controls Glioblastoma Cell Migration/Invasion. *Nucleic Acids Res.* 2018, 46, 2045–2059.
108. Shoshan, E.; Mobley, A.K.; Braeuer, R.R.; Kamiya, T.; Huang, L.; Vasquez, M.E.; Salameh, A.; Lee, H.J.; Kim, S.J.; Ivan, C.; et al. Reduced Adenosine-to-Inosine MiR-455-5p Editing Promotes Melanoma Growth and Metastasis. *Nat. Cell Biol.* 2015, 17, 311–321.
109. Velazquez-Torres, G.; Shoshan, E.; Ivan, C.; Huang, L.; Fuentes-Mattei, E.; Paret, H.; Kim, S.J.; Rodriguez-Aguayo, C.; Xie, V.; Brooks, D.; et al. A-to-I MiR-378a-3p Editing Can Prevent Melanoma Progression via Regulation of PARVA Expression. *Nat. Commun.* 2018, 9, 461.
110. Anadón, C.; Guil, S.; Simó-Riudalbas, L.; Moutinho, C.; Setien, F.; Martínez-Cardús, A.; Moran, S.; Villanueva, A.; Calaf, M.; Vidal, A.; et al. Gene Amplification-Associated Overexpression of the RNA Editing Enzyme ADAR1 Enhances Human Lung Tumorigenesis. *Oncogene* 2016, 35, 4407–4413.
111. Amos, H.; Korn, M. 5-Methyl Cytosine in the RNA of Escherichia Coli. *Biochim. Biophys. Acta* 1958, 29, 444–445.
112. Dunn, D.B. The Isolation of 5-Methylcytidine from RNA. *Biochim. Biophys. Acta* 1960, 38, 176–178.
113. Motorin, Y.; Lyko, F.; Helm, M. 5-Methylcytosine in RNA: Detection, Enzymatic Formation and Biological Functions. *Nucleic Acids Res.* 2010, 38, 1415–1430.

114. Dubin, D.T.; Taylor, R.H. The Methylation State of Poly A-Containing-Messenger RNA from Cultured Hamster Cells. *Nucleic Acids Res.* 1975, 2, 1653–1668.
115. Amort, T.; Soulière, M.F.; Wille, A.; Jia, X.-Y.; Fiegl, H.; Wörle, H.; Micura, R.; Lusser, A. Long Non-Coding RNAs as Targets for Cytosine Methylation. *RNA Biol.* 2013, 10, 1002–1008.
116. Aguilo, F.; Li, S.; Balasubramaniyan, N.; Sancho, A.; Benko, S.; Zhang, F.; Vashisht, A.; Rengasamy, M.; Andino, B.; Chen, C.; et al. Deposition of 5-Methylcytosine on Enhancer RNAs Enables the Coactivator Function of PGC-1 α . *Cell Rep.* 2016, 14, 479–492.
117. David, R.; Burgess, A.; Parker, B.; Li, J.; Pulsford, K.; Sibbritt, T.; Preiss, T.; Searle, I.R. Transcriptome-Wide Mapping of RNA 5-Methylcytosine in Arabidopsis MRNAs and Noncoding RNAs. *Plant. Cell* 2017, 29, 445–460.
118. Reid, R.; Greene, P.J.; Santi, D.V. Exposition of a Family of RNA m(5)C Methyltransferases from Searching Genomic and Proteomic Sequences. *Nucleic Acids Res.* 1999, 27, 3138–3145.
119. Goll, M.G.; Kirpekar, F.; Maggert, K.A.; Yoder, J.A.; Hsieh, C.-L.; Zhang, X.; Golic, K.G.; Jacobsen, S.E.; Bestor, T.H. Methylation of TRNAAsp by the DNA Methyltransferase Homolog Dnmt2. *Science* 2006, 311, 395–398.
120. Bourgeois, G.; Ney, M.; Gaspar, I.; Aigueperse, C.; Schaefer, M.; Kellner, S.; Helm, M.; Motorin, Y. Eukaryotic RRNA Modification by Yeast 5-Methylcytosine-Methyltransferases and Human Proliferation-Associated Antigen P120. *PLoS ONE* 2015, 10, e0133321.
121. Tuorto, F.; Liebers, R.; Musch, T.; Schaefer, M.; Hofmann, S.; Kellner, S.; Frye, M.; Helm, M.; Stoecklin, G.; Lyko, F. RNA Cytosine Methylation by Dnmt2 and NSun2 Promotes TRNA Stability and Protein Synthesis. *Nat. Struct. Mol. Biol.* 2012, 19, 900–905.
122. Schosserer, M.; Minois, N.; Angerer, T.B.; Amring, M.; Dellago, H.; Harreither, E.; Calle-Perez, A.; Pircher, A.; Gerstl, M.P.; Pfeifenberger, S.; et al. Methylation of Ribosomal RNA by NSUN5 Is a Conserved Mechanism Modulating Organismal Lifespan. *Nat. Commun.* 2015, 6, 6158.
123. Liu, R.-J.; Long, T.; Li, J.; Li, H.; Wang, E.-D. Structural Basis for Substrate Binding and Catalytic Mechanism of a Human RNA:M5C Methyltransferase NSun6. *Nucleic Acids Res.* 2017, 45, 6684–6697.
124. Schaefer, M.; Pollex, T.; Hanna, K.; Tuorto, F.; Meusburger, M.; Helm, M.; Lyko, F. RNA Methylation by Dnmt2 Protects Transfer RNAs against Stress-Induced Cleavage. *Genes Dev.* 2010, 24, 1590–1595.
125. Xing, J.; Yi, J.; Cai, X.; Tang, H.; Liu, Z.; Zhang, X.; Martindale, J.L.; Yang, X.; Jiang, B.; Gorospe, M.; et al. NSun2 Promotes Cell Growth via Elevating Cyclin-Dependent Kinase 1 Translation. *Mol. Cell. Biol.* 2015, 35, 4043–4052.

126. Tang, H.; Fan, X.; Xing, J.; Liu, Z.; Jiang, B.; Dou, Y.; Gorospe, M.; Wang, W. NSun2 Delays Replicative Senescence by Repressing P27 (KIP1) Translation and Elevating CDK1 Translation. *Aging* 2015, 7, 1143–1155.
127. Li, Q.; Li, X.; Tang, H.; Jiang, B.; Dou, Y.; Gorospe, M.; Wang, W. NSUN2-Mediated M5C Methylation and METTL3/METTL14-Mediated M6A Methylation Cooperatively Enhance P21 Translation. *J. Cell. Biochem.* 2017, 118, 2587–2598.
128. Sun, Z.; Xue, S.; Zhang, M.; Xu, H.; Hu, X.; Chen, S.; Liu, Y.; Guo, M.; Cui, H. Aberrant NSUN2-Mediated m⁵C Modification of H19 LncRNA Is Associated with Poor Differentiation of Hepatocellular Carcinoma. *Oncogene* 2020, 39, 6906–6919.
129. Hussain, S.; Sajini, A.A.; Blanco, S.; Dietmann, S.; Lombard, P.; Sugimoto, Y.; Paramor, M.; Gleeson, J.G.; Odom, D.T.; Ule, J.; et al. NSun2-Mediated Cytosine-5 Methylation of Vault Noncoding RNA Determines Its Processing into Regulatory Small RNAs. *Cell Rep.* 2013, 4, 255–261.
130. Van Haute, L.; Dietmann, S.; Kremer, L.; Hussain, S.; Pearce, S.F.; Powell, C.A.; Rorbach, J.; Lantaff, R.; Blanco, S.; Sauer, S.; et al. Deficient Methylation and Formylation of Mt-TRNA Met Wobble Cytosine in a Patient Carrying Mutations in NSUN3. *Nat. Commun.* 2016, 7, 12039.
131. Metodiev, M.D.; Spåhr, H.; Polosa, P.L.; Meharg, C.; Becker, C.; Altmueller, J.; Habermann, B.; Larsson, N.-G.; Ruzzenente, B. NSUN4 Is a Dual Function Mitochondrial Protein Required for Both Methylation of 12S rRNA and Coordination of Mitochondrial Assembly. *PLoS Genet.* 2014, 10, e1004110.
132. Yang, Y.; Wang, L.; Han, X.; Yang, W.-L.; Zhang, M.; Ma, H.-L.; Sun, B.-F.; Li, A.; Xia, J.; Chen, J.; et al. RNA 5-Methylcytosine Facilitates the Maternal-to-Zygotic Transition by Preventing Maternal mRNA Decay. *Mol. Cell* 2019, 75, 1188–1202.e11.
133. Chen, X.; Li, A.; Sun, B.-F.; Yang, Y.; Han, Y.-N.; Yuan, X.; Chen, R.-X.; Wei, W.-S.; Liu, Y.; Gao, C.-C.; et al. 5-Methylcytosine Promotes Pathogenesis of Bladder Cancer through Stabilizing mRNAs. *Nat. Cell Biol.* 2019, 21, 978–990.
134. Flores, J.V.; Cordero-Espinoza, L.; Oeztuerk-Winder, F.; Andersson-Rolf, A.; Selmi, T.; Blanco, S.; Taylor, J.; Dietmann, S.; Frye, M. Cytosine-5 RNA Methylation Regulates Neural Stem Cell Differentiation and Motility. *Stem Cell Rep.* 2016, 8, 112–124.
135. Trixl, L.; Amort, T.; Wille, A.; Zinni, M.; Ebner, S.; Hechenberger, C.; Eichin, F.; Gabriel, H.; Schoberleitner, I.; Huang, A.; et al. RNA Cytosine Methyltransferase Nsun3 Regulates Embryonic Stem Cell Differentiation by Promoting Mitochondrial Activity. *Cell. Mol. Life Sci. CMLS* 2018, 75, 1483–1497.
136. Wang, W. mRNA Methylation by NSUN2 in Cell Proliferation. *Wiley Interdiscip. Rev. RNA* 2016, 7, 838–842.

137. Bi, J.; Huang, Y.; Liu, Y. Effect of NOP2 Knockdown on Colon Cancer Cell Proliferation, Migration, and Invasion. *Transl. Cancer Res.* 2019, 8.
138. Hong, J.; Lee, J.H.; Chung, I.K. Telomerase Activates Transcription of Cyclin D1 Gene through an Interaction with NOL1. *J. Cell Sci.* 2016, 129, 1566–1579.
139. Chellamuthu, A.; Gray, S.G. The RNA Methyltransferase NSUN2 and Its Potential Roles in Cancer. *Cells* 2020, 9, 1758.
140. Zhang, Y.; Zhang, X.; Shi, J.; Tuorto, F.; Li, X.; Liu, Y.; Liebers, R.; Zhang, L.; Qu, Y.; Qian, J.; et al. Dnmt2 Mediates Intergenerational Transmission of Paternally Acquired Metabolic Disorders through Sperm Small Non-Coding RNAs. *Nat. Cell Biol.* 2018, 20, 535–540.
141. Cheray, M.; Etcheverry, A.; Jacques, C.; Pacaud, R.; Bougras-Cartron, G.; Aubry, M.; Denoual, F.; Peterlongo, P.; Nadaradjane, A.; Briand, J.; et al. Cytosine Methylation of Mature MicroRNAs Inhibits Their Functions and Is Associated with Poor Prognosis in Glioblastoma Multiforme. *Mol. Cancer* 2020, 19, 36.
142. Carissimi, C.; Laudadio, I.; Loreface, E.; Azzalin, G.; De Paolis, V.; Fulci, V. Bisulfite MiRNA-Seq Reveals Widespread CpG and Non-CpG 5-(Hydroxy)methyl-Cytosine in Human MicroRNAs. *RNA Biol.* 2021.
143. Sajini, A.A.; Choudhury, N.R.; Wagner, R.E.; Bornelöv, S.; Selmi, T.; Spanos, C.; Dietmann, S.; Rappsilber, J.; Michlewski, G.; Frye, M. Loss of 5-Methylcytosine Alters the Biogenesis of Vault-Derived Small RNAs to Coordinate Epidermal Differentiation. *Nat. Commun.* 2019, 10, 2550.
144. Barbieri, I.; Tzelepis, K.; Pandolfini, L.; Shi, J.; Millán-Zambrano, G.; Robson, S.C.; Aspris, D.; Migliori, V.; Bannister, A.J.; Han, N.; et al. Promoter-Bound METTL3 Maintains Myeloid Leukaemia by m⁶A-Dependent Translation Control. *Nature* 2017, 552, 126–131.
145. Rouleau, S.G.; Garant, J.-M.; Bolduc, F.; Bisaillon, M.; Perreault, J.-P. G-Quadruplexes Influence Pri-MicroRNA Processing. *RNA Biol.* 2018, 15, 198–206.
146. Furuichi, Y.; Morgan, M.; Muthukrishnan, S.; Shatkin, A.J. Reovirus Messenger RNA Contains a Methylated, Blocked 5'-Terminal Structure: M-7G(5')Ppp(5')G-MpCp-. *Proc. Natl. Acad. Sci. USA* 1975, 72, 362–366.
147. Furuichi, Y.; LaFiandra, A.; Shatkin, A.J. 5'-Terminal Structure and mRNA Stability. *Nature* 1977, 266, 235–239.
148. Pei, Y.; Shuman, S. Interactions between Fission Yeast mRNA Capping Enzymes and Elongation Factor Spt5. *J. Biol. Chem.* 2002, 277, 19639–19648.
149. Muthukrishnan, S.; Both, G.W.; Furuichi, Y.; Shatkin, A.J. 5'-Terminal 7-Methylguanosine in Eukaryotic mRNA Is Required for Translation. *Nature* 1975, 255, 33–37.

150. Wallace, R.B.; Aujame, L.; Freeman, K.B. Chemical and Physical Properties of Mammalian Mitochondrial Aminoacyl-Transfer RNAs II. Analysis of 7-Methylguanosine in Mitochondrial and Cytosolic Aminoacyl-Transfer RNAs. *Biochim. Biophys. Acta BBA Nucleic Acids Protein Synth.* 1978, 518, 321–325.
151. Choi, Y.C.; Busch, H. Modified Nucleotides in T1 RNase Oligonucleotides of 18S Ribosomal RNA of the Novikoff Hepatoma. *Biochemistry* 1978, 17, 2551–2560.
152. Guy, M.P.; Phizicky, E.M. Two-Subunit Enzymes Involved in Eukaryotic Post-Transcriptional tRNA Modification. *RNA Biol.* 2015, 11, 1608–1618.
153. Zhang, L.-S.; Liu, C.; Ma, H.; Dai, Q.; Sun, H.-L.; Luo, G.; Zhang, Z.S.; Zhang, L.; Hu, L.; Dong, X.; et al. Transcriptome-Wide Mapping of Internal N7-Methylguanosine Methylome in Mammalian Messenger RNA. *Mol. Cell* 2019, 74, 1304–1316.e8.
154. Alexandrov, A.; Martzen, M.R.; Phizicky, E.M. Two Proteins That Form a Complex Are Required for 7-Methylguanosine Modification of Yeast tRNA. *RNA* 2002, 8, 1253–1266.
155. Tian, Q.-H.; Zhang, M.-F.; Zeng, J.-S.; Luo, R.-G.; Wen, Y.; Chen, J.; Gan, L.-G.; Xiong, J.-P. METTL1 Overexpression Is Correlated with Poor Prognosis and Promotes Hepatocellular Carcinoma via PTEN. *J. Mol. Med. Berl. Ger.* 2019, 97, 1535–1545.
156. Pandolfini, L.; Barbieri, I.; Bannister, A.J.; Hendrick, A.; Andrews, B.; Webster, N.; Murat, P.; Mach, P.; Brandi, R.; Robson, S.C.; et al. METTL1 Promotes Let-7 MicroRNA Processing via M7G Methylation. *Mol. Cell* 2019, 74, 1278–1290.e9.
157. Mirihana Arachchilage, G.; Dassanayake, A.C.; Basu, S. A Potassium Ion-Dependent RNA Structural Switch Regulates Human Pre-MiRNA 92b Maturation. *Chem. Biol.* 2015, 22, 262–272.
158. Pandey, S.; Agarwala, P.; Jayaraj, G.G.; Gargallo, R.; Maiti, S. The RNA Stem-Loop to G-Quadruplex Equilibrium Controls Mature MicroRNA Production inside the Cell. *Biochemistry* 2015, 54, 7067–7078.
159. Liu, Y.; Zhang, Y.; Chi, Q.; Wang, Z.; Sun, B. Methyltransferase-like 1 (METTL1) Served as a Tumor Suppressor in Colon Cancer by Activating 7-Methylguanosine (M7G) Regulated Let-7e miRNA/HMGA2 Axis. *Life Sci.* 2020, 249, 117480.

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