



Writers, readers and erasers of RNA modifications in cancer

Rosaura Esteve-Puig^{a,1}, Alberto Bueno-Costa^{a,1}, Manel Esteller^{a,b,c,d,*}

^a Josep Carreras Leukaemia Research Institute (IJC), Badalona, Barcelona, Catalonia, Spain

^b Centro de Investigacion Biomedica en Red Cancer (CIBERONC), Madrid, Spain

^c Institutio Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Catalonia, Spain

^d Physiological Sciences Department, School of Medicine and Health Sciences, University of Barcelona (UB), Barcelona, Catalonia, Spain



ARTICLE INFO

Keywords:

Epigenetics
RNA modifications
RNA-Modifying enzymes
RNA-Editing

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

* Corresponding author. Josep Carreras Leukaemia Research Institute (IJC), Carretera de Can Ruti, Camí de les Escoles s/n, 08916, Badalona, Barcelona, Catalonia, Spain.

E-mail address: mesteller@carrerasresearch.org (M. Esteller).

¹ These authors contributed equally to this work.

<https://doi.org/10.1016/j.canlet.2020.01.021>

Received 15 November 2019; Received in revised form 9 January 2020; Accepted 21 January 2020

0304-3835/© 2020 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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 mRNA	Gastrointestinal Cancer (Onc)	[46]		
		TRMT10C (W)	A9 tRNA mitochondrial	Gastrointestinal Cancer (Onc)	[46]		
		TRMT61A (W)	A58 tRNA 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]		
A	ms2i6A	CDK5RAP1 (W)	A58 tRNA	Breast Cancer (Onc)	[49]		
			A37 tRNA mitochondrial	Ovarian Cancer (Onc)	[49]		
				Cervix Cancer (Onc)	[50]		
				Breast Cancer (Onc)	[51]		
				Melanoma (Onc)	[52]		
A	i6A	TRIT1 (W)	A37 tRNA-SelenoCys	Lung Cancer (TS)	[53]		
A	m6A	METTL3 (W)	mRNA (5'UTR, ORF, 3'UTR)	Gastric Cancer	[54]		
				Endometrial Cancer (TS)	[24]		
				Glioblastoma (TS)	[33]		
				Breast Cancer (Onc)	[55]		
				Hepatocarcinoma (Onc)	[56]		
		FTO (E)	mRNA	AML (Onc)	[33]		
				Glioblastoma (Onc)	[57]		
				Cervix Cancer (Onc)	[58]		
				AML (Onc)	[38]		
				Melanoma (Onc)	[59]		
ALKBH5 (E)	mRNA	Gastric Cancer (Onc)	[60]				
		Breast Cancer (Onc)	[30]				
		Pancreatic Cancer (TS)	[61]				
		AML (TS)	[32]				
		Glioblastoma (Onc)	[62]				
YTHDC2 (R)	mRNA	YTHDF2 (R)	mRNA	Breast Cancer (Onc)	[63]		
				Colorectal Cancer (Onc)	[64]		
				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]
		ALKBH3 (E)	C32, C47 tRNA	NSUN1 (W)	C4447 rRNA-28S	Cervix Cancer	[50]
						Leukemia (Onc)	[71]
						Ovarian Cancer (TS)	[72]
						Skin Cancer (TS)	[73]
						Squamous-Cell Carcinoma (Onc)	[74]
NSUN2 (W)	C34, C47, C48, C49, C50 tRNA	mRNA		Breast Cancer (Onc)	[75]		
				Bladder Cancer (Onc)	[25]		
				Non-Small Cell Lung Cancer	[76]		
				Breast and Prostate Cancer	[77]		
				Glioblastoma (TS)	[26]		
DNMT2 (W)	C38 tRNA-Asp	NAT10 (W)	C12 tRNA-Leu/Ser	Colorectal Cancer (Onc)	[78]		
				Ovaric Cancer	[79]		
				Hepatocarcinoma	[80]		
				Colorectal Cancer (Onc)	[81]		
				Breast Cancer (Onc)	[82]		
G	m7Gpp(pN)	RNMT (W)	mRNA (5'Cap)	T-ALL (TS)	[2]		
		NUDT16 (E)	mRNA (5'Cap)				
G	m7G	METTL1 (W)	G46 tRNA	Hepatocarcinoma	[83]		
				miRNA	Lung Cancer (TS)	[84]	
				BUD23 (W)	G1639 rRNA-18S	Metastasis in p53+ tumours (Onc)	[85]
				TRMT1 (W)	G26 tRNA	Breast Cancer	[86]
				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]		
				Breast Cancer (TS)	[92]		
				Breast Cancer (Onc)	[93]		
				Breast Cancer (Onc)	[93]		
U	m5U	TRMT2A (W)	U54 (tRNA)				
		ELP3 (W)	U34 tRNA-Lys/Gln/Glu				
U	mcm5U	ELP3 (W)	U34 tRNA-Lys/Gln/Glu				
		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 hnRNP2B1 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 ncRNA 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

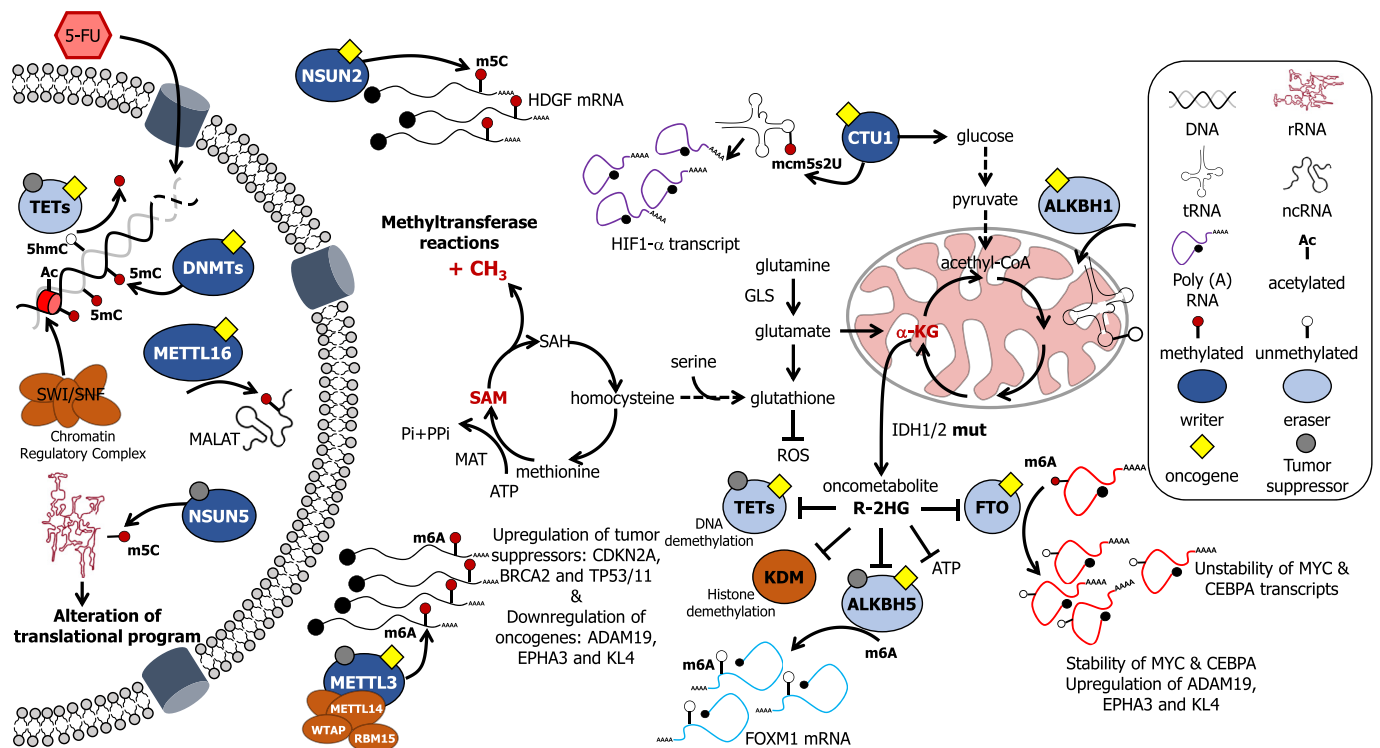


Fig. 3. Crosstalk between the epitranscriptome and metabolism in cancer initiation and progression. Epigenetic RNA modification pathways in cancer representing the effect of RNA-modifying enzymes and their respective RNA modifications of the expression of genes involved in metabolism and tumorigenesis. 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, METTL3, 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 epitranscriptomics 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 Quimatrix. The other authors declare that they have no conflict of interest.

Acknowledgements

We apologize for not referencing relevant work that could not be cited due to a limit of 100 references. We thank CERCA Programme/ Generalitat de Catalunya for institutional support. ABC is a fellow of the Spanish Ministry of Education and Vocational Training, under FPU contract no. FPU17/02423. ME is an ICREA Research Professor. Research by the authors has received funding from the Secretariat for Universities and Research of the Ministry of Business and Knowledge of the Government of Catalonia (2017SGR1080); MCIU/AEI/FEDER, UE (RTI2018-094049-B-I00 and SAF2014-55000) and Olga Torres Foundation.

References

- [1] Y. Saleh, K. Meyer, J. Korlach, I.D. Vilfan, S. Jaffrey, C.E. Mason, The birth of the Epitranscriptome: deciphering the function of RNA modifications, *Genome Biol.* 13 (2012) 175.
- [2] C. Anadón, G. van Tetering, H.J. Ferreira, C. Moutinho, A. Martínez-Cardús, A. Villanueva, M. Soler, H. Heyn, S. Moran, M. Castro de Moura, F. Setien, A. Vidal, E. Genescà, J.M. Ribera, J.F. Nomdedeu, S. Guil, M. Esteller, Epigenetic loss of the RNA decapping enzyme NUDT16 mediates C-MYC activation in T-cell acute lymphoblastic leukemia, *Leukemia* 31 (2017) 1622–1625.
- [3] L. Piqué, A. Martínez de Paz, D. Piñeyro, A. Martínez-Cardús, M. Castro de Moura, P. Llinàs-Arias, F. Setien, J. Gomez-Miragaya, E. Gonzalez-Suarez, S. Sigurdsson, J.G. Jonasson, A. Villanueva, A. Vidal, V. Davalos, M. Esteller, Epigenetic inactivation of the splicing RNA-binding protein CELF2 in human breast cancer, *Oncogene* 38 (2019) 7106–7112.
- [4] E.A. Obeng, C. Stewart, O. Abdel-Wahab, Altered RNA processing in cancer pathogenesis and therapy, *Cancer Discov.* (2019) 2159–8290 candisc CD-19-0399vol. 1.
- [5] C. Anadón, S. Guil, L. Simó-Riudalbas, C. Moutinho, F. Setien, A. Martínez-Cardús, S. Moran, A. Villanueva, M. Calaf, A. Vidal, P.A. Lazo, I. Zondervan, S. Savola, T. Kohno, J. Yokota, L. Ribas de Pouplana, M. Esteller, Gene amplification-associated overexpression of the RNA editing enzyme ADAR1 enhances human lung tumorigenesis, *Oncogene* 35 (2016) 4407–4413.
- [6] J.S. Mugridge, J. Collier, J.D. Gross, Structural and molecular mechanisms for the control of eukaryotic 5′–3′ mRNA decay, *Nat. Struct. Mol. Biol.* 25 (2018) 1077–1085.
- [7] A. Tudek, M. Schmid, T.H. Jensen, Escaping nuclear decay: the significance of mRNA export for gene expression, *Curr. Genet.* 65 (2019) 473–476.
- [8] A.L. Karamyshev, Z.N. Karamysheva, Lost in translation: ribosome-associated mRNA and protein quality controls, *Front. Genet.* 9 (2018) 431.
- [9] I.A. Roundtree, M.E. Evans, T. Pan, C. He, Dynamic RNA modifications in gene expression regulation, *Cell* 169 (2017) 1187–1200.
- [10] M.A. Dawson, T. Kouzarides, Cancer epigenetics: from mechanism to therapy, *Cell* 150 (2012) 12–27.
- [11] H. Shi, J. Wei, C. He, Where, when, and how: context-dependent functions of RNA methylation writers, readers, and erasers, *Mol. Cell.* 74 (2019) 640–650.
- [12] N. Jonkhout, J. Tran, M.A. Smith, N. Schonrock, J.S. Mattick, E.M. Novoa, The RNA modification landscape in human disease, *RNA* 23 (2017) 1754–1769.
- [13] J.A. Bokar, M.E. Rath-Shambaugh, R. Ludwiczak, P. Narayan, F. Rottman, Characterization and partial purification of mRNA N6-adenosine methyltransferase from HeLa cell nuclei. Internal mRNA methylation requires a multi-subunit complex, *J. Biol. Chem.* 269 (1994) 17697–17704.
- [14] S. Schwartz, M.R. Mumbach, M. Jovanovic, T. Wang, K. Maciag, G.G. Bushkin, P. Mertins, D. Ter-Ovanesyan, N. Habib, D. Cacchiarelli, N.E. Sanjana, E. Freinkman, M.E. Pacold, R. Sattija, T.S. Mikkelsen, N. Hacohen, F. Zhang, S.A. Carr, E.S. Lander, A. Regev, Perturbation of m6A writers reveals two distinct classes of mRNA methylation at internal and 5′ sites, *Cell Rep.* 8 (2014) 284–296.
- [15] S. Liao, H. Sun, C. Xu, YTH domain: a family of N6-methyladenosine (m6A) readers, *Dev. Reprod. Biol.* 16 (2018) 99–107.
- [16] H. Huang, H. Weng, W. Sun, X. Qin, H. Shi, H. Wu, B.S. Zhao, A. Mesquita, C. Liu, C.L. Yuan, Y.-C. Hu, S. Hüttelmaier, J.R. Skibbe, R. Su, X. Deng, L. Dong, M. Sun, C. Li, S. Nachtergaele, Y. Wang, C. Hu, K. Ferchen, K.D. Greis, X. Jiang, M. Wei, L. Qu, J.-L. Guan, C. He, J. Yang, J. Chen, Recognition of RNA N6-methyladenosine by IGF2BP proteins enhances mRNA stability and translation, *Nat. Cell Biol.* 20 (2018) 285–295.
- [17] X. Yang, Y. Yang, B.-F. Sun, Y.-S. Chen, J.-W. Xu, W.-Y. Lai, A. Li, X. Wang, D.P. Bhattarai, W. Xiao, H.-Y. Sun, Q. Zhu, H.-L. Ma, S. Adhikari, M. Sun, Y.-J. Hao, B. Zhang, C.-M. Huang, N. Huang, G.-B. Jiang, Y.-L. Zhao, H.-L. Wang, Y.-P. Sun, Y.-G. Yang, 5-methylcytosine promotes mRNA export - NSUN2 as the methyltransferase and ALYREF as an m5C reader, *Cell Res.* 27 (2017) 606–625.
- [18] M. Esteller, P.P. Pandolfi, The epitranscriptome of noncoding RNAs in cancer, *Canc. Discov.* 7 (2017) 359–368.
- [19] V. Davalos, S. Blanco, M. Esteller, SnapShot: messenger RNA modifications, *Cell* 174 (2018) 498–498.e1.
- [20] W.E. Cohn, Some results of the applications of ion-exchange chromatography to nucleic acid chemistry, *J. Cell. Physiol. Suppl.* 38 (1951) 21–40.
- [21] N.A. Fedorov, M.J. Bogomazov, [Urinary excretion of purine bases and pseudouridine normal human and in cancer patients before and after radiotherapy, *Radiobiol. Radiother. (Berl.)* 10 (1969) 605–608.
- [22] P. Boccaletto, M.A. Machnicka, E. Purta, P. Piatkowski, B. Baginski, T.K. Wirecki, V. de Crécy-Lagard, R. Ross, P.A. Limbach, A. Kotter, M. Helm, J.M. Bujnicki, MODOMICS: a database of RNA modification pathways. 2017 update, *Nucleic Acids Res.* 46 (2018) D303–D307.
- [23] H. Weng, H. Huang, H. Wu, X. Qin, B.S. Zhao, L. Dong, H. Shi, J. Skibbe, C. Shen, C. Hu, Y. Sheng, Y. Wang, M. Wunderlich, B. Zhang, L.C. Dore, R. Su, X. Deng, K. Ferchen, C. Li, M. Sun, Z. Lu, X. Jiang, G. Marcucci, J.C. Mulloy, J. Yang, Z. Qian, M. Wei, C. He, J. Chen, METTL14 inhibits hematopoietic stem/progenitor differentiation and promotes leukemogenesis via mRNA m6A modification, *Cell Stem Cell* 22 (2) (2018 Feb 1) 191–205 e9.
- [24] J. Liu, M.A. Eckert, B.T. Harada, S.-M. Liu, Z. Lu, K. Yu, S.M. Tienda, A. Chryplewicz, A.C. Zhu, Y. Yang, J.-T. Skubbe, S.-M. Chen, Z.-G. Xu, X.-H. Leng, X.-C. Yu, J. Cao, Z. Zhang, J. Liu, E. Lengyel, C. He, m6A mRNA methylation regulates AKT activity to promote the proliferation and tumorigenicity of endometrial cancer, *Nat. Cell Biol.* 20 (2018) 1074–1083.
- [25] M. Janin, V. Ortiz-Barahona, M.C. de Moura, A. Martínez-Cardús, P. Llinàs-Arias, M. Soler, D. Nachmani, J. Pelletier, U. Schumann, M.E. Calleja-Cervantes, S. Moran, S. Guil, A. Bueno-Costa, D. Piñeyro, M. Perez-Salvia, M. Rosselló-Tortella, L. Piqué, J.J. Bech-Serra, C. De La Torre, A. Vidal, M. Martínez-Iniesta, J.F. Martín-Tejera, A. Villanueva, A. Arias, I. Cuartas, A.M. Aransay, A.M. La Madrid, A.M. Carcaboso, V. Santa-Maria, J. Mora, A.F. Fernandez, M.F. Fraga, I. Aldecoa, L. Pedrosa, F. Graus, N. Vidal, F. Martínez-Soler, A. Tortosa, C. Carrato, C. Balañá, M.W. Boudreau, P.J. Hergenrother, P. Kötter, K.-D. Entian, J. Hench, S. Frank, S. Mansouri, G. Zadeh, P.D. Dans, M. Orozco, G. Thomas, S. Blanco, J. Seoane, T. Preiss, P.P. Pandolfi, M. Esteller, Epigenetic loss of RNA-methyltransferase NSUN5 in glioma targets ribosomes to drive a stress adaptive translational program, *Acta Neuropathol.* 138 (2019) 1053–1074.
- [26] X. Chen, A. Li, B.-F. Sun, Y. Yang, Y.-N. Han, X. Yuan, R.-X. Chen, W.-S. Wei, Y. Liu, C.-C. Gao, Y.-S. Chen, M. Zhang, X.-D. Ma, Z.-W. Liu, J.-H. Luo, C. Lyu, H.-L. Wang, J. Ma, Y.-L. Zhao, F.-J. Zhou, Y. Huang, D. Xie, Y.-G. Yang, 5-methylcytosine promotes pathogenesis of bladder cancer through stabilizing mRNAs, *Nat. Cell Biol.* 21 (2019) 978–990.
- [27] L. Chen, Y. Li, C.H. Lin, T.H.M. Chan, R.K.K. Chow, Y. Song, M. Liu, Y.-F. Yuan, L. Fu, K.L. Kong, L. Qi, Y. Li, N. Zhang, A.H.Y. Tong, D.L.-W. Kwong, K. Man, C.M. Lo, S. Lok, D.G. Tenen, X.-Y. Guan, Recoding RNA editing of AZIN1 predisposes to hepatocellular carcinoma, *Nat. Med.* 19 (2013) 209–216.
- [28] L. Fu, Y.-R. Qin, X.-Y. Ming, X.-B. Zuo, Y.-W. Diao, L.-Y. Zhang, J. Ai, B.-L. Liu, T.-X. Huang, T.-T. Cao, B.-B. Tan, D. Xiang, C.-M. Zeng, J. Gong, Q. Zhang, S.-S. Dong, J. Chen, H. Liu, J.-L. Wu, R.Z. Qi, D. Xie, L.-D. Wang, X.-Y. Guan, RNA editing of SLC22A3 drives early tumor invasion and metastasis in familial esophageal cancer, *Proc. Natl. Acad. Sci. U. S. A.* 114 (2017) E4631–E4640.
- [29] M.A. Zipeto, A.C. Court, A. Sadarangani, N.P. Delos Santos, L. Balaian, H.-J. Chun, G. Pineda, S.R. Morris, C.N. Mason, I. Geron, C. Barrett, D.J. Goff, R. Wall, M. Pellecchia, M. Minden, K.A. Frazer, M.A. Marra, L.A. Crews, Q. Jiang, C.H.M. Jamieson, ADAR1 activation drives leukemia stem cell self-renewal by impairing let-7 biogenesis, *Cell Stem Cell* 19 (2016) 177–191.
- [30] A. Tan, Y. Dang, G. Chen, Z. Mo, Overexpression of the fat mass and obesity associated gene (FTO) in breast cancer and its clinical implications, *Int. J. Clin. Exp.*

- Pathol. 8 (2015) 13405–13410.
- [31] L.P. Vu, B.F. Pickering, Y. Cheng, S. Zaccara, D. Nguyen, G. Minuesa, T. Chou, A. Chow, Y. Saletore, M. MacKay, J. Schulman, C. Famulare, M. Patel, V.M. Klimek, F.E. Garrett-Bakelman, A. Melnick, M. Carroll, C.E. Mason, S.R. Jaffrey, M.G. Kharas, The N6-methyladenosine (m6A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells, *Nat. Med.* 23 (2017) 1369–1376.
- [32] C.-T. Kwok, A.D. Marshall, J.E.J. Rasko, J.L.L. Wong, Genetic alterations of m6A regulators predict poorer survival in acute myeloid leukemia, *J. Hematol. Oncol.* 10 (2017) 39.
- [33] Q. Cui, H. Shi, P. Ye, L. Li, Q. Qu, G. Sun, G. Sun, Z. Lu, Y. Huang, C.-G. Yang, A.D. Riggs, C. He, Y. Shi, m6A RNA methylation regulates the self-renewal and tumorigenesis of glioblastoma stem cells, *Cell Rep.* 18 (2017) 2622–2634.
- [34] Z. Li, H. Weng, R. Su, X. Weng, Z. Zuo, C. Li, H. Huang, S. Nachtergaele, L. Dong, C. Hu, X. Qin, L. Tang, Y. Wang, G.-M. Hong, H. Huang, X. Wang, P. Chen, S. Gurbuxani, S. Arnovitz, Y. Li, S. Li, J. Strong, M.B. Neilly, R.A. Larson, X. Jiang, P. Zhang, J. Jin, C. He, J. Chen, FTO plays an oncogenic role in acute myeloid leukemia as a N6-methyladenosine RNA demethylase, *Canc. Cell* 31 (2017) 127–141.
- [35] J. Mauer, X. Luo, A. Blanjoie, X. Jiao, A.V. Grozhik, D.P. Patil, B. Linder, B.F. Pickering, J.-J. Vasseur, Q. Chen, S.S. Gross, O. Elemento, F. Debart, M. Kiledjian, S.R. Jaffrey, Reversible methylation of m6Am in the 5' cap controls mRNA stability, *Nature* 541 (2017) 371–375.
- [36] X. Qiu, S.-S. Xie, L. Min, X.-M. Wu, L.-Y. Zhu, L. Zhu, Spatial organization of enzymes to enhance synthetic pathways in microbial chassis: a systematic review, *Microb. Cell Factories* 17 (2018) 120.
- [37] Y. Xiang, B. Laurent, C.-H. Hsu, S. Nachtergaele, Z. Lu, W. Sheng, C. Xu, H. Chen, J. Ouyang, S. Wang, D. Ling, P.-H. Hsu, L. Zou, A. Jambhekar, C. He, Y. Shi, RNA m6A methylation regulates the ultraviolet-induced DNA damage response, *Nature* 543 (2017) 573–576.
- [38] R. Su, L. Dong, C. Li, S. Nachtergaele, M. Wunderlich, Y. Qing, X. Deng, Y. Wang, X. Weng, C. Hu, M. Yu, J. Skibbe, Q. Dai, D. Zou, T. Wu, K. Yu, H. Weng, H. Huang, K. Ferchen, X. Qin, B. Zhang, J. Qi, A.T. Sasaki, D.R. Plas, J.E. Bradner, M. Wei, G. Marcucci, X. Jiang, J.C. Mulloy, J. Jin, C. He, J. Chen, R.-Z.H.G. Exhibits, Anti-tumor activity by targeting FTO/m6A/MYC/CEBPA signaling, *Cell* 172 (2018) 90–105.e23.
- [39] J.A. Brown, C.G. Kinzig, S.J. DeGregorio, J.A. Steitz, Methyltransferase-like protein 16 binds the 3'-terminal triple helix of MALAT1 long noncoding RNA, *Proc. Natl. Acad. Sci. U. S. A.* 113 (2016) 14013–14018.
- [40] F. Rapino, S. Delaunay, F. Rambow, Z. Zhou, L. Tharun, P. De Tullio, O. Sin, K. Shostak, S. Schmitz, J. Piepers, B. Ghesquière, L. Karim, B. Charloteaux, D. Jamart, A. Florin, C. Lambert, A. Rorive, G. Jerusalem, E. Leucci, M. Dewaele, M. Vooijs, S.A. Leidel, M. Georges, M. Voz, B. Peers, R. Büttner, J.-C. Marine, A. Chariot, P. Close, Codon-specific translation reprogramming promotes resistance to targeted therapy, *Nature* 558 (2018) 605–609.
- [41] O. Sundheim, C.B. Vågbø, M. Bjørås, M.M.L. Sousa, V. Talstad, P.A. Aas, F. Drablos, H.E. Krokan, J.A. Tainer, G. Slupphaug, Human ABH3 structure and key residues for oxidative demethylation to reverse DNA/RNA damage, *EMBO J.* 25 (2006) 3389–3397.
- [42] D. Dominissini, S. Moshitch-Moshkovitz, S. Schwartz, M. Salmon-Divon, L. Ungar, S. Osenberg, K. Cesarikas, J. Jacob-Hirsch, N. Amariglio, M. Kupiec, R. Sorek, G. Rechavi, Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq, *Nature* 485 (2012) 201–206.
- [43] A.A. Beharry, S. Lacoste, T.R. O'Connor, E.T. Kool, Fluorescence monitoring of the oxidative repair of DNA alkylation damage by ALKBH3, a prostate cancer marker, *J. Am. Chem. Soc.* 138 (2016) 3647–3650.
- [44] D. Han, J. Liu, C. Chen, L. Dong, Y. Liu, R. Chang, X. Huang, Y. Liu, J. Wang, U. Dougherty, M.B. Bissonnette, B. Shen, R.R. Weichselbaum, M.M. Xu, C. He, Anti-tumor immunity controlled through mRNA m6A methylation and YTHDF1 in dendritic cells, *Nature* 566 (2019) 270–274.
- [45] J.J. Ishizuka, R.T. Manguso, C.K. Cheruiyot, K. Bi, A. Panda, A. Iracheta-Vellve, B.C. Miller, P.P. Du, K.B. Yates, J. Dubrot, I. Buchumenski, D.E. Comstock, F.D. Brown, A. Ayer, I.C. Kohnle, H.W. Pope, M.D. Zimmer, D.R. Jen, S.K. Lane-Retticker, E.J. Robitschek, G.K. Griffin, N.B. Collins, A.H. Dong, J.G. Doenck, D. Kozono, E.Y. Levanon, W.N. Haining, Loss of ADAR1 in tumours overcomes resistance to immune checkpoint blockade, *Nature* 565 (2019) 43–48.
- [46] Y. Zhao, Q. Zhao, P.J. Kaboli, J. Shen, M. Li, X. Wu, J. Yin, H. Zhang, Y. Wu, L. Lin, L. Zhang, L. Wan, Q. Wen, X. Li, C.H. Cho, T. Yi, J. Li, Z. Xiao, m1A regulated genes modulate PI3K/AKT/mTOR and ErbB pathways in gastrointestinal cancer, *transl. Oncol.* 12 (2019) 1323–1333.
- [47] A. Wagner, O. Hofmeister, S.G. Rolland, A. Maiser, K. Aasumets, S. Schmitt, K. Schorpp, A. Feuchtinger, K. Hadian, S. Schneider, H. Zischka, H. Leonhardt, B. Conrad, J.M. Gerhold, A. Wolf, Mitochondrial Alkbh1 localizes to mRNA granules and its knockdown induces the mitochondrial UPR in humans and *C. elegans*, *J. Cell Sci.* 132 (2019).
- [48] I. Yamato, M. Sho, K. Shimada, K. Hotta, Y. Ueda, S. Yasuda, N. Shigi, N. Konishi, K. Tsujikawa, Y. Nakajima, PCA-1/ALKBH3 contributes to pancreatic cancer by supporting apoptotic resistance and angiogenesis, *Cancer Res.* 72 (2012) 4829–4839.
- [49] H.-H. Woo, S.K. Chambers, Human ALKBH3-induced m1A demethylation increases the CSF-1 mRNA stability in breast and ovarian cancer cells, *Biochim. Biophys. Acta BBA - Gene Regul. Mech.* 1862 (2019) 35–46.
- [50] M. Spinola, A. Galvan, C. Pignatiello, B. Conti, U. Pastorino, B. Nicander, R. Paroni, T.A. Dragani, Identification and functional characterization of the candidate tumor suppressor gene TRIT1 in human lung cancer, *Oncogene* 24 (2005) 5502–5509.
- [51] H. Wang, L. Wei, C. Li, J. Zhou, Z. Li, CDK5RAP1 deficiency induces cell cycle arrest and apoptosis in human breast cancer cell line by the ROS/JNK signaling pathway, *Oncol. Rep.* 33 (2015) 1089–1096.
- [52] J. Xiong, Y. Wang, Y. Gu, Y. Xue, L. Dang, Y. Li, CDK5RAP1 targeting NF-κB signaling pathway in human malignant melanoma A375 cell apoptosis, *Oncol. Lett.* 15 (2018) 4767–4774.
- [53] M. Spinola, A. Galvan, C. Pignatiello, B. Conti, U. Pastorino, B. Nicander, R. Paroni, T.A. Dragani, Identification and functional characterization of the candidate tumor suppressor gene TRIT1 in human lung cancer, *Oncogene* 24 (2005) 5502–5509.
- [54] S. Chen, Z. Zheng, J. Tang, X. Lin, X. Wang, J. Lin, Association of polymorphisms and haplotypes in the region of TRIT1, MYCL1 and MFS2A with the risk and clinicopathological features of gastric cancer in a southeast Chinese population, *Carcinogenesis* 34 (2013) 1018–1024.
- [55] X. Cai, X. Wang, C. Cao, Y. Gao, S. Zhang, Z. Yang, Y. Liu, X. Zhang, W. Zhang, L. Ye, HBXIP-elevated methyltransferase METTL3 promotes the progression of breast cancer via inhibiting tumor suppressor let-7g, *Canc. Lett.* 415 (2018) 11–19.
- [56] M. Chen, L. Wei, C.-T. Law, F.H.-C. Tsang, J. Shen, C.L.-H. Cheng, L.-H. Tsang, D.W.-H. Ho, D.K.-C. Chiu, J.M.-F. Lee, C.C.-L. Wong, I.O.-L. Ng, C.-M. Wong, RNA N6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2, *Hepatology* 67 (2018) 2254–2270.
- [57] Q. Cui, H. Shi, P. Ye, L. Li, Q. Qu, G. Sun, G. Sun, Z. Lu, Y. Huang, C.-G. Yang, A.D. Riggs, C. He, Y. Shi, m6A RNA methylation regulates the self-renewal and tumorigenesis of glioblastoma stem cells, *Cell Rep.* 18 (2017) 2622–2634.
- [58] S. Zhou, Z.-L. Bai, D. Xia, Z.-J. Zhao, R. Zhao, Y.-Y. Wang, H. Zhe, FTO regulates the chemo-radiotherapy resistance of cervical squamous cell carcinoma (CSCC) by targeting β-catenin through mRNA demethylation, *Mol. Carcinog.* 57 (2018) 590–597.
- [59] S. Yang, J. Wei, Y.-H. Cui, G. Park, P. Shah, Y. Deng, A.E. Aplin, Z. Lu, S. Hwang, C. He, Y.-Y. He, m6A mRNA demethylase FTO regulates melanoma tumorigenicity and response to anti-PD-1 blockade, *Nat. Commun.* 10 (2019) 2782.
- [60] D. Xu, W. Shao, Y. Jiang, X. Wang, Y. Liu, X. Liu, FTO expression is associated with the occurrence of gastric cancer and prognosis, *Oncol. Rep.* 38 (2017) 2285–2292.
- [61] Y. He, H. Hu, Y. Wang, H. Yuan, Z. Lu, P. Wu, D. Liu, L. Tian, J. Yin, K. Jiang, Y. Miao, ALKBH5 inhibits pancreatic cancer motility by decreasing long non-coding RNA KCN15-AS1 methylation, *Cell. Physiol. Biochem.* 48 (2018) 838–846.
- [62] S. Zhang, B.S. Zhao, A. Zhou, K. Lin, S. Zheng, Z. Lu, Y. Chen, E.P. Sulman, K. Xie, O. Bögler, S. Majumder, C. He, S. Huang, m6A demethylase ALKBH5 maintains tumorigenicity of glioblastoma stem-like cells by sustaining FOXM1 expression and cell proliferation program, *Canc. Cell* 31 (2017) 591–606.e6.
- [63] C. Zhang, D. Samanta, H. Lu, J.W. Bullen, H. Zhang, I. Chen, X. He, G.L. Semenza, Hypoxia induces the breast cancer stem cell phenotype by HIF-dependent and ALKBH5-mediated m6A-demethylation of NANOG mRNA, *Proc. Natl. Acad. Sci. U. S. A.* 113 (2016) E2047–E2056.
- [64] A. Tanabe, K. Tanikawa, M. Tsunetomi, K. Takai, H. Ikeda, J. Konno, T. Torigoe, H. Maeda, G. Kutomi, K. Okita, M. Mori, H. Sahara, RNA helicase YTHDC2 promotes cancer metastasis via the enhancement of the efficiency by which HIF-1α mRNA is translated, *Canc. Lett.* 376 (2016) 34–42.
- [65] J. Chen, Y. Sun, X. Xu, D. Wang, J. He, H. Zhou, Y. Lu, J. Zeng, F. Du, A. Gong, M. Xu, YTH domain family 2 orchestrates epithelial-mesenchymal transition/proliferation dichotomy in pancreatic cancer cells, *Cell Cycle* 16 (2017) 2259–2271.
- [66] M. Chen, L. Wei, C.-T. Law, F.H.-C. Tsang, J. Shen, C.L.-H. Cheng, L.-H. Tsang, D.W.-H. Ho, D.K.-C. Chiu, J.M.-F. Lee, C.C.-L. Wong, I.O.-L. Ng, C.-M. Wong, RNA N6-methyladenosine methyltransferase-like 3 promotes liver cancer progression through YTHDF2-dependent posttranscriptional silencing of SOCS2, *Hepatology* 67 (2018) 2254–2270.
- [67] J. Li, S. Meng, M. Xu, S. Wang, L. He, X. Xu, X. Wang, L. Xie, Downregulation of N6-methyladenosine binding YTHDF2 protein mediated by miR-493-3p suppresses prostate cancer by elevating N6-methyladenosine levels, *Oncotarget* 9 (2018) 3752–3764.
- [68] M.L. Gatzka, G.O. Silva, J.S. Parker, C. Fan, C.M. Perou, An integrated genomics approach identifies drivers of proliferation in luminal-subtype human breast cancer, *Nat. Genet.* 46 (2014) 1051–1059.
- [69] X.-L. Tan, A.M. Moyer, B.L. Fridley, D.J. Schaid, N. Niu, A.J. Bartzler, G.D. Jenkins, R.P. Abo, L. Li, J.M. Cunningham, Z. Sun, P. Yang, L. Wang, Genetic variation predicting cisplatin cytotoxicity associated with overall survival in lung cancer patients receiving platinum-based chemotherapy, *Clin. Canc. Res. Off. J. Am. Assoc. Canc. Res.* 17 (2011) 5801–5811.
- [70] C.-J. Ma, J.-H. Ding, T.-T. Ye, B.-F. Yuan, Y.-Q. Feng, AlkB homologue 1 demethylates N3-methylcytosine in mRNA of mammals, *ACS Chem. Biol.* 14 (2019) 1418–1425.
- [71] J.X. Cheng, L. Chen, Y. Li, A. Cloe, M. Yue, J. Wei, K.A. Watanabe, J.M. Shammoo, J. Anastasi, Q.J. Shen, R.A. Larson, C. He, M.M. Le Beau, J.W. Vardiman, RNA cytosine methylation and methyltransferases mediate chromatin organization and 5-azacytidine response and resistance in leukaemia, *Nat. Commun.* 9 (2018) 1163.
- [72] J.-C. Yang, E. Risch, M. Zhang, C. Huang, H. Huang, L. Lu, Association of tRNA methyltransferase NSUN2/IGF-II molecular signature with ovarian cancer survival, *Future Oncol.* 13 (2017) 1981–1990.
- [73] S. Blanco, R. Bandiera, M. Papis, S. Hussain, P. Lombard, J. Aleksic, A. Sajini, H. Tanna, R. Cortés-Garrido, N. Gkatza, S. Dietmann, M. Frye, Stem cell function and stress response are controlled by protein synthesis, *Nature* 534 (2016) 335–340.
- [74] M. Frye, F.M. Watt, The RNA methyltransferase Misu (NSun2) mediates Myc-induced proliferation and is upregulated in tumors, *Curr. Biol.* 16 (2006) 971–981.
- [75] J. Yi, R. Gao, Y. Chen, Z. Yang, P. Han, H. Zhang, Y. Dou, W. Liu, W. Wang, G. Du, Y. Xu, J. Wang, Overexpression of NSUN2 by DNA hypomethylation is associated with metastatic progression in human breast cancer, *Oncotarget* 8 (2017) 20751–20765.
- [76] B. Job, A. Bernheim, M. Beau-Faller, S. Camilleri-Broët, P. Girard, P. Hofman, J. Mazières, S. Toujani, L. Lacroix, J. Laffaire, P. Dessen, P. Fouret, LG Investigators, Genomic aberrations in lung adenocarcinoma in never smokers,

- PloS One 5 (2010) e15145.
- [77] S.P. Kar, J. Beesley, A. Amin Al Olama, K. Michailidou, J. Tyrer, Zs Kote-Jarai, K. Lawrenson, S. Lindstrom, S.J. Ramus, D.J. Thompson, ABCTB Investigators, A.S. Kibel, A. Dansonka-Mieszkowska, A. Michael, A.K. Dieffenbach, A. Gentry-Maharaj, A.S. Whittemore, A. Wolk, A. Monteiro, A. Peixoto, A. Kierzek, A. Cox, A. Rudolph, A. Gonzalez-Neira, A.H. Wu, A. Lindblom, A. Swerdlow, AOCs Study Group & Australian Cancer Study (Ovarian Cancer), APCB BioResource, A. Ziogas, A.B. Ekici, B. Burwinkel, B.Y. Karlan, B.G. Nordestgaard, C. Blomqvist, C. Phelan, C. McLean, C.L. Pearce, C. Vachon, C. Cybulski, C. Slavov, C. Stegmaier, C. Maier, C.B. Ambrosone, C.K. Høgdall, C.C. Teerlink, D. Kang, D.C. Tessier, D.J. Schaid, D.O. Stram, D.W. Cramer, D.E. Neal, D. Eccles, D. Flesch-Janys, D.R.V. Edwards, D. Wokożarczyk, D.A. Levine, D. Yannoukakos, E.J. Sawyer, E.V. Bandera, E.M. Poole, E.L. Goode, E. Khusnutdinova, E. Høgdall, F. Song, F. Bruinsma, F. Heitz, F. Modugno, F.C. Hamdy, F. Wiklund, G.G. Giles, H. Olsson, H. Wildiers, H.-U. Ulmer, H. Pandha, H.A. Risch, H. Darabi, H.B. Salvesen, H. Nevanlinna, H. Gronberg, H. Brenner, H. Brauch, H. Anton-Culver, H. Song, H.-Y. Lim, I. McNeish, I. Campbell, I. Vergote, J. Gronwald, J. Lubinski, J.L. Stanford, J. Benitez, J.A. Doherty, J.B. Permuth, J. Chang-Claude, J.L. Donovan, J. Dennis, J.M. Schildkraut, J. Schleutker, J.L. Hopper, J. Kupryjanczyk, J.Y. Park, J. Figueroa, J.A. Clements, J.A. Knight, J. Peto, J.M. Cunningham, J. Pow-Sang, J. Batra, K. Czene, K.H. Lu, K. Herkommer, K.-T. Khaw, kConFab Investigators, K. Matsuo, K. Muir, K. Offitt, K. Chen, K.B. Moysich, K. Aittomäki, K. Oduani, L.A. Kiemeny, L.F.A.G. Massuger, L.M. Fitzgerald, L.S. Cook, L. Cannon-Albright, M.J. Hoening, M.C. Pike, M.K. Bolla, M. Luedeke, M.R. Teixeira, M.T. Goodman, M.K. Schmidt, M. Riggan, M. Aly, M.A. Rossing, M.W. Beckmann, M. Moisse, M. Sanderson, M.C. Southey, M. Jones, M. Lush, M.A.T. Hildebrandt, M.-F. Hou, M.J. Schoemaker, M. Garcia-Closas, N. Bogdanova, N. Rahman, N.B.C.S. Investigators, N.D. Le, N. Orr, N. Wentzensen, N. Pashayan, P. Peterlongo, P. Guénel, P. Brennan, P. Paulo, P.M. Webb, P. Broberg, P.A. Fasching, P. Devilee, Q. Wang, Q. Cai, Q. Li, R. Kaneva, R. Butzow, R.K. Kopperud, R.K. Schmutzler, R.A. Stephenson, R.J. MacInnis, R.N. Hoover, R. Winqvist, R. Ness, R.L. Milne, R.C. Travis, S. Benlloch, S.H. Olson, S.K. McDonnell, S.S. Tworoger, S. Maia, S. Berndt, S.C. Lee, S.-H. Teo, S.N. Thibodeau, S.E. Bojesen, S.M. Gapstur, S.K. Kjær, T. Pejovic, T.L.J. Tammela, GENICA Network, PRACTICAL consortium, T. Dörk, T. Brüning, T. Wahlfors, T.J. Key, T.L. Edwards, U. Menon, U. Hamann, V. Mitev, V.-M. Kosma, V.W. Setiawan, V. Kristensen, V. Arndt, W. Vogel, W. Zheng, W. Sieh, W.J. Blot, W. Kluzniak, X.-O. Shu, Y.-T. Gao, F. Schumacher, M.L. Freedman, A. Berchuck, A.M. Dunning, J. Simard, C.A. Haiman, A. Spurdle, T.A. Sellers, D.J. Hunter, B.E. Henderson, P. Kraft, S.J. Chanock, F.J. Couch, P. Hall, S.A. Gayther, D.F. Easton, G. Chenevix-Trench, R. Eeles, P.D.P. Pharoah, D. Lambrechts, Genome-wide meta-analyses of breast, ovarian, and prostate cancer association studies identify multiple new susceptibility loci shared by at least two cancer types, *Canc. Discov.* 6 (2016) 1052–1067.
- [78] M. Schaefer, S. Hagemann, K. Hanna, F. Lyko, Azacytidine inhibits RNA methylation at DNMT2 target sites in human cancer cell lines, *Cancer Res.* 69 (2009) 8127–8132.
- [79] T.Z. Tan, Q.H. Miow, R.Y.-J. Huang, M.K. Wong, J. Ye, J.A. Lau, M.C. Wu, L.H. Bin Abdul Hadi, R. Soong, M. Choolani, B. Davidsen, J.M. Nesland, L.-Z. Wang, N. Matsumura, M. Mandai, I. Konishi, B.-C. Goh, J.T. Chang, J.P. Thiery, S. Mori, Functional genomics identifies five distinct molecular subtypes with clinical relevance and pathways for growth control in epithelial ovarian cancer, *EMBO Mol. Med.* 5 (2013) 1051–1066.
- [80] B.R. Tschida, N.A. Temiz, T.P. Kuka, L.A. Lee, J.D. Riordan, C.A. Tierrablanca, R. Hullsieck, S. Wagner, W.A. Hudson, M.A. Linden, K. Amin, P.J. Beckmann, R.A. Heuer, A.L. Sarver, J.D. Yang, L.R. Roberts, J.H. Nadeau, A.J. Dupuy, V.W. Keng, D.A. Largaespada, Sleeping beauty insertional mutagenesis in mice identifies drivers of steatosis-associated hepatic tumors, *Cancer Res.* 77 (2017) 6576–6588.
- [81] H. Zhang, W. Hou, H.-L. Wang, H.-J. Liu, X.-Y. Jia, X.-Z. Zheng, Y.-X. Zou, X. Li, L. Hou, M.A. McNutt, B. Zhang, GSK-3 β -regulated N-acetyltransferase 10 is involved in colorectal cancer invasion, *Clin. Canc. Res.* 20 (2014) 4717–4729.
- [82] S. Dunn, O. Lombardi, R. Lukoszek, V.H. Cowling, Oncogenic PIK3CA mutations increase dependency on the mRNA cap methyltransferase, RNMT, in breast cancer cells, *Open Biol.* 9 (2019) 190052.
- [83] Q.-H. Tian, M.-F. Zhang, J.-S. Zeng, R.-G. Luo, Y. Wen, J. Chen, L.-G. Gan, J.-P. Xiong, METTL1 overexpression is correlated with poor prognosis and promotes hepatocellular carcinoma via PTEN, *J. Mol. Med.* 97 (2019) 1535–1545.
- [84] L. Pandolfini, I. Barbieri, A.J. Bannister, A. Hendrick, B. Andrews, N. Webster, P. Murat, P. Mach, R. Brandi, S.C. Robson, V. Migliori, A. Alendar, M. d'Onofrio, S. Balasubramanian, T. Kouzarides, METTL1 promotes let-7 MicroRNA processing via m7G methylation, *Mol. Cell.* 74 (2019) 1278–1290 e9.
- [85] M. Kohli, S.M. Riska, D.W. Mahoney, H.S. Chai, D.W. Hillman, D.N. Rider, B.A. Costello, R. Qin, J. Lamba, D.M. Sahasrabudhe, J.R. Cerhan, Germline predictors of androgen deprivation therapy response in advanced prostate cancer, *Mayo Clin. Proc.* 87 (2012) 240–246.
- [86] S.-H. Cho, B.H. Jung, S.H. Lee, W.-Y. Lee, G. Kong, B.C. Chung, Direct determination of nucleosides in the urine of patients with breast cancer using column-switching liquid chromatography-tandem mass spectrometry, *Biomed. Chromatogr.* 20 (2006) 1229–1236.
- [87] D.Y. Zhang, D.W. Mahoney, S.M. Riska, J.R. Cerhan, R.J.T. Ribeiro, R. Medeiros, C. Monteiro, A. Nogueira, J. Mauricio, A.M. Fraga, F. Calais-Da-Silva, B.A. Costello, R.S. Dronca, H.C. Pitot, T.J. Moynihan, F. Quevedo, M. Kohli, Variation in TRMT11 gene as a prognostic marker in advanced-stage castrate-resistant prostate cancer (CRPC) patients, *J. Clin. Oncol.* (2015).
- [88] C. Pathak, Y.K. Jaiswal, M. Vinayak, Modulation in the activity of lactate dehydrogenase and level of c-Myc and c-Fos by modified base queuine in cancer, *Canc. Biol. Ther.* 7 (2008) 85–91.
- [89] S. Ishiwata, Y. Ozawa, J. Katayama, S. Kaneko, H. Shindo, Y. Tomioka, T. Ishiwata, G. Asano, S. Ikegawa, M. Mizugaki, Elevated expression level of 60-kDa subunit of tRNA-guanine transglycosylase in colon cancer, *Canc. Lett.* 212 (2004) 113–119.
- [90] K. Wang, M. Zheng, Y. Ren, Overexpression of TRMT12 may independently predict poor overall survival in patients with head and neck squamous cell carcinoma, *OncoTargets Ther.* 12 (2019) 7269–7279.
- [91] V. Rodriguez, Y. Chen, A. Elkahoulou, A. Dutra, E. Pak, S. Chandrasekharappa, Chromosome 8 BAC array comparative genomic hybridization and expression analysis identify amplification and overexpression of TRMT12 in breast cancer, *Genes Chromosomes Cancer* 46 (2007) 694–707.
- [92] Y.-H. Chang, S. Nishimura, H. Oishi, V.P. Kelly, A. Kuno, S. Takahashi, TRMT2A is a novel cell cycle regulator that suppresses cell proliferation, *Biochem. Biophys. Res. Commun.* 508 (2019) 410–415.
- [93] S. Delaunay, F. Rapino, L. Tharun, Z. Zhou, L. Heukamp, M. Termathe, K. Shostak, I. Klevernic, A. Florin, H. Desmecht, C.J. Desmet, L. Nguyen, S.A. Leidel, A.E. Willis, R. Büttner, A. Chariot, P. Close, ELP3 links tRNA modification to IRES-dependent translation of LEF1 to sustain metastasis in breast cancer, *J. Exp. Med.* 213 (2016) 2503–2523.
- [94] T. Kato, Y. Daigo, S. Hayama, N. Ishikawa, T. Yamabuki, T. Ito, M. Miyamoto, S. Kondo, Y. Nakamura, A novel human tRNA-dihydrouridine synthase involved in pulmonary carcinogenesis, *Cancer Res.* 65 (2005) 5638–5646.
- [95] M. Penzo, L. Casoli, C. Ceccarelli, D. Trerè, V. Ludovini, L. Crinò, L. Montanaro, DKC1 gene mutations in human sporadic cancer, *Histol. Histopathol.* 28 (2013) 365–372.
- [96] P. Sieron, C. Hader, J. Hatina, R. Engers, A. Wlazlinski, M. Müller, W.A. Schulz, DKC1 overexpression associated with prostate cancer progression, *Br. J. Canc.* 101 (2009) 1410–1416.
- [97] L. Montanaro, M. Brigotti, J. Clohessy, S. Barbieri, C. Ceccarelli, D. Santini, M. Taffurelli, M. Calienni, J. Teruya-Feldstein, D. Trerè, P.P. Pandolfi, M. Derenzini, Dyskerin expression influences the level of ribosomal RNA pseudouridylation and telomerase RNA component in human breast cancer, *J. Pathol.* 210 (2006) 10–18.
- [98] B. Liu, J. Zhang, C. Huang, H. Liu, Dyskerin overexpression in human hepatocellular carcinoma is associated with advanced clinical stage and poor patient prognosis, *PloS One* 7 (2012) e43147.
- [99] I. Fernandez-Garcia, T. Marcos, A. Muñoz-Barrutia, D. Serrano, R. Pio, L.M. Montuenga, C. Ortiz-de-Solorzano, Multiscale in situ analysis of the role of dyskerin in lung cancer cells, *Integr. Biol. Quant. Biosci.* 5 (2013) 402–413.
- [100] V. Marcel, S.E. Ghayad, S. Belin, G. Therizols, A.-P. Morel, E. Solano-González, J.A. Vendrell, S. Hacot, H.C. Mertani, M.A. Albaret, J.-C. Bourdon, L. Jordan, A. Thompson, Y. Tafer, R. Cong, P. Bouvet, J.-C. Saurin, F. Catez, A.-C. Prats, A. Puisieux, J.-J. Diaz, p53 acts as a safeguard of translational control by regulating fibrillarin and rRNA methylation in cancer, *Canc. Cell* 24 (2013) 318–330.
- [101] A.M. Hoff, S. Alagaratnam, S. Zhao, J. Bruun, P.W. Andrews, R.A. Lothe, R.I. Skotheim, Identification of novel fusion genes in testicular germ cell tumors, *Cancer Res.* 76 (2016) 108–116.
- [102] B. Xhemalce, S.C. Robson, T. Kouzarides, Human RNA methyltransferase BCDIN3D regulates microRNA processing, *Cell* 151 (2012) 278–288.
- [103] S.B. Shelton, N.M. Shah, N.S. Abell, S.K. Devanathan, M. Mercado, B. Xhemalce, Crosstalk between the RNA methylation and histone-binding activities of MePCE regulates P-TEFb activation on chromatin, *Cell Rep.* 22 (2018) 1374–1383.
- [104] S.-W. Han, H.-P. Kim, J.-Y. Shin, E.-G. Jeong, W.-C. Lee, K.Y. Kim, S.Y. Park, D.-W. Lee, J.-K. Won, S.-Y. Jeong, K.J. Park, J.-G. Park, G.H. Kang, J.-S. Seo, J.-I. Kim, T.-Y. Kim, RNA editing in RHOQ promotes invasion potential in colorectal cancer, *J. Exp. Med.* 211 (2014) 613–621.
- [105] T.H.M. Chan, A. Qamra, K.T. Tan, J. Guo, H. Yang, L. Qi, J.S. Lin, V.H.E. Ng, Y. Song, H. Hong, S.T. Tay, Y. Liu, J. Lee, S.Y. Rha, F. Zhu, J.B.Y. So, B.T. Teh, K.G. Yeoh, S. Rozen, D.G. Tenen, P. Tan, L. Chen, ADAR-mediated RNA editing predicts progression and prognosis of gastric cancer, *Gastroenterology* 151 (2016) 637–650 e10.
- [106] L.-D. Xu, M. Öhman, ADAR1 editing and its role in cancer, *Genes* 10 (2018) 12.
- [107] M.A. Zipeto, A.C. Court, A. Sadarangani, N.P. Delos Santos, L. Balaian, H.-J. Chun, G. Pineda, S.R. Morris, C.N. Mason, I. Geron, C. Barrett, D.J. Goff, R. Wall, M. Pellecchia, M. Minden, K.A. Frazer, M.A. Marra, L.A. Crews, Q. Jiang, C.H.M. Jamieson, ADAR1 activation drives leukemic stem cell self-renewal by impairing let-7 biogenesis, *Cell Stem Cell* 19 (2016) 177–191.
- [108] S. Yamanaka, M.E. Balestra, L.D. Ferrell, J. Fan, K.S. Arnold, S. Taylor, J.M. Taylor, T.L. Innerarity, Apolipoprotein B mRNA-editing protein induces hepatocellular carcinoma and dysplasia in transgenic animals, *Proc. Natl. Acad. Sci. U.S.A.* 92 (1995) 8483–8487.
- [109] Q. Ding, C.-J. Chang, X. Xie, W. Xia, J.-Y. Yang, S.-C. Wang, Y. Wang, J. Xia, L. Chen, C. Cai, H. Li, C.-J. Yen, H.-P. Kuo, D.-F. Lee, J. Lang, L. Huo, X. Cheng, Y.-J. Chen, C.-W. Li, L.-B. Jeng, J.L. Hsu, L.-Y. Li, A. Tan, S.A. Curley, L.M. Ellis, R.N. Dubois, M.-C. Hung, APOBEC3G promotes liver metastasis in an orthotopic mouse model of colorectal cancer and predicts human hepatic metastasis, *J. Clin. Invest.* 121 (2011) 4526–4536.