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Writers, readers and erasers of RNA modifications in cancer

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ABSTRACT

Although cancer was originally considered a disease driven only by genetic mutations, it has now been proven that it is also an epigenetic disease driven by DNA hypermethylation-associated silencing of tumor suppressor genes and aberrant histone modifications. Very recently, a third component has emerged: the so-called epitranscriptome understood as the chemical modifications of RNA that regulate and alter the activity of RNA molecules. In this regard, the study of genetic and epigenetic disruption of the RNA-modifying proteins is gaining momentum in advancing our understanding of cancer biology. Furthermore, the development of epitranscriptomic anticancer drugs could lead to new promising and unexpected therapeutic strategies for oncology in the coming years.

1. Introduction

Cancer was fundamentally considered a genetic disease. However, it is not until most recently that it has also been recognized as an epigenetic and metabolic disease, beyond genetics. The impairment of metabolic programs in cancer has a deep effect on epigenetic regulation, which contributes to genomic instability and alters the epigenetic landscape. Improved understanding of the common tumor-promoting metabolic preferent pathways in cancer progression and of metabolic plasticity in cancer drug resistance, have revealed promising therapeutic targets based on tumor metabolic and epigenetic vulnerabilities rather than the extreme variation of the genetic profiles of tumours.

A limited repertoire of epigenetic modifications in DNA is documented compared to epitranscriptomic modifications. DNA methylation is the best-characterized epigenetic mechanism. It mainly occurs on cytosines (5 mC, 5hmC, 5 fC, and 5caC) and is the most abundant and stable epigenetic mark in eukaryotes that is closely involved in gene regulation.

In contrast, much less is known about the more than 170 distinct RNA chemical modifications, their roles, and their respective RNA-modifying proteins that deposit, remove, and recognize them on the specific RNA species found. Indeed, the study of the RNA epigenome or epitranscriptome is just the tip of the iceberg [1] and is starting to emerge, revealing the mechanisms and functions of RNA modification biology. In particular, RNA modifications have a broad spectrum of functions in RNA metabolism, including RNA processing [2], splicing [3,4], polyadenylation, editing [5], structure [6], stability [7], localization, translation initiation [8], and gene expression regulation [9].

In the past two decades, remarkable advances in high throughput technologies, such as the Next-Generation Sequencing (NGS) methods, genome-wide DNA methylation profiling, proteomics, and metabolomics, along with the era of collaborations and interdisciplinary research teams, have enabled us to achieve a more complete understanding of tumor biology and to accelerate biomedical research. Thus, the integration of cancer multi-omics approaches and datasets is likely to reflect the biological complexity of cancer biology (Fig. 1). Moreover, the discovery of the epitranscriptome revealed another omic layer and a new dimension of gene expression regulation, the study of which is beginning to elucidate the complex orchestration of the gene expression programs and the roles of RNA modification pathways in cancer.

Within the last ten years, the field of traditional cancer drug discovery, which has mainly focused on oncogenic drivers, has brought about major advances in clinical oncology. However, in many cases, patients ultimately acquire cancer drug resistance, which often arises as

Abbreviations: RMPs, RNA-Modifying Proteins; NSCLC, Non-Small Cell Lung Cancer; AML, Acute Myeloid Leukemia; NGS, Next-Generation Sequencing; m6A, N6-Methyladenosine; METTL, Methyltransferase-like

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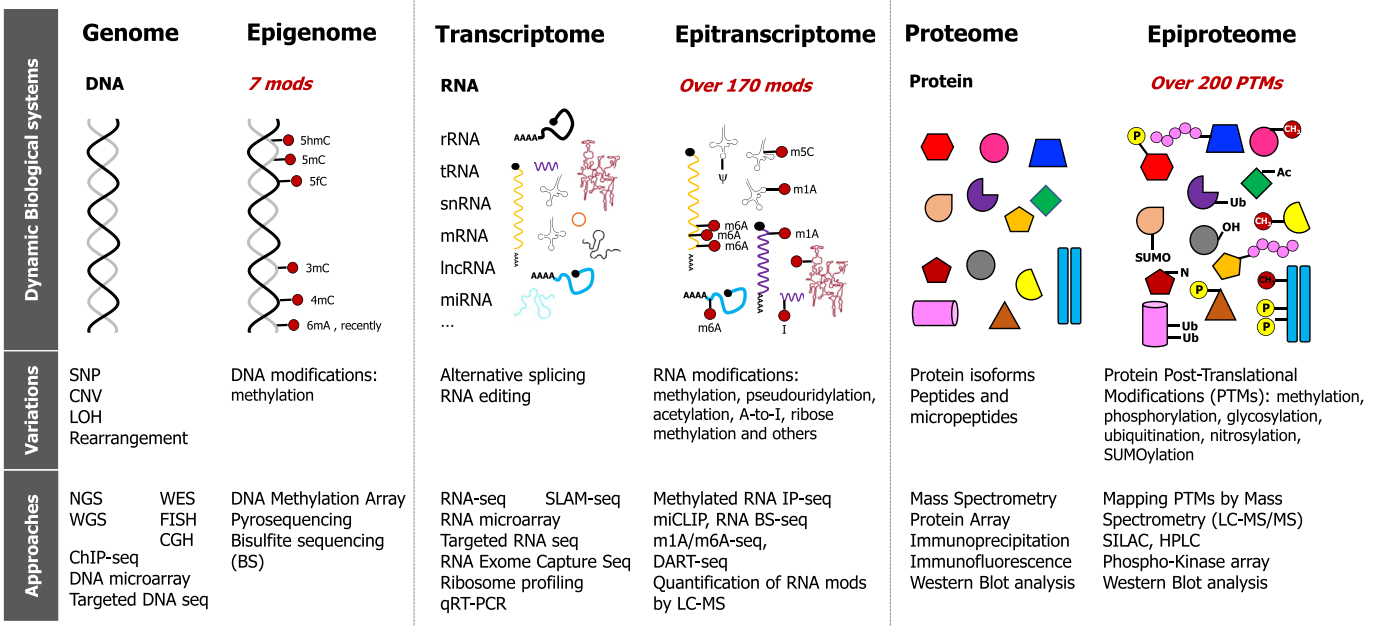

Fig. 1. Linking "omic" approaches to cancer: seeking a comprehensive picture of tumor biology. Multi-omics from the genome, epigenome, transcriptome, epitranscriptome, proteome, and epiproteome.

a consequence of the epigenetic and metabolic plasticity of cancer cells [10]. Therefore, because little is currently known about the development of epigenetic cancer drugs, the RNA-modifying proteins could represent a promising new class of anticancer target for drug discovery, to better leverage advances in cancer treatment and to improve patient outcomes.

2. Proteins involved in RNA chemical modifications

The epitranscriptome is characterized by over a hundred chemical marks on cellular RNAs that regulate the activities of the transcripts [11]. These RNA modifications are recognized at specific regions of a transcript by "readers" and are catalyzed by effectors capable of depositing and removing them [11]. Collectively, these proteins are known as RNA-modifying proteins (RMPs), in a close analogy to epigenetic regulation mediated by modifications of DNA, histones, and chromatin, known as chromatin-modifying proteins. RMPs fall into three groups: "writers", the enzymes that deposit RNA chemical marks; "erasers", the enzymes that remove them; and "readers", the proteins that selectively recognize and bind to specific RNA chemical modifications. Dysregulation and mutations in RMPs have been associated with human diseases [12], including neurological diseases, cancer, genetic birth defects, obesity, and infertility. The first RMP identified as being involved in human disease was the m6A "eraser" FTO, which was associated with obesity and cancer.

The deposition of chemical modifications onto RNAs is catalyzed by multiprotein writer complexes. The first methyltransferase-like (METTL) gene family member, *METTL3*, was identified in 1994 [13]. METTL3 form a multicomponent methyltransferase complex that transfers a methyl group at the N6 position of the adenosine base (m6A) in specific RNA transcripts (mRNAs and ncRNAs). Methylation is one of the most common modifications in RNA. RNA methyltransferase enzymes catalyze methylation via a methyl synthase mechanism using the ubiquitous methyl donor S-adenosylmethionine (SAM) as a source and cofactor to methylate RNA. They are a well-known and diverse group of "writers" involved in human diseases such as METTL3 in lymphoid malignancies and NSUN5 in glioblastoma. Recent studies suggest, however, that mRNA methylation might require synergy among the member proteins of the methyltransferase complexes for efficient RNA methylation, which could vary depending on the cellular phenotypes and the disease processes in play [14].

Many enzymes have been identified as being RNA methyltransferases, such as METTL, NSUN, TRMT, MePCE, BCDIN3D, ALKBH8, RNMT, and TRMT family of proteins. Examples of non-methyltransferases are DKC1, NAT10, and TRIT1, which are "writers" for RNA modifications pseudouridine (Ψ), N4-acetylcytosine, and N6-isopentenyladenosine, respectively.

Fat mass and obesity-associated protein (FTO) was the first RNA "eraser" discovered in 2011. It was found to demethylate m6A in DNA and RNA, and the methylation at m6A in RNA proved to be reversible and dynamic, leading to the coining of the term epitranscriptome. Another m6A RNA demethylase was subsequently identified, the alpha-ketoglutarate-dependent dioxygenase known as alkb homolog 5 (ALKBH5). In particular, both FTO and ALKBH5 enzymes belong to the same ALKBH family.

Proteins that produce a cellular response by recognizing RNA modifications are known as RNA "readers". The YTH domain proteins are the most well-studied family of RNA "readers" [15]. They bind to m6A-modified mRNA and fulfill several functions: YTHDC1 binds to nascent m6A-methylated mRNA in the nucleus, participating in exon selection during splicing events; YTHDF1 binds to m6A-modified mRNA in the cytoplasm, increasing translation efficiency independent of the m7G cap; on the other hand, YTHDF2 recruits the CCR4-NOT complex to the bound mRNA, increasing rate of decay. Other m6A "readers" are the IGF2BP family of proteins, which increase the stability of the m6A-methylated mRNAs [16]. And m5C "reader" ALYREF recognizes m5C modification in mRNA, promoting its nucleus-to-cytosol export [17].

Unidirectional and nonreversible RNA-editing mechanisms alter the

Table 1
RNA modifications and RNA-modifying proteins related to cancer development.Legend: W: Writer, E: Eraser, R: Reader, TS: Tumor suppressor, Onc: Oncogene.

Nt.	RNA Modification	RNA-modifying proteins	Site-specific position & RNA specie	Associated Cancer	Cancer Ref.
A	m1A	TRMT6 (W)	A58 tRNA-Met	Gastrointestinal Cancer (Onc)	[46]
			mRNA	Gastrointestinal Cancer (Onc)	[46]
		TRMT10C (W)	A9 tRNA mitchondrial	Gastrointestinal Cancer (Onc)	[46]
		TRMT61A (W)	A58 tRNA	Gastrointestinal Cancer (Onc)	[46]
			mRNA	Gastrointestinal Cancer (Onc)	[46]
		ALKBH1 (E)	A58 tRNA	Cervix Cancer (Onc)	[47]
		ALKBH3 (E)	mRNA (5′UTR near Start Codon)	Pancreatic Cancer (Onc)	[48]
				Breast Cancer (Onc)	[49]
				Ovarian Cancer (Onc)	[49]
			A58 tRNA	Cervix Cancer (Onc)	[50]
A	ms2i6A	CDK5RAP1 (W)	A37 tRNA mitochondrial	Breast Cancer (Onc)	[51]
				Melanoma (Onc)	[52]
A	i6A	TRIT1 (W)	A37 tRNA-SelenoCys	Lung Cancer (TS)	[53]
				Gastric Cancer	[54]
A	m6A	METTL3 (W)	mRNA (5′UTR, ORF, 3′UTR)	Endometrial Cancer (TS)	[24]
				Glioblastoma (TS)	[33]
				Breast Cancer (Onc)	[55]
				Hepatocarcinoma (Onc)	[56]
				AML (Onc)	[33]
		FTO (E)	mRNA	Glioblastoma (Onc)	[57]
				Cervix Cancer (Onc)	[58]
				AML (Onc)	[38]
				Melanoma (Onc)	[59]
				Gastric Cancer (Onc)	[60]
				Breast Cancer (Onc)	[30]
		ALKBH5 (E)	mRNA	Pancreatic Cancer (TS)	[61]
				AML (TS)	[32]
				Glioblastoma (Onc)	[62]
				Breast Cancer (Onc)	[63]
		YTHDC2 (R)	mRNA	Colorectal Cancer (Onc)	[64]
		YTHDF2 (R)	mRNA	Pancreatic Cancer (Dual Effect)	[65]
				Hepatocarcinoma (Onc)	[66]
				Prostate Cancer (Onc)	[67]
C	m3C	METTL6 (W)	C32 tRNA-Ser	Breast Cancer (Onc)	[68]
				Lung Cancer (Onc)	[69]
		METTL8 (W)	mRNA	Hepatocarcinoma (TS)	[70]
		ALKBH1 (E)	C32 tRNA	Hepatocarcinoma (Onc)	[70]
			C34 tRNA mitochondrial	Hepatocarcinoma (Onc)	[70]
				Cervix Cancer (Onc)	[47]
		ALKBH3 (E)	C32, C47 tRNA	Cervix Cancer	[50]
C	m5C	NSUN1 (W)	C4447 rRNA-28S	Leukemia (Onc)	[71]
		NSUN2 (W)	C34, C47, C48, C49, C50 tRNA	Ovarian Cancer (TS)	[72]
				Skin Cancer (TS)	[73]
			mRNA	Squamous-Cell Carcinoma (Onc)	[74]
				Breast Cancer (Onc)	[75]
				Bladder Cancer (Onc)	[25]
		NSUN3 (W)	C34 tRNA mitochondrial	Non-Small Cell Lung Cancer	[76]
		NSUN4 (W)	C841 rRNA-12S	Breast and Prostate Cancer	[77]
		NSUN5 (W)	C3782 rRNA-28S	Glioblastoma (TS)	[26]
		DNMT2 (W)	C38 tRNA-Asp	Colorectal Cancer (Onc)	[78]
C	ac4C	NAT10 (W)	C12 tRNA-Leu/Ser	Ovaric Cancer	[79]
			mRNA (ORF)	Hepatocarcinoma	[80]
			C1337 rRNA-18S	Colorectal Cancer (Onc)	[81]
G	m7Gpp(pN)	RNMT (W)	mRNA (5′Cap)	Breast Cancer (Onc)	[82]
		NUDT16 (E)	mRNA (5′Cap)	T-ALL (TS)	[2]
G	m7G	METTL1 (W)	G46 tRNA	Hepatocarcinoma	[83]
			miRNA	Lung Cancer (TS)	[84]
		BUD23 (W)	G1639 rRNA-18S	Metastasis in p53+ tumours (Onc)	[85]
G	m2,2G	TRMT1 (W)	G26 tRNA	Breast Cancer	[86]
G	m2G	TRMT11 (W)	G6, G10, G26 tRNA	Prostate Cancer	[87]
G	Q	TGT (W)	G34 tRNA-Asn/Asp/His/Tyr	T-Cell Lymphoma (TS)	[88]
				Colon Cancer (Onc)	[89]
G	yW (and derivatives)	TYW2 (W)	G37 tRNA-Phe	Head and Neck (Onc)	[90]
				Breast Cancer (Onc)	[91]
U	m5U	TRMT2A (W)	U54 (tRNA)	Breast Cancer (TS)	[92]
U	ncm5U	ELP3 (W)	U34 tRNA-Lys/Gln/Glu	Breast Cancer (Onc)	[93]
U	mcm5U	ELP3 (W)	U34 tRNA-Lys/Gln/Glu	Breast Cancer (Onc)	[93]
		ALKBH8 (W)			
U	mcm5s2U	CTU1 (W)	U34 tRNA-Lys/Gln/Glu	Breast Cancer (Onc)	[93]
				Melanoma (Onc)	[40]
		CTU2 (W)		Breast Cancer (Onc)	[93]
				Melanoma (Onc)	[40]
		ELP3 (W)		Breast Cancer (Onc)	[93]
		ALKBH8 (W)		Breast Cancer (Onc)	[93]

(*continued on next page*)

Table 1 (*continued*)

Nt.	RNA Modification	RNA-modifying proteins	Site-specific position & RNA specie	Associated Cancer	Cancer Ref.
U	D	DUS2 (W)	U20 tRNA	Lung Cancer	[94]
U	Ψ	DKC1 (W)	rRNA (~36 sites in 18S, ~57 sites in 28S)	X-Linked Dyskeratosis congenita	[95]
				Prostate Cancer (Onc)	[96]
				Breast Cancer (Onc)	[97]
				Hepatocarcinoma (Onc)	[98]
				Lung Cancer (Onc)	[99]
Others	Nm	Fibrillarin (W)	rRNA (41 sites in 18S, 67 sites in 28S. U14 and G75 in 5.8S)	Breast Cancer (Onc)	[100]
		HENMT1 (W)	piRNA	Testicular tumours	[101]
Others	m(pN)	BCDIN3D (W)	miRNA (5′Cap)	Breast Cancer (Onc)	[102]
		MePCE (W)	7SK RNA	Breast Cancer (Onc)	[103]
Editing	A-to-I	ADAR1 (W)	mRNA	Hepatocarcinoma (Onc)	[27]
				Colorectal Cancer (Onc)	[104]
				Gastric Cancer (Onc)	[105]
				Esophageal Cancer (Onc)	[28]
				Glioblastoma (Onc)	[106]
				Lung Cancer (Onc)	[5]
			miRNA	Leukemia (Onc)	[107]
		ADAR2 (W)	mRNA	Gastric Cancer (Onc)	[105]
Editing	C-to-U	APOBEC1 (W)	mRNA	Hepatocarcinoma (Onc)	[108]
		APOBEC3G (W)	mRNA	Hepatocarcinoma (Onc)	[109]

RNA modifications: m1A: 1-methyladenosine, ms2i6A: 2-methylthio-N6-isopentenyl-adenosine, i6A: N6-isopentenyladenosine, m6A: N6-methyladenosine, m3C: 3-methylcytosine, m5C: 5-methylcytosine, ac4C: N4-acetylcytosine, m7Gpp(pN): 7-methylguanosine cap, m7G: 7-methylguanosine internal, m2,2G: N2,N2,-dimethylguanosine, m2G: N2-methylguanosine, Q: queuosine, yW et al.: Wybutosine and derivatives, m5U: 5-methyluridine, ncm5U: 5-carbamoyl-methyluridine, mcm5U: 5-methoxycarbonyl-methyluridine, mcm5s2U: 5-methoxycarbonylmethyl-2-thiouridine, D: dihydrouridine, Ψ: pseudouridine, Nm: 2′-O-Methylnucleotide, m(pN): 5′ phosphate monomethylation, A-to-I: Deamination of Adenosine, C-to-U: Deamination of Cytosine. **RNA modifying enzymes:** ADAR1-3: Adenosine Deaminase RNA Specific 1–3, ALKBH1/3/5/8: AlkB Homolog 1/3/5/8, APOBEC1/3G: Apolipoprotein B mRNA Editing Enzyme Catalytic Subunits 1/3G, BCDIN3D: BCDIN3 Domain Containing RNA Methyltransferase, BUD23: RRNA Methyltransferase And Ribosome Maturation Factor, CDK5RAP1: CDK5 Regulatory Subunit Associated Protein 1, CMTR1/2: Cap Methyltransferase 1/2, CTU1/2: Cytosolic Thiouridylase Subunit 1/2, DKC1: Dyskerin Pseudouridine Synthase 1, DNMT2: tRNA Aspartic Acid Methyltransferase 1, DUS2: Dihydrouridine Synthases 2, ELP3: Elongator Acetyltransferase Complex Subunit 3, FTO: FTO Alpha-Ketoglutarate Dependent Dioxygenase, HENMT1: HEN Methyltransferase 1, METTL1/2/3/6/8/14/16: Methyltransferase Like-1/2/3/6/8/16, NAT10: N-Acetyltransferase 10, NSUN1-5: NOP2/Sun RNA Methyltransferase 1–5, NUDT16: Nudix Hydrolase 16, RNMT: RNA Guanine-7 Methyltransferase, TGT: Queuine TRNA-Ribosyltransferase Catalytic Subunit 1, TRIT1: tRNA Isopentenyltransferase 1, TRMT1/2A/2B1/5/6/10C/11/61A/61B/112: tRNA Methyltransferase Subunits, TYW2: tRNA-YW Synthesizing Protein 2 Homolog.

RNA sequences and lead to changes in the transcriptome brought about by RNA-editing enzymes that regulate metabolism. Adenosine-to-inosine (A-to-I) editing, along with pseudouridine and ribose 2′-O-methylation, is one of the most common types of RNA modification in eukaryotes. The conversion of A-to-I is a unidirectional and irreversible modification catalyzed by adenosine deaminases such as ADAR and ADAT family proteins that act on mRNAs and tRNAs, respectively. A-to-I editing has several cellular implications, such as altering enzymatic protein activity, alternative splicing and cellular response to stress conditions as well as regulating the innate immune response and modulating miRNA biogenesis and function. Another kind of RNA editing, known as C-to-U editing, is catalyzed by the cytidine deaminase family of proteins known as AADs (AID/APOBEC).

In summary, the dynamic RNA changes brought about by RNA-modifying enzymes modulate RNA metabolism and functions, thereby affecting cell fate and differentiation. These enzymes involve complex mechanisms and metabolic conditions. As an example, methyltransferase reactions consume 12–13 molecules of ATP (Fig. 3). Thus, the high-energy cost of RNA modification pathways indicates that the RNA-modifying enzymes have important consequences in overall cellular metabolism, suggesting that they have important roles in the progression of several types of human cancer.

3. RNA-modifying proteins and their respective chemical marks in cancer

One of the major discoveries of clinical importance in the field of epitranscriptomics is the identification of coding and noncoding RNA modifications linked to several human diseases, including cancer [18]. Many RNA-modifying enzymes with crucial roles in human diseases have been identified over the past decade, attracting interest from cancer researchers. The time is ripe to face the challenge of understanding and characterizing the mechanisms and roles of RNA-modifying enzymes and their respective RNA modifications.

3.1. RNA modifications linked to cancer

Due to technological limitations, studies performed over recent decades have primarily focused on RNA chemical modifications present in the most highly abundant RNA species (tRNA and rRNA). At present, technological advances in mass spectrometry, transcriptome-wide analysis of RNA modifications by NGS technologies, and antibody immunoprecipitation have enabled the study of several RNA modifications that are present in low-abundance RNA species, such as mRNAs and miRNAs [19].

The first RNA modifications were identified almost 70 years ago. Pseudouridine (Ψ) was the first to be found in RNA, particularly in yeast tRNA [20]. Pseudouridine is the most abundant nucleotide modification in rRNA and tRNA and is also present in mammalian and yeast mRNA. It plays a role in RNA folding and secondary structure, stability and translation, and was the first RNA modification to be linked to cancer [21].

As mentioned earlier, over 170 RNA chemical modifications thus far have been found in different organisms, and over 60 RNA modifications have been identified in eukaryotes (Modomics database: http://modomics.genesilico.pl/) [22]. The role of RNA modifications is not only determined by the incorporation, removal or recognition of RNA marks at selective sites on specific nucleotides of a variety RNA molecules, but also by specific cellular settings, such as cell-context-specific and cell-state-dependent patterns. RNA modifications influence a distinct and broad spectrum of functions in RNA metabolism, including RNA stability, splicing, processing, editing, structure, localization,

translation initiation, and gene regulation. Thus, although the existence of these modifications is well known, the mechanisms and functions of many of them remain largely unknown. Dissecting the functions of RNA modifications is challenging because RNA transcripts are diverse (coding and noncoding), highly structured, relatively short-lived with highly variable half-lives, located in several cellular compartments and amplified through transcription (low- or high-abundance RNAs). Accurate and precise methods are needed to detect and quantify them alongside integrated multi-omics research for a better understanding of their molecular mechanisms and roles. Hence, an exciting new era is emerging to decode the epitranscriptome, a complex layer of RNAs decorated with chemical marks (Fig. 1).

Alteration of RNA modification patterns is well-understood and is associated with various human diseases such as cancer [12]. Table 1 compiles all the RNA modifications and RNA-modifying enzymes that have, to date, been linked to cancer.

One of the most well-studied RNA modifications linked to cancer is N6-methyladenosine (m6A). This modification is reversible and is the most prevalent modified nucleotide found in eukaryotic mRNAs and in low-abundance ncRNA (miRNA), affecting more than 7000 mRNAs in mammalian cells and exerting many regulatory functions affecting RNA metabolism; these include increasing turnover of mRNA through binding to the reader YTHDF2 (Fig. 2B), promoting mRNA translation through binding to YTHDF1, promoting exon inclusion during splicing by binding to YTHDC1, promoting pri-miRNA processing by recruiting hnRNPA2B1 and DGRC8, and regulating transcript nuclear export. Many new functions of m6A are still being discovered. Depending on the cancer cell type, m6A can promote or suppress tumorigenesis. On the one hand, a high amount of m6A mark promotes the translation of key oncogenic drivers such as MYC, retaining pluripotency attributes and blocking cell differentiation in Acute Myeloid Leukemia (AML) cells [23], but on the other hand, the low amount of m6A is also associated with oncogenic functions, downregulating the expression of *PHLPP2*, a negative regulator of AKT, and thereby enhancing tumorigenesis in endometrial cancer cells [24]. Thus, the m6A role in cancer progression depends entirely on the cell type and mRNA affected.

Another significant RNA modification is 5-methylcytosine (m5C), which is present in many types of RNA, including mRNA, rRNA, tRNA and other types of ncRNA. Similar to the m6A mark, m5C acts as an oncogene and tumor suppressor. For example, the enrichment of the methyl mark m5C in mRNAs of certain oncogenes promotes bladder cancer progression through the stabilization of multiple mRNA transcripts including *HDGF* and *RAB11* [25]. More recently, it was reported that the loss of m5C mark in the position C3782 of 28S rRNA leads to glioblastoma progression by epigenetic silencing of *NSUN5*, associated with depletion of global protein synthesis and a shift of the translational profile to a more stress-resistant phenotype [26] (Figs. 2C and 3).

Inosine is the product of the enzymatic deamination of adenosine and is a highly conserved RNA-editing mechanism that changes the encoded information of RNA, since inosine preferentially pairs with cytidine instead of thymine. This modification occurs only in double-stranded regions of mRNA, tRNA, rRNA, and miRNAs. In mRNA, inosine can recode a protein-coding mRNA sequence and alter splice sites, while in ncRNA, it alters nRNA structure and can thereby alter the capacity to bind to other molecules. Impaired editing of key transcripts can lead to certain types of cancer, in which highly edited *NEIL1* and miR-381 transcripts enhance the growth of the Non-Small-Cell Lung Cancer (NSCLC) A459 cells [5].

An important number of RNA modifications related to cancer affect the wobbling and dangling positions of tRNAs (bases 34 and 37, respectively). These two positions can harbor many different types of modifications, which facilitate the decoding of multiple synonymous mRNA codons and restrict pairing with non-cognate codons. More precisely, defects in tRNAs modifications at position 34 (queuosine, mcm5s2U, m5C, and m3C), and position 37 (wybutosine and derivatives, N6-isopentenyladenosine, and ms2i6A), are related with translational shifts that may lead to cancer progression (summarized in Table 1 and Fig. 2A).

There are many other types of RNA modifications related to cancer progression. However, they are not all described in this review. In brief, the deposition or removal of RNA modification in various RNA species regulates a broad spectrum of RNA regulatory processes that results in the regulation of a specific sets of genes. Thus, the molecular destiny of any given RNA transcript is determined by the context of the RNA molecule and the RNA effector enzymes in question. The crucial factors that determine RNA modification metabolism are subcellular localization of both RNAs and RNA-modifying proteins, the number of transcripts of specific cellular RNAs, the various types of RNAs, the folding and structure of RNAs, RNA-protein interactions, and responses to stress stimuli such DNA and RNA damage [11]. Remarkably, defects in any of these processes may lead to cancer progression.

3.2. RNA-modifying enzymes and their RNA modifications associated with cancer

The number of RNA-modifying enzymes is steadily increasing and accounts for about 350 enzymes (Modomics database) [22], opening up new lines of research in the field of epitranscriptomics. Gene amplifications and mutations of RMPs have been reported in cancer [12], demonstrating that alterations in these enzymes are associated with tumor initiation and progression, metastasis, and cancer drug resistance.

The examples of RNA-modifying enzymes implicated in cancer are shown and listed in Table 1, containing the RNA modification enzymes linked to a specific RNA chemical modifications and the related cancer types. The most relevant findings of RNA-modifying enzymes are summarized below with a special focus on “writers” and “erasers”.

The gene amplification of RNA-editing enzyme ADAR1 is associated with lung [5], liver [27] and esophageal cancers [28], as well as chronic myelogenous leukemia [29]. In particular, ADAR1 promotes lung cancer through A-to-I editing of coding *NEIL1* mRNA and non-coding miRNA miR-381 [5].

As an example of RNA “writers” and “erasers”, it has been documented that the overexpression of the RNA-modifying enzymes FTO [30], METTL3 [31], and NSUN2 [26 promotes pathogenesis through stabilizing specific sets of mRNAs in breast cancer, AML, and bladder cancer, respectively (Fig. 3). Furthermore, the loss of ALKBH5 [32] in AML and METTL3 [33] and NSUN5 [26] in glioblastoma promotes disease progression. Additionally, dysregulation of RNA readers also has implications in cancer progression. For m6A readers, YTHDC2 has been implicated in colorectal cancer and YTHDF2 dysregulation is related to pancreatic, hepatic, and prostate cancers (Table 1).

Paradoxically, some RNA-modifying enzymes might exhibit both oncogenic and tumor suppressors functions. For instance, m6A methyltransferase METTL3 was reported to have dual roles in cancer, acting as an oncogene in AML, breast, and liver cancers, and as a tumor suppressor in glioblastoma and endometrial cancers. Analogously, ALKBH5 and TGT were identified to have similar dual roles as oncogenes and tumor suppressors in different types of cancer, indicating that the role of RNA-modifying enzymes is cell-type-specific and tissue-context-dependent (see Fig. 2 and Table 1 for more details). Moreover, some studies focused on understanding the role in cancer of m6A and its associated enzymes have unexpectedly indicated that m6A may enhance oncogenesis, yet in other instances may inhibit cell proliferation and transformation. In particular, METTL3 as methyltransferase of m6A was identified as an oncogene in AML and demonstrated that the overexpression of wild-type METTL3 inhibits cell differentiation and increases cell growth through its ability to catalyze the deposition of m6A and enhance the translational activation of *C-MYC, BCL2* and *PTEN* mRNA transcripts in AML cells [31]. However, another study showed that m6A demethylase FTO [34] is highly expressed in certain subtypes of AMLs and plays a critical oncogenic role in AML by

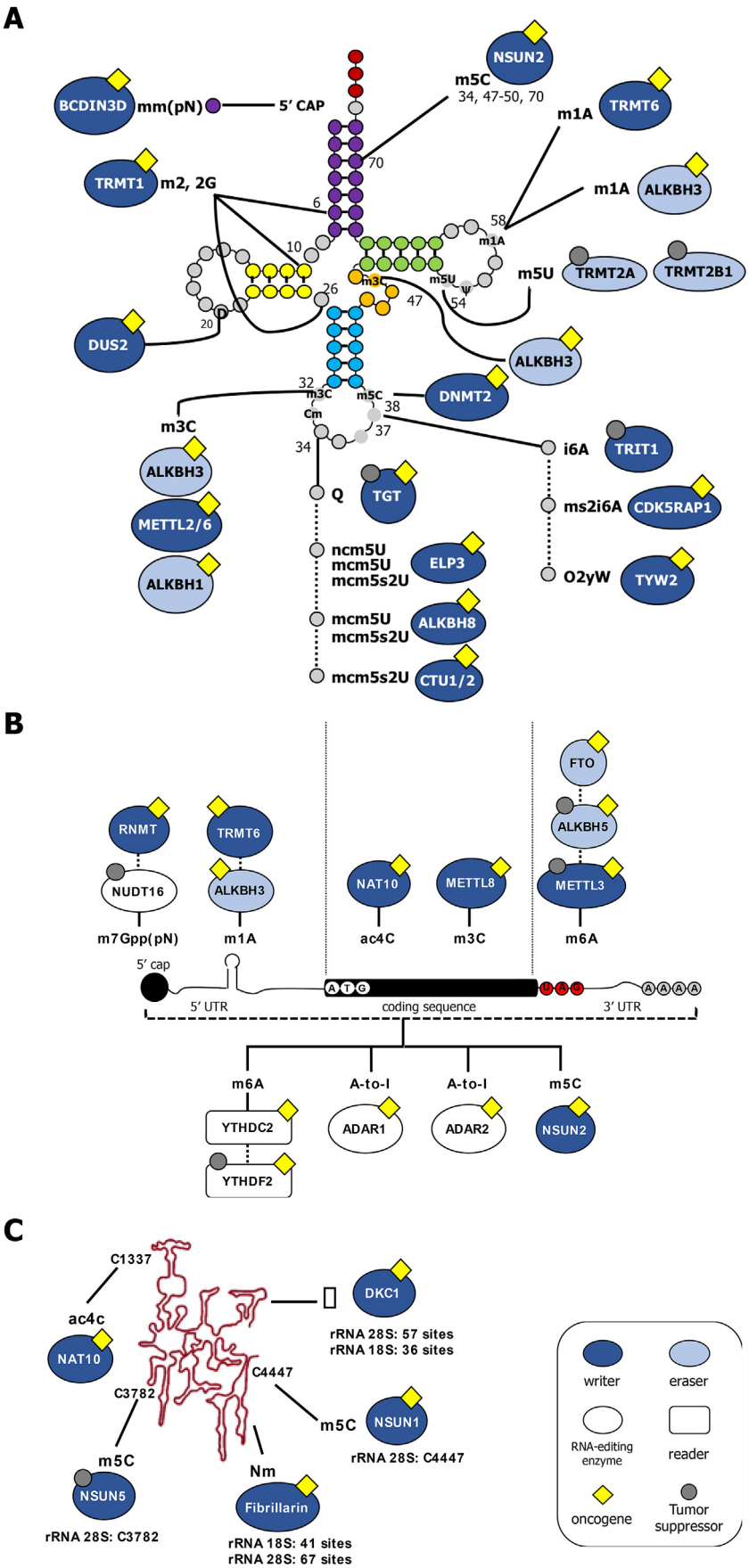

Fig. 2. Landscape of tRNA, rRNA, and mRNA modifications associated with RNA modifications, and their respective RNA-modifying proteins associated with cancer. A. Schematic representation of the tRNA molecule with the specific location and types of predominant RNA modifications and their respective RNA-modifying proteins involved in cancer. B. mRNA. C. rRNA.

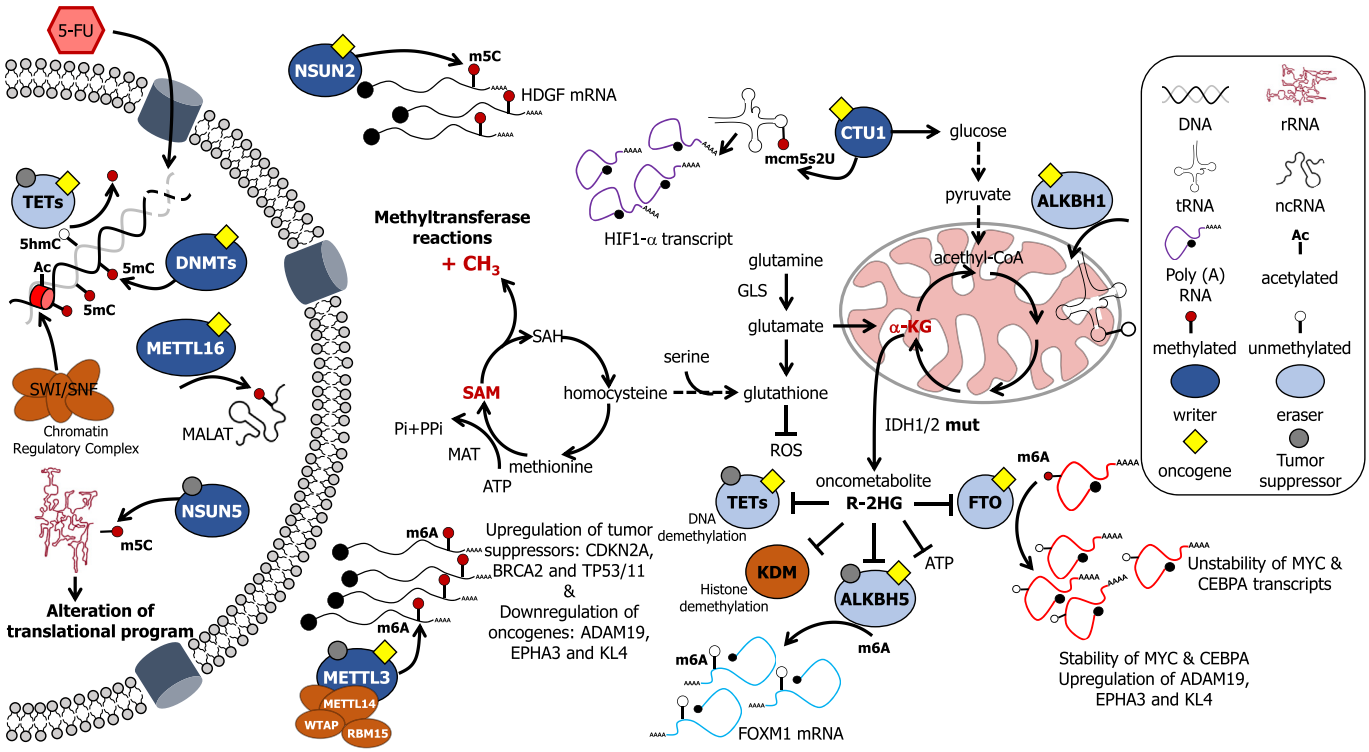

Fig. 3. Crosstalk between the epitranscriptome and metabolism in cancer initiation and progression. Epigenetic RNA modification pathways in cancer representing the effect of RNA-modifying enzymes and their respective RNA modifications of the expression of genes involved in metabolism and tumorigenesis. Illustration of RNA "writers" such as METTL3, NSUN2, NSUN5, and CTU1, and "erasers" such as FTO, ALKBH5, and ALKBH1.

reducing the amount of m6A in ASB2 and RARA mRNA transcripts. Nevertheless, FTO activity as an m6A "eraser" is still a contentious issue. Work led by Jaffrey has revealed that FTO preferentially demethylates m6Am (N6,2′-O-dimethyladenosine) present in 5′-caps of mRNAs, rather than m6A [35]. Moreover, many m6A detection technologies inadvertently map m6Am modifications as m6A sites. Thus, the concept of reversible m6A is still controversial, since the biological role and evidence of its removal are not fully understood, adding a layer of complexity when trying to associate m6A with cancer progression.

Overall, evidence accumulated to date reveals that the roles of RNA-modifying enzymes differ between different cell subtypes, suggesting that the depletion of m6A in different subtypes of AML induces cellular differentiation and apoptosis [31], whereas in other subtypes of AML m6a depletion upregulates oncogenes that promote cell proliferation and suppress apoptosis [34]. Furthermore, recent discoveries emphasize the importance of the different cellular and molecular contexts in which RNA modifications are regulated. RNA-modifying enzymes modulate RNA chemical marks at specific regions of any given RNA molecule in a context-dependent manner, resulting in different cell fate decisions and functional outcomes. First, subcellular localization of enzymes modulates accessibility to substrates and substrate preference. Second, localization and expression of RNA-modifying enzymes can be regulated by their post-translational modifications, contributing to the spatial regulation of the enzymes [36]. Third, the expression patterns of some RNA-modifying enzymes differ between tissues and interact with different protein interaction partners, resulting in the participation of different signaling pathways. And fourth, the expression of a specific set of RNAs could be modulated by environmental signals, hypoxia, nutrient levels, cytokine signaling, and in response to stimuli, DNA damage [37], and stress. For more details, these findings have recently been extensively reviewed in depth elsewhere [11].

Altogether, RNA-modifying enzymes linked to cancer are crucial regulators of cell fate decisions and cell differentiation by regulating RNA metabolism and expression of specific genes required for cell proliferation, transformation, invasion, and cancer drug resistance. The impact of RNA modifications and their enzymes affects almost every aspect of RNA fate and is dependent on cell and tissue-type-specific context, subcellular localization of the enzymes, responses to several stimuli such as DNA damage, signal transduction pathways, and the availability of energy sources, metabolic substrates, and oxygen.

Henceforth, recent cancer epitranscriptomics research is focused on the complex cellular context and heterogeneity of RNA molecules and cancer, in order to better understand the potential roles of RNA modifications and their enzymes and explore RNA-modifying enzymes as potential anticancer drug targets.

4. Interplay between metabolism and epitranscriptomics in cancer

The impairment of metabolic programs in cancer has remarkable effects on epigenetic regulation, contributing to genomic instability. Metabolites, cosubstrates, and cofactors such as iron, oxygen, ATP, acetyl-CoA, SAM, and 2-oxoglutarate have a direct impact on the activity of the epigenetic modification enzymes. These epigenetic enzymes that transfer methyl, acetyl, and other groups are involved in chemical modifications that influence gene regulation, RNA metabolism, and chromatin remodeling (Fig. 3).

Cancer cells metabolize glucose, lactate, pyruvate, and glutamine at a higher rate than normal cells. In particular, many tumor cells exhibit an altered Krebs or tricarboxylic acid (TCA) cycle, thereby causing an accumulation of certain metabolites such as alpha-ketoglutarate (α-KG) that increases the activity of the α-KG-dependent enzymes such as those of the TET and ALKBH protein families. Thus, the metabolites affect the cancer epigenetic landscape.

The metabolic reprogramming of tumor cells not only enables cells to adapt to extreme environmental conditions such as stress and hypoxia, but also induces metabolic plasticity and heterogeneity by regulating gene expression, cellular differentiation, and the tumor

microenvironment. Crosstalk between the complex cancer-associated metabolic reprogramming and cancer epigenetics and epitranscriptomics has a critical role in tumorigenesis and a deeper understanding of the metabolism and epitranscriptomics in cancer could improve clinical outcomes in cancer treatment [12].

α-KG is an essential endogenous intermediary metabolite in the Krebs cycle that regulates DNA "erasers" and histone modifiers as well as RNA-modifying enzymes such as ALKBH family members (FTO and ALKBH5) (Fig. 3).

R-2-hydroxyglutarate, also known as the oncometabolite R-2HG, is accumulated at high concentrations by the mutant isocitrate dehydrogenases 1/2 (IDH1/2) in tumor cells such as gliomas of grade II-III, secondary glioblastoma, and AML. Also, R-2HG is produced by other enzymes and can cause metabolic alterations in cells lacking IDH mutations. R-2HG and α-KG share a similar structure, resulting in R-2HG binding to the same site place as α-KG. Thus, R-2HG acts as a competitive inhibitor of α-KG, binding to the active sites of specific enzymes such as α-KG-dependent dioxygenases. As previously discussed, m6A "eraser" FTO, a homolog of the Fe(II) α-KG acid-dependent ALKBH family dioxygenase, is overexpressed in AML. In particular, the FTO demethylase plays a role as an oncogene, responsible for the demethylation of m6A on ASB2 and RARA mRNA transcripts and ultimately promoting cell transformation and leukemogenesis [34]. It has been documented that inhibition of the FTO demethylase by the oncometabolite R-2HG suppresses leukemia progression by stabilizing *MYC/CEBPA* transcripts [38] (Fig. 3). Different findings indicate, on the one hand, that R-2HG acts as an oncometabolite in certain subtypes of cancer harboring IDH1/2 mutations and, on the other hand, that R-2HG inhibits FTO and promotes antitumor effects. Again, these findings demonstrate the importance of taking specific contextual factors into consideration local contexts such as the type of enzyme, the subcellular localization of the enzyme and the cell-type specific context.

To date, a total of 36 RNA methyltransferases have been identified in humans, according to the MODOMICS database. These enzymes catalyze methylation via a methyl synthase mechanism, using SAM as the source and cofactor to methylate RNA molecules, and importantly, they are a well-known broad group of "writers" involved in human diseases such as cancer [12]. In particular, m6A "writer" METTL3 is the best-characterized RNA methyltransferase enzyme associated with cancer, regulating m6A in mRNAs of critical oncogenes and tumor suppressors in a cell-type-specific manner. The majority of human RNA methyltransferases (over 27 enzymes) are linked to cancer. Some examples are ALKBH8, BCDIN3D, BUD23, CDK5RAP1, DNMT2, ELP3, Fibrillarin, HENMT1, MePCE, METTL1, 3, 6, 8 and 16, NSUN1-5, RNMT, TRMT1, TRMT10C, 11, 2A, 6, 61A and 61B. METLL16 is an informative example of an important class of SAM-dependent RNA methyltransferases: METTL16 has been reported to interact with cancer-associated lncRNA MALAT1 [39], which transcriptionally regulates the expression of MAT2A mRNA, which encodes the SAM synthetase (Fig. 3). Under SAM-limiting conditions, METTL16 promotes MAT2A splicing, indicating that cells control SAM homeostasis by regulating SAM synthetase gene expression.

Hypoxia in cancer leads to the inhibition of biosynthetic reactions that require oxygen, switching from oxidative phosphorylation to anaerobic glycolysis, resulting in ER stress induction and apoptosis in tumor cells. For example, it has been reported that the U34 enzymes that catalyze modification of wobble uridine 34 tRNA promote glycolysis, survival, and resistance to melanoma therapy through the maintenance of a high amount of HIF1-α protein [40]. In particular, U34 enzymes CTU1 and CTU2, play a central role in the 2-thiolation of mcm5S2U modification on tRNA and were found to be upregulated in BRAF mutant melanoma, conferring survival and drug resistance. Interestingly, NRAS mutant melanoma cells exhibited upregulation of *HIF1-α* mRNA transcripts and were sensitive to the silencing of U34 enzymes, indicating that the dependence on U34 enzymes in melanoma relies mostly on their metabolic status, rather than mutational status (Fig. 3). In summary, RNA-modifying enzymes have been associated with metabolic and translational reprogramming that ensures enhanced glycolytic metabolism in cancer. Furthermore, the depletion of the mcm5s2U "writers" (CTU1 and 2) resensitized drug-resistant melanoma cells, indicating their potential as anticancer drug targets.

Taken together, RNA-modifying enzymes are susceptible to changes in the concentrations of cosubstrates and cofactors such as SAM, 2-oxoglutarate, ATP, and acetyl-CoA and are crucial regulators of RNA and cell metabolism, thereby altering metabolic pathways such as glycolysis, mitochondrial respiratory chain complex activity, and hypoxia (see examples above). In the past decade, it has been reported that aberrant RNA modifications patterns and RNA-modifying enzymes were involved in cancer initiation and progression, and also in drug resistance. Thus, RNA modifications and RNA-modifying enzymes have been demonstrated to affect multiple aspects of RNA metabolism and function, resulting in altered cell fate and differentiation in response to cellular signaling and environmental stimuli such as hypoxia, stress, and DNA damage [41]. Regarding the latter, numerous DNA damaging drugs such as the classical DNA-damaging chemotherapy, not only damage and modify DNA, but also affect RNA, opening up a promising new avenue for chemotherapy response prediction [18].

Although the emergent field of the development of epitranscriptomic drugs is still in its infancy, technological advancement has been essential in significantly accelerating advances in our understanding of epitranscriptomics that have been made in recent years, indicating that RNA-modifying enzymes may be considered as novel druggable targets for cancer treatment. Therefore, it is crucial to investigate the molecular mechanisms and the roles of RNA modifications and RNA-modifying enzymes in the appropriate cellular contexts in order to better leverage advances in cancer treatment.

5. Discussion

5.1. Challenges in mapping RNA modifications and emerging applications

Decoding the complex layer of the epitranscriptome has, up to now, been very challenging. Recent technological advances have, in the past decade, enabled mapping of certain RNA modifications such as m6A and pseudouridine. For instance, the pioneering detection of the m6A modification was done by antibody-based Next Generation Sequencing, which allows the capture and sequencing of immunoprecipitated RNA targets [42]. Some mapping approaches presented several limitations such as false-positive mapping results, lack of detection of low-abundance modifications, possible contaminations of RNA species, low antibody specificity, and Dimroth rearrangement (conversion of m1A to m6A). Currently, the major challenges are the quantification of RNA modifications directly at modification sites with higher resolution, precision, and sensitivity as well as improving our understanding of the molecular mechanisms and functional roles of RNA modifications and RNA-modifying enzymes. However, technology is rapidly progressing and novel methodologies for more precise and sensitive detection, imaging and quantification of RNA modifications are emerging, such as deamination adjacent to RNA modification targets (DART-seq), phage display antibody technology and direct sequencing through nanopores [12] (third-generation sequencing technologies), and fluorescent nucleobases [43] will enable the global detection and determination of stoichiometries of RNA modifications, even for RNA modifications at very low stoichiometries, as well as the study of concomitant and combinatorial RNA modification profiles.

5.2. Clinical oncology impact

One of the major discoveries made in the field of epitranscriptomics with regard to their clinical implications is the identification of mRNA and noncoding RNA modifications linked to human diseases including, but not limited to metabolic and neurological diseases and cancer.

The interplay between complex cancer-associated metabolic reprogramming and cancer epigenetics and epitranscriptomics has a critical role in tumorigenesis. A deeper understanding of the crosstalk between metabolism and epitransciptomics in cancer is necessary to elucidate the roles of RNA modifications and RNA-modifying enzymes and to understand their contributions in this disease.

In the past 20 years, it has been documented that DNA methylation, histone modification, nucleosome remodeling, and noncoding RNAs are important for biological processes, regulating cell differentiation, division, and development. For example, post-translational modifications of proteins and chromatin modifications are frequently dysregulated in cancer and have been used as successful epigenetic drug targets. In line with this, RNA-modifying enzymes as regulators of RNA metabolism and gene expression indicate that targeting RNA-modifying enzymes could also be a promising therapeutic strategy to improve cancer treatment and patient outcomes. Furthermore, new research works have very recently appeared in the literature that link the inhibition of certain RMPs, such as “reader” YTHDF1 [44] and RNA-editing enzyme ADAR1 [45], with a better response to immunotherapeutic agents. Thus, RNA-modifying proteins may be important for cancer drug discovery as emerging anticancer drug targets.

CRediT authorship contribution statement

Rosaura Esteve-Puig: Writing - original draft. **Alberto Bueno-Costa:** Writing - original draft. **Manel Esteller:** Writing - original draft.

Declaration of competing interest

ME is a consultant of Ferrer International and Quimatryx. The other authors declare that they have no conflict of interest.

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