RNA Biology

ISSN: 1547-6286 (Print) 1555-8584 (Online) Journal homepage: https://www.tandfonline.com/loi/krnb20

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To cite this article: Phensinee Haruehanroengra, Ya Ying Zheng, Yubin Zhou, Yun Huang & Jia Sheng (2020): RNA modifications and cancer, RNA Biology, DOI: 10.1080/15476286.2020.1722449

To link to this article: https://doi.org/10.1080/15476286.2020.1722449

Accepted author version posted online: 29 Jan 2020.
Published online: 07 Feb 2020.

RNA BIOLOGY
https://doi.org/10.1080/15476286.2020.1722449

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REVIEW

RNA modifications and cancer

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ABSTRACT

RNA plays essential roles in not only translating nucleic acids into proteins, but also in gene regulation, environmental interactions and many human diseases. Nature uses over 150 chemical modifications to decorate RNA and diversify its functions. With the fast-growing RNA research in the burgeoning field of 'epitranscriptome', a term describes post-transcriptional RNA modifications that can dynamically change the transcriptome, it becomes clear that these modifications participate in modulating gene expression and controlling the cell fate, thereby igniting the new interests in RNA-based drug discovery. The dynamics of these RNA chemical modifications is orchestrated by coordinated actions of an array of writer, reader and eraser proteins. Deregulated expression of these RNA modifying proteins can lead to many human diseases including cancer. In this review, we highlight several critical modifications, namely m^6A, m^1A, m^5C, inosine and pseudouridine, in both coding and non-coding RNAs. In parallel, we present a few other cancer-related tRNA and rRNA modifications. We further discuss their roles in cancer promotion or tumour suppression. Understanding the molecular mechanisms underlying the biogenesis and turnover of these RNA modifications will be of great significance in the design and development of novel anticancer drugs.

ARTICLE HISTORY
Received 23 September 2019
Revised 26 November 2019
Accepted 1 January 2020

KEYWORDS
RNA modifications; epitranscriptome; cancer

Introduction

The past four decades have witnessed the growth of nucleic acid research, ranging from the discovery of new functions of RNAs as catalysts and regulators of numerous biochemical reactions to their conventional roles as carriers of genetic information, the adapters in protein synthesis and the structural scaffolds in subcellular organelles [1–5]. Accordingly, the essential roles that RNA can play as protein in the biological processes also led to the great interests in RNA-based drug discovery [6]. However, compared to proteins that contain 20 different amino acid residues, RNA only has four types of nucleobases. In order to achieve structural and functional diversity, nature uses a variety of chemical modifications to decorate RNAs in all the three primary domains of life [7]. Since the discovery of the first RNA modification almost 60 years ago in yeast, over 150 additional modifications have been identified in all types of RNA [8]. Great efforts have also been dedicated to the development of bioinformatic approaches (e.g. RNA Modification Database and MODOMICS [9]) to bridge the chemistry, the interacting enzymes and the biological effects of these modifications. Many of these modifications play critical roles in human diseases and biological processes such as embryonic stem cell differentiation, development, circadian rhythms, temperature adaptation, meiotic progression, and the regulation of RNA-RNA and RNA-protein binding interactions [10–16]. More interestingly, it is believed that these chemical modifications are the most evolutionarily conserved properties in RNAs, and some of the modified nucleobases are relics of the RNA World, where they may have enhanced the chemical diversity of RNA prior to protein [17].

Similar as epigenetic modifications at the DNA and protein levels, these posttranscriptional RNA modifications, also called 'epitranscriptome', can be dynamically and reversibly regulated by specific enzymes termed as 'reader' (translator), 'writer' (installer) and 'eraser' (demodifier), which represent a group of potential drug targets because of their ability to modulate RNA functions. Indeed, the linkages between several RNA modifying proteins to human diseases have been illustrated by the fast-growing applications of next-generation sequencing in genome-wide association studies (GWAS) [8]. With the most recent exciting progress focus on messenger RNA (mRNA), the core connection between DNA and protein, the significance of epitranscriptomics changes as new layers of gene regulation has been appreciated in other major RNA species, including transfer RNA (tRNA), which actually contains the most abundant and diverse modifications, ribosomal RNA (rRNA), small nuclear RNA (snRNA), microRNA (miRNA) and other non-coding RNAs responding to different physiological and environmental conditions. For example, methylation, the dominant RNA modification in mRNA as various forms like N^6-methyladenosine (m^6A), N^1-methyladenosine (m^1A), N^7-methylguanidine (m^7G), 5-methylcytidine (m^5C) and 2′-O-methylation (Nm), is widely present in all types of RNAs. Interestingly, even targeting the same type of methylation, the sets of methyltransferases and

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demethylase as its writers and erasers could be different in various types of RNA species [7]. These methylated moieties can modulate biological and pathological processes such as cell differentiation, stress response and tumorigenesis by providing diverse functions and dynamic regulation of RNA molecules. The research progress in this area has been extensively summarized [2,7,14,16,18–25]. In this review, we highlight several critical modifications, namely m^6A, m^1A, m^5C, inosine and pseudouridine, which are relatively abundant and have been systematically detected, in both coding and non-coding RNA (ncRNA) contexts, and present their known roles in tumorigenesis. In addition, we summarize a few other cancer-related tRNA and rRNA modifications. The modifications are listed in Table 1 along with the types of cancer where it has been directly quantified or extrapolated from the expression level of writers or erasers enzymes. The chemical structures of modified nucleotides and the simplified catalytic pathways were depicted in Fig. 1. These modifications could play vital roles either as tumour-suppressive or tumour-promoting factors depending on the cellular and tumour types. As emerging new research areas, mapping new RNA modifications, studying the biological functions of RNA modification-related genes and understanding their pathogenic mechanisms will be of great significance in the design and development of novel anticancer drugs.

N^6-methyladenosine (m^6A)

m^6A in mRNA

Since our knowledge on structural mechanisms and functions of mRNA evolved from merely an adaptor molecule between DNA and protein to a gene regulator that can be modified and edited, manipulating mRNA has become a potential tool in developing novel therapeutics to treat a broad spectrum of diseases [35]. Among the various mRNA modifications, m^6A is the most abundant form in eukaryotic cells, accounting for ~80% of all mRNA modifications, which is also represented by the extensive research in recent years. Using m^6A specific antibodies to perform immunoprecipitation combined with high-throughput sequencing (MeRIP-seq), Meyer *et al* have shown that m^6A was enriched in the three-prime untranslated region (3′-UTR) and near stop codons [36]. Another study showed that m^6A at the 5′-UTR can promote cap-independent translation activities [37]. These lines of evidence suggested that site-specific modification could potentially affect the efficiency of translation and could possibly be an important regulator and even target for anticancer therapy. It has also been shown that the correct deposition of m^6A in mRNA is essential for embryonic development and cell differentiation, which provides unique signalling in regulatory transcripts [13].

To further understand m^6A modification in relation to cancer, one must first decipher the catalytic mediators of its writer, eraser and reader proteins. The reader proteins decode the message and signal downstream processes. There are many reader proteins have been identified for m^6A, namely the YTH domain-containing proteins [38], eukaryotic initiation factor 3 (eIF3) [19], heterogeneous nuclear ribonucleoprotein (HNRNP) protein families [20] and insulin-like growth factor 2 mRNA-binding proteins (IGF2BP) which can recognize m^6A in RNA and enhance mRNA stability and translation [39]. Two eraser proteins, fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), both of which are demethylase, have been demonstrated to effectively oxidize and demethylate the target m^6A residues [40,41]. Liu *et al.* reported that m^6A RNA methylation was catalysed by its writer protein complex consisting of human methyltransferase-like 14 (METTL14) and methyltransferase-like 3 (METTL3). The two proteins form a stable heterodimer, which functions in deposition of methyl on nuclear RNAs using SAM (S-adenosylmethionine) as cofactor [42]. Genetic inactivation or depletion of mouse and human METTL3 resulted in prolonged *NANOG* expression and delays embryonic stem cell (ESC) turnover from self-renewal, which in turns prevented the stem cell from differentiation into downstream lineages in the absence of m^6A [43]. This indicates that m^6A is required for stem cell signalling and regulation [10]. Another study has

Table 1. The known prominent RNA modifications associated with cancer types. Genes that have been analysed are shown in parentheses.

RNA modifications	Cancer types (relevant genes)
m^6A	Lung adenocarcinoma [57], AML [46], HER2 overexpressing subtypes breast cancer [26] and NANOG [53], t(11q23)/MLL rearranged, t (15;17)/PML-RARA, FLT3-ITD, and/or NPM1-mutated AMLs (ASB2 and RARA) [27] and GBM (FOXM1) [64].
2′-O-methylation	Breast cancer [28,190], primary and metastatic prostate cancers [29] and squamous cell cervical carcinoma [30]
Pseudouridine (Ψ)	Leukaemia, lymphoma and multiple myeloma [113–115]
Inosine (A to I editing)	BLCA, BRCA, COAD, HNSC, LUAD, THCA, KICH [119,120], NSCLC (NEIL1 [122], AZIN1 [126], miR-381 [122]), SCLC (AZIN1) [119], HCC (AZIN1 [123], FLNB [128], GC (PODXL) [130], ESCC (FLNB) [124], ESCC (IGFBP7) [31], cervical cancer [121], CRC (RHOQ) [129], AML (PTPN6) [32], KIRP, KIC [119,120], breast cancer (Gabra3) [33], glioblastoma (GluR-B) [131], onco miR-21, miR-221, miR-222 [134], Glioma (miR-376a*) [135] and melanoma [34] (miR-455-5p) [136].
$5mC/m^5C$	Circulating tumour cells in lung cancer [149]
m^1A/m^3C	PAAD [99], ESCA, COADREAD, LIHC, STAD [86], BLCA [83,84], LUAD [91], human prostate carcinoma [90], urothelial carcinomas [85], CRC (DLD-1), HCT116 [92], breast and ovarian cancer cells [87]

AML: acute myeloid leukaemia; HER2: human epidermal growth factor receptor type 2; MLL: mixed lineage leukaemia; PML/RARA: promyelocytic leukaemia/retinoic acid receptor alpha; FLT3-ITD: Fms-related tyrosine kinase 3–internal tandem duplication; NPM1: nucleophosmin 1; RARA: retinoic acid receptor alpha; GBM: glioblastoma multiforme; BLCA: bladder urothelial carcinoma; BRCA: breast invasive carcinoma; COAD: colon adenocarcinoma; FOXM1: forkhead box protein M1; HNSC: head and neck squamous cell carcinoma; LUAD: lung adenocarcinoma; THCA: thyroid carcinoma; KICH: kidney chromophobe; NSCLC: non-small cell lung cancer; NEIL1: NEI-like protein 1; AZIN1: antizyme inhibitor 1; SCLC: small cell lung cancer; HCC: hepatocellular carcinoma; FlnB: Filamin B; GC: gastric cancer; PODXL: podocalyxin- like; ASB2: Ankyrin repeat and SOCS box containing 2; ESCC: oesophageal cell carcinoma; CRC: colorectal cancer; RHOQ: Ras homolog family member Q; PTPN6: protein tyrosine phosphatase non-receptor type 6; KIRP: kidney renal papillary cell carcinoma; Gabra3: Alpha-3 subunit of gamma-aminobutyric acid type A; GluR-B: glutamate R-B; IGFBP7: insulin-like growth factor-binding protein 7; PAAD: pancreatic adenocarcinoma; ESCA: oesophageal carcinoma; COADREAD: colorectal adenocarcinoma; LIHC: liver hepatocellular carcinoma; STAD: stomach adenocarcinoma.

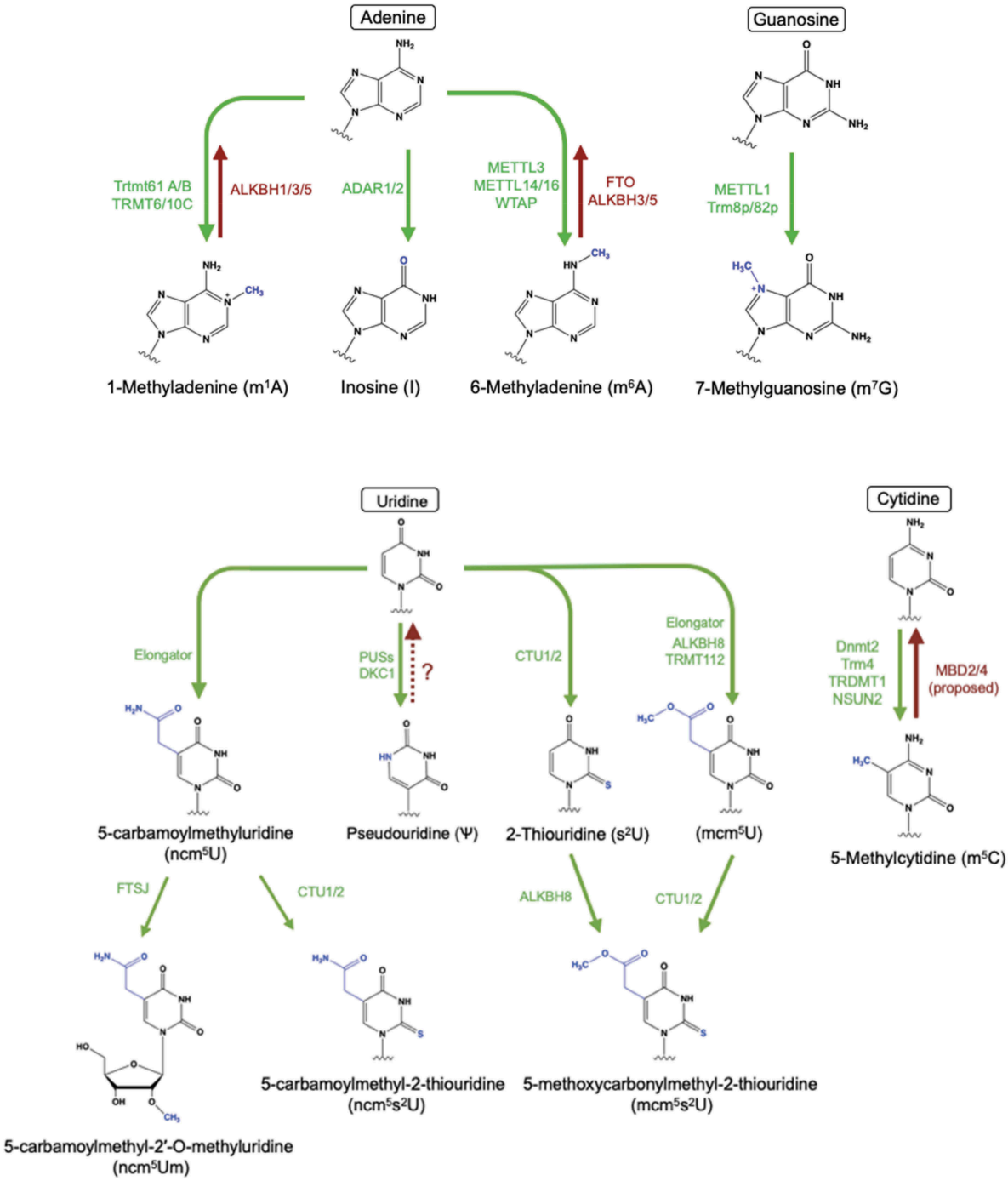

Figure 1. Chemical structures of RNA modifications on adenosine, cytosine and uridine. In green are the enzymes catalysing the reaction of the modification (writer) and in red are the putative enzymes removing the modification (erasers). The modification sites are coloured in blue. The abbreviations of the modified nucleosides are shown in the parenthesis.

shown that in a mouse model, METTL3 knockout resulted in depletion of m^{6}A in mRNA and subsequently led to early embryonic lethality [44]. This demonstrated the importance of m^{6}A in embryo development and initiating the cell differentiation program. Another protein, Wilms' tumour 1-associating protein (WTAP) also affects the methylation activities since in the absence of WTAP, the RNA-binding capability of METTL3 is strongly reduced, which suggested that WTAP is a regulatory subunit of the RNA m^{6}A methyltransferase [45].

METTL3 mRNA and protein are found overexpressed in acute myeloid leukaemia (AML) cells compared to the healthy haematopoietic stem/progenitor cells (HSPCs) or other types of tumour cells [46]. It is also reported that METTL3 can control myeloid differentiation by conditionally depleting METTL3 in leukaemia cells, which resulted in cell differentiation and apoptosis and delayed leukaemia progression in recipient mice *in vivo* [46]. Mutations in METTL3 protein are known to be associated with poor haematopoietic

proliferation and differentiation with the consequence leading to the accumulation of malignancy in myeloid cells [47]. Human hepatocellular carcinoma (HCC) is a dominant type of liver disease with low survival rate and therefore is considered to be one of the common cancer-related worldwide death [48]. METTL3 overexpression was also observed in human hepatocellular carcinoma (HCC). Knockdown of METTL3 *in vitro* showed that proliferation and colony formation of HCC cell are reduced. Moreover, knockout of METTL3 *in vivo* showed to suppress HCC tumorigenesis and lung metastasis. On the contrary, overexpression of METTL3 significantly promoted HCC growth [49]. Glioblastoma is the most common invasive malignant brain tumour diagnosed in the USA and associated with short life expectancy and poor prognosis [50]. A recent study showed that knockdown of METTL3 and METTL14 led to decreased level of m^{6}A and resulted in self-renewal and tumorigenesis of glioblastoma stem cells [51]. Another report indicates that METTL3 is associated with breast cancer, in which METTL3 and oncogene hepatitis B X-interacting protein (HBXIP) are positively correlated in a way that HBXIP upregulates METTL3 and promotes the progression of breast cancer via inhibiting tumour suppressor miRNA let-7g [52]. Moreover, ALKBH5 can mediate m^{6}A demethylation of *NANOG* in mRNA, leading to higher expression of NANOG mRNA and protein resulting in the breast cancer stem cell phenotype [53].

Another study also suggested that truncated membrane-associated guanylate kinase, WW and PDZ domain Containing 3 (MAGI3) mRNA lead to premature polyadenylation. This premature polyadenylation of MAGI3 mRNA is associated with low levels of m^{6}A modification and can no longer function as tumour suppressor genes but turn into a non-functional gene in breast cancer [54]. Despite intensive research, breast cancer remains to be the top malignant tumour afflicting women and is responsible for high mortality rate and large number of deaths each year [50]. Likewise, cervical cancer is caused by human papillomavirus, and although it is a preventable disease, it is still the fourth most common cancer among women [55]. A myriad of evidence indicate that m^{6}A is required for survival of health cells and reduced level of m^{6}A in mRNA which is linked to the progression of human cervical cancer [56]. Non-small cell lung carcinoma (NSCLC) is the most common type of lung cancer accounts for about 85% of all cases, other 15% are small cell lung carcinoma [50]. METTL3 is also associated with NSCLC. It was demonstrated that the elevated level of METTL3 contributes to the tumorigenicity of lung cancer cells by enhancing the translation of oncogenic mRNA, such as epidermal growth factor receptor (RGFR) and protein coding gene Tafazzin (TAZ) [57]. Final remark to conclude this m^{6}A modification in disease is that both METTL3 and METTL4 are overexpressed in human haematopoietic stem and progenitor cells (HSPCs), but are subsequently down-regulated during the HSPC differentiation, suggesting that these two genes actually inhibit cell differentiation (Fig. 2) [56,57].

m^{6}A in lncRNA

As previously noted, m^{6}A is not only the most prevalent modification in mRNA but also is present in long-noncoding RNAs (lncRNAs). This modification can alter the secondary structure of lncRNA, and hence, affect many cellular processes such as splicing, transcription, translation and mRNA stability [58]. The writer methyltransferase includes the heterodimeric METTL3/METTL14 complex and WTAP. Two eraser demethylases are alkylated DNA repair protein B family named FTO and ALKBH5. Reader decoding proteins include YTH N^6 methyladenosine RNA-binding protein 1–3 (YTHDF1-3) which belongs to the family of YT521-B homology domain [59]. METTL16 is a U6 small nuclear RNA (snRNA) methyltransferase which has the ability to regulate SAM synthetase and control SAM homoeostasis and promote intron retention [60]. METTL16 can also bind to the 3′-terminal triple helix of metastasis associated with lncRNA of lung adenocarcinoma transcript 1 (MALAT1) [61]. In addition to lncRNA, microRNAs (miRNA), the small non-coding RNAs with about 18–25 nucleotides in length, have been demonstrated to play important roles in cell development, differentiation and the regulation of cell cycle in plants and animals by complementary base pairing with the 3′-untranslated regions (3′UTR) of mRNA for cleavage or translational repression [62]. Methylated miRNAs are involved in apoptosis, proliferation, cell migration, angiogenesis and metastasis, indicating the broad impact of methylation on

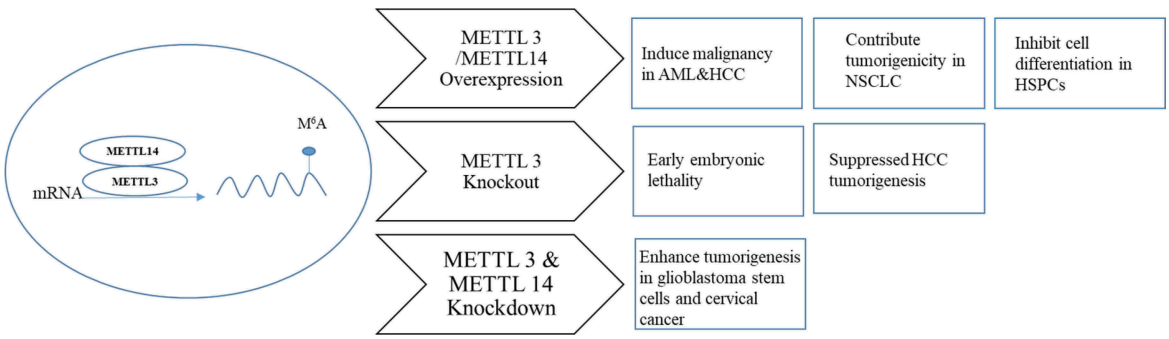

Figure 2. METTL3 is the main writer protein and works together with the substrate-recognizing subunit METTL14 to catalyse the methylation of m^{6}A on mRNA. Overexpression of METTL3 was observed in acute myeloid leukaemia (AML), human hepatocellular carcinoma (HCC) and NSCLC (non-small cell lung carcinoma). Overexpression of both METTL3 and METTL4 was found in human haematopoietic stem and progenitor cells (HSPCs). Knockout of METTL3 in vivo causes early embryonic lethality and suppresses HCC tumorigenesis. By contrast, knockdown of both METTL3 and METTL 14 promoted tumorigenesis in brain and cervical cancers.

the process of oncogenic signalling pathways in cancer cells [63].

m^6A in tRNA

ALKBH5 is regarded as a demethylase of m^6A in transfer RNA (tRNA). It has been reported to play an oncogenic role in the development of glioblastoma (GBM) and breast cancer by affecting the self-renewal and proliferation of cancer stem cells [53,64,65]. The crystal structure of the N-terminal RNA-recognition motif (RRM) of ALKBH5 showed the recognition of hypermodification in tRNAs. In addition, demethylase from the same AlkB family, ALKBH3, was reported to form a complex with the activating signal cointegrator complex (ASCC) which is crucial for cancer cell proliferation [66]. A potential new mechanism by which ALKBH3 may promote tumour progression is associated with m^6A demethylation in tRNA [67], although the activities of ALKBH3 that are most relevant in cancer are as yet unclear. Nevertheless, inhibiting ALKBH3 demethylase activity with small-molecule inhibitors shows high promises in preclinical cancer models [68–71].

N^1- methyladenosine (m^1A)

m^1A in mRNA

N1 methylation on adenosine is another crucial posttranscriptional modification in RNA [72,73]. The addition of this methyl group is known to disrupt the base-pairing specificity, suggesting the regulatory functions of this modification in RNA [74]. The presence of m^1A has been reported in mRNA, tRNA, rRNA and mitochondrial transcripts [75]. In mRNA, it predominantly appeared at the start codon upstream of the first splice site specifically enriched in the 5′-UTR of mRNA and influence the translation [76]. In addition, it has the ability to stall reverse transcription and responds to stimuli in cellular stress environment [74]. The enzymes that recognize this modification site, 'reader' (YTHDF1, YTHDF2, YTHDF3, and YTHDC1) [73], and the ones regulate the level of m^1A, the 'writer' (TRMT10C, Trmt61B, TRMT6/61A) and 'eraser' (ALKBH1, ALKBH3), have shown significant roles at the posttranscriptional stage of mRNA and ncRNAs [73,77–79]. It is worth mentioning that ALKBH1 and ALKBH3 were found as an eraser of m^1A in single-stranded DNA and RNA [80–82].

The increased m^1A level associated with hTrm6p/hTrm61p was found to promote urinary bladder cancer [83,84]. The loss of methylation by its demethylase, ALKBH3, led to progression, angiogenesis, and invasion of urothelial carcinomas by modulation through NADPH oxidase-2-reactive oxygen species (NOX-2-ROS) and the signals of the following complex: TNF-like weak inducer of apoptosis (TWEAK)/Fibroblast growth factor-inducible 14 (Fn14) and Vascular endothelial growth factor (VEGF) [85]. The recent report suggested that m1A regulates erb-b2 receptor tyrosine kinase 2 (ErbB2) and mechanistic target of rapamycin kinase (mTOR) pathways in gastrointestinal cancer (GI) [86]. In GI cancer cells, the level of the protein involved with modification m^1A (writer: TRMT6, TRMT61A and TRT10C) (reader: ALKBH1/3) (eraser: YTHDF1-3 and YTHDC1) were observed to be mostly higher than the normal cell [86]. The demethylation of m^1A has been shown to promote the breast and ovarian cancer cell invasiveness by stabilizing the mRNA of cytokine macrophage colony-stimulating factor (CSF-1) [87]. The longer the lifetime of CSF-1, the higher the activation of CSF-1R leading to promotion of metastasis. The expression of both ALKBH3 and CSF-1 is low in normal breast cell which agrees with the higer level of m^1A on CFS-1 mRNA in normal breast cell in comparison to the cancer cells [87].

m^1A in tRNA

Similar as the case of mRNA, the m1A modification in human mitochondria and cytoplasmic tRNA was catalysed by Trmt61B, TRMT6/61A and TRMT10C [78,79,88]; and the demethylation was catalysed by ALKBH1 and ALKBH3 [89]. The dynamic methylation of tRNA affects the cellular level of $tRNA_{iMet}$ and regulates translation initiation [89]. It has been reported that expression of ALKBH3 is elevated in pancreatic [90], lung [91] and urothelial cancers [85]. Also, ALKBH3 is suggested to promote the growth and progression of colorectal [92] and lung cancer cells [91]. ALKBH3 is a demethylase of m^1A and m^3C of tRNA in both HeLa and human embryonic kidney 293 cells, while not affecting the m^7G, m^1G and m^5C levels [77]. The demethylation step leads to the progression of cancer. *In vivo* study showed that ALKBH3 can promote cancer cell proliferation, migration and invasion in addition to having the ability to regulate the growth of tumour xenografts. It was proposed that the demethylation of m^1A leads to an increasing number of tRNA-derived small RNAs (tDRs) due to the higher susceptible of binding to angiogenin (ANG) cleavage (Fig. 3). The tRNA-derived fragment (tRFs) or tRNA-derived small RNAs (tDRs) are well conserved. They can strengthen the ribosome assembly and increase the translation rate and interactions with cytochrome C in order to prevent cell apoptosis [77]. In a non-small cell lung cancer model, tRF-Leu-CAG promoted cell proliferation and caused the G0/G1 cell cycle progression. The downregulation of tRF-Leu-CAG also repressed AURKA, indicating that tRF-Leu-CAG may be involved in regulating AURKA expression [93]. The high expression of tRF in a panel of cancer cell lines was also reported with strong relevance to cell proliferation [94].

tsRNAs are tDRs that generated through the cleavage of the 3′-end of pre-tRNA [95]. The dysregulation of tsRNA may exert oncogenic or tumour-suppressor functions in cancer [95,96]. Balatti *et al.* demonstrated that the overexpression of ts-46, ts-53 and ts-47 significantly reduced the clonal formation in lung cancer cells. They also showed the inhibitory effects in KRAS mutation cell lines and potential effects on the p53 pathway [96]. tRFs suppressed the invasion and metastatic lung colonization through the binding to Y-box binding protein1 (YBX1) protein, thereby resulting in the degradation of oncogenic transcripts (Fig. 3) [97]. YBX1 binding to P53 has been reported previously, which increased the DNA binding activity of p53, while simultaneously reduced the binding of YBX1 to the Y-box region of mRNA [98]. Together with the previous reports of tsRNA binding to YBX1 and releasing mRNA from YBX1-mRNA complex, tRFs may also be able to displace the YBX1 and release P53 from the P53-YBX1

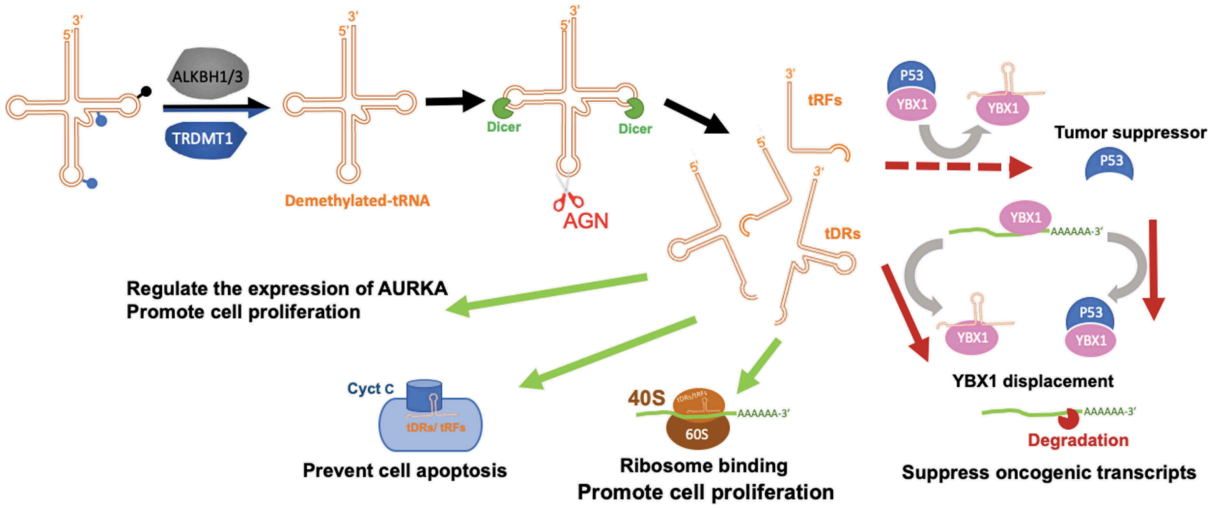

Figure 3. tRNA-derived small RNAs (tDRs) and tRNA-derived fragment (tRFs) affect multiple pathways to regulate gene expression and cell fate. The m6A, m1A and m3C on tRNA can be demethylated by ALKBH1 and ALKBH3 while TRDMT1 catalyzes 5mC demethylation. Demethylated-tRNA is prone to the formation of tDRs/tRFs through dicer and angiogenin (AGN) pathways. The tDRs promote cancer cell proliferation through three possible mechanisms (green arrows). On the contrary, the red arrow shows the modulation of invasion and metastatic lung colonization through tDRs-YBX1 binding, which tends to suppress oncogenic transcripts.

complex with introducing another layer of gene regulation. The free tumour suppressor, P53, can bind to the YBX1 from YBX1-oncogenic transcripts, thus leading to a cancer-suppressive effect (dashed-red arrow in Fig. 3).

m^{1}A in lncRNA

In addition to mRNA and tRNA, m^{1}A modification is found in some lncRNAs. Although the exact roles of m^{1}A still remain elusive and the writers of m^{1}A are yet to be defined, the m^{1}A modification level is positively correlated with protein production and the translational efficiency [76]. Two eraser proteins ALKBH1 and ALKBH3 are believed to account for the reversal of m^{1}A modifications in lncRNAs [89]. High levels of ALKBH3 are found to be associated with human pancreatic cancer by supporting apoptotic resistance angiogenesis [99]. The readers are the same as m^{6}A, including several YTH domain family: YTHDF1-3, and YTHDC1 [100].

Pseudouridine (ψ)

Pseudouridine (Ψ) is another RNA modification abundantly present in mRNA, tRNA, rRNA, snRNA and lncRNA. The single-base resolution mapping and precise quantification of this modification have been achieved recently. It was determined that the Ψ fractions in mRNA and lncRNA range from 30% to 84% in human cell lines [101]. The majority of ψ in mRNA functions as a regulator in response to environmental stress such as nutrient deprivation. It has also been shown that this modification plays a role in stabilizing RNA structure, altering translation initiation efficiency, ribosome pausing, RNA localization and RNA interference, thus providing an additional layer of control over gene expression [102]. The introduction of Ψ into eukaryotic RNA is mediated by the RNA-dependent H/ACA BOX snoRNA pseudouridine synthases (PUSs) or guide RNA-independent PUSs. A recent review by Penzo *et al.* has summarized the functional roles of pseudouridines in human pathologies [101,103].

The gene encoding the pseudouridine synthase dyskerin is DKC1, and the mutation of this gene could lead to the pseudouridylation defect and cause the X-linked Dyskeratosis Congenita (X-DC), a genetically uncommon and inherited disorder with mucocutaneous abnormalities and bone marrow failure in an X-lined autosomal dominant or recessive manner [104]. In addition to DKC1 mutations, it has also been shown that the autosomal form of X-DC is associated with the mutations in H/ACA-resembling domains in the RNA component of telomerase RNP, which are required for telomerase accumulation, stability, and 3′-end processing [104–106].

Patients with X-DC have been reported to exhibit a higher risk for cancer development [107]. It has been hypothesized that a synergistic outcome of the impaired pseudouridylation on rRNA might account for the higher cancer susceptibility. As the studies in hypomorphic Dkc1-mutant mice suggested, the dysregulation of rRNA pseudouridylation indeed precedes cancer onset. The DKC1 mutation also results in the defect of the internal ribosome entry site (IRES), which is an RNA element allowing for translation initiation in a cap-independent manner, thus causing translational defect in some IRES-containing mRNAs. Similarly, ribosomes with the pseudouridine mutated rRNA show a much weaker binding affinity to the IRES elements [108]. Consequently, in hypomorphic DKC-1 mice, the translation of IRES-containing mRNAs, including the tumour suppressors p27 and p53, was perturbed, resulting in a higher incidence of cancer development in these mice [109–112]. Impaired translation of tumour suppressor mRNA might also be a key driving force of cancer in X-DC patients (Fig. 4B). Moreover, recent identification of widespread Ψ in mRNA introduces an additional layer of complexity and regulation of target RNA expressions [102]. Other than X-DC associated cancers, the downregulation of specific subsets of dyskerin-associated

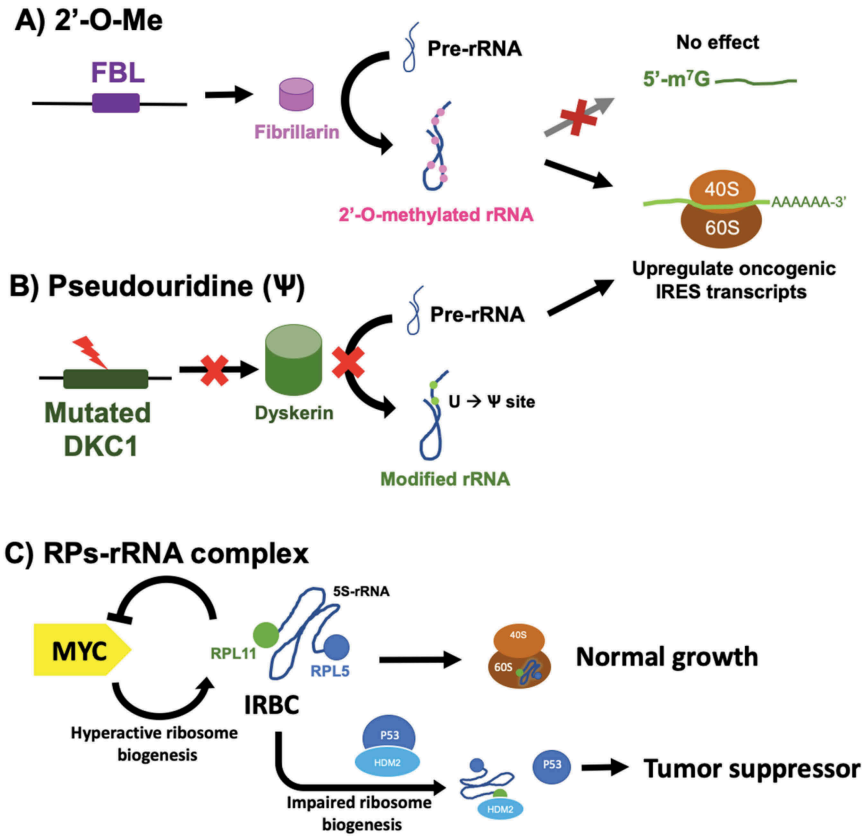

Figure 4. 2′-O-methylated rRNA showed direct correlation to cancer progression while pseudouridine modification was reported to have a negative correlation with cancer progression. (A) FBL regulates the methylation on rRNA leading to the upregulation of IRES-containing oncogenic transcripts, but has limited effects on m^7G cap-dependent translation. (B) Pseudouridine on rRNA is regulated by DKC1. The knockdown DKC1 gene downregulates tumour suppressor proteins (P53 and P27) while upregulates the translation of VEGF. (C) The ribosomal protein complex with 5S-rRNA (IRBC) to regulate tumour proliferation by binding to HDM2 of the p53-HDM2 complex [220].

H/ACA snoRNAs has also been reported in haematological malignancies such as leukaemia, lymphoma and multiple myeloma [113–115], further strengthening the correlation between aberrant pseudouridylation and cancer.

Inosine

Another common type of post-transcriptional modification is adenosine to inosine (A-to-I) RNA editing which is catalysed by the ADAR (adenosine deaminases acting on RNA) family of enzymes that include ADAR1-4 [116]. ADARs introduce inosine in both coding and non-coding RNAs to regulate transcription and translation.

Both hypo and hyper A-to-I editing occurred in the coding or noncoding RNA can affect fundamental cellular processes and thereby give rise to diverse diseases [117]. Most of the editing activities occur in the 3′UTR region, introns and other intergenic regions [118]. Studies focused on investigating the level of editing on non-coding region of mRNA such as introns of Arthrobacter luteus (Alu) and non-Alu mediated by ADAR 1 in tumour tissues in contrast to healthy tissues. The comparison was done by utilizing and analysing the database from The Cancer Genome Atlas (TCGA) project [119,120]. The result showed that high Alu editing levels in tumour tissues are a common feature among bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), colon adenocarcinoma (COAD), head and neck squamous cell carcinoma (HNSC), lung adenocarcinoma (LUAD) and lastly, thyroid carcinoma (THCA) [117,121]. High ADAR1 expression was also noted in non-small cell lung cancer (NSCLC), causing the mutation on the NEI-like protein 1 (NEIL1) with single amino acid changed from lysine to arginine [122]. Encoding antizyme inhibitor 1 (AZIN1) was also upregulated by ADAR1 editing in hepatocellular carcinoma (HCC). ADAR1 not only increased the conversion of A to I but also caused serine to glycine substitution in AZIN1 proteins in promotion of tumorigenesis [117,123]. Other studies have reported similar aberrant editing activities by ADAR1 in oesophageal squamous cell carcinoma (ESCC) and breast cancer [124,125]. Recently, Hu *et al.* demonstrated that RNA editing of AZIN1 could promote malignant progression in non-small-cell lung cancers (NSCLC) [126]. Fritzell *et al.* reported similar trends in prostate, liver, chronic myoelogenous leukaemia (CML), colorectal and cervical cancers due to upregulation of ADAR1 within targeted mRNAs such as DHFR, AZIN1, BLCAP, RRUNE, thus promoting cancer progression [127]. Filamin B (FLNB) editing was shown to have an effect on both HCC and ESCC. ADAR1 hyperedited and ADAR 2 hypoedited the substitution of valine by methionine, attributing to HCC pathogenesis [128]. On the other hand, only ADAR1 hyperedited FLNB in ESCC [124].

Another editing event was reported on RhoQ gene with unidentified ADAR. The increased RhoQ mRNA editing is linked to colorectal cancer (CRC) and facilitates aggressiveness

in metastasis [129]. High level of editing in miRNA also plays a role in cancer development. Overexpression of ADAR1 on miR381 was linked to NSCLC which caused enhancing of lung tumorigenesis [122]. Rather than hyperediting, kidney chromophobe (KICH) and kidney renal papillary cells both showed hypotherditing of ADAR 1 [120]. A low level of ADAR1 expression was also proposed to be linked with alpha-3 subunit of gamma-aminobutyric acid type A (Gabra3), which played a role in tumour progression in breast cancer. Gumireddy *et al.* reported that A-I mRNA editing was mainly found in non-invasive breast cancer which suggested that editing suppresses GABRA3-mediated Akt activation and breast cancer metastasis [120].

Hypoedited ADAR2 in podocalyxin-like (PODXL) was reported to be associated with gastric cancer. The editing caused a single amino acid change from histidine to arginine, which resulted in slower tumour growth and reduced invasive capability [130]. Hypoedited ADAR2 in GluR-B caused a glutamine-to-arginine substitution and led to malignant glioblastoma [131]. Insulin-like growth factor-binding protein 7 (*IGFBP7*), can be a target for ADAR2 mediated editing on the coding exon of position 284 from (AAG) lysine to (AIG) arginine with Inosine being read as Guanosine. This editing promoted apoptosis in ESCC. IGFBP 7 can potentially be a regulator of either promoting tumorigenesis in the case of under editing or cancer suppressor when over-edited [121]. In parallel to the mRNA hypoedition, low miRNA editing can also contribute to cancer development. Studies have suggested that ADAR2 editing is essential to suppress tumour growth in glioblastoma. This inhibition activity may be attributable to the regulation of onco-miRNA miR21, miR221 and miR222 [132,133]. ADAR2 served to reduce onco-miRNAs by editing miR21, miR221 and miR222 and thereby prevented them from maturing into onco-miRNA. The decreasing of microRNA editing activity mediated by ADAR2 can promote tumorigenesis in glioblastoma [134]. Moreover, Fritzell *et al.* reported that astrocytoma, glioblastoma, gastric, oesophageal and liver cancers all showed low editing activity of ADAR2, indicating that ADAR2 downregulation induced proto-oncogenic miRNA [127]. In human brain, microRNA-376a* can undergo A to I editing and its aberrant editing is associated with glioblasoma. Yukti *et al.* reported that attenuated A to I editing of miRNA-376a* could promote tumorigenesis and progression of cancer [135]. miRNA-455-4p can also be the target for ADAR1 editing. In the study conducted by Shoshan *et al.*, it has been shown that under the increasing level of A to I caused by hypoediting of ADAR1 on miR-455-5p can inhibit the expression of tumour suppressor gene cytoplasmic polyadenylation element-binding protein (CPEB1), which leads to melanoma growth and metastasis [136]. Recent study on the level of ADAR3 in glioma cell reported that ADAR3 acted like a tumour suppressor and high level of ADAR3 can be predicted in lower-grade glioma (LGG) [137].

5-methylcytidine (m^5c)

5-methylcytosine (m^5C) has been identified in rRNA, tRNA and recently in mRNAs. It is particularly enriched in untranslated regions near Argonaute binding sites [138]. The methylation process was catalysed by the DNA methyltransferase homolog (Dnmt2) and the NOP2/Sun (NSUN 2 and 4) RNA methyltransferase family as m^5C writers [139–141]. NSUN2 was reported to be targeted by critical transforming proteins such as c-MYC [140] and Aurora kinase B [142]. NSUN2 is reported to be upregulated in some tumour types by copy-number gains [143]. The overexpression of NSUN2 by DNA hypomethylation is associated with metastatic progression in human breast cancer [144]. However, there was also an observation of downregulation of NSUN2 in other classes of malignancies such as skin cancer, resulting in a reduction in protein translation rates and increase in the tumour-initiating population [145]. Mutations in NSUN2 can cause autosomal-recessive intellectual disability [146], and mutations in NSUN7 can cause sperm motility defects and infertility in male mice [147]. Evidence has also shown that m^5C is actively involved in promoting mRNA export via m^5C reader protein ALYREF, which acts as mRNA export adaptor in both *in vitro* and *in vivo* [148]. Although the detailed activities of these enzymes in tumorigenesis currently remain elusive and further investigation of the roles that m^5C can play in cancer development is still required, the m^5C levels have been increasingly recognized as a cancer marker. For example, increased RNA m^5C levels could be detected in circulating tumour cells from lung cancer patients compared to those in whole blood cells [149].

In addition, it is also known that m^5C in tRNA could regulate cancer progression through tRNA fragmentation process [150]. DNMT2 was found to be responsible for methylating cytidine at position 38 of tRNA specific for aspartate, which is similar to TRDMT1 activity [141]. Somatic cancer mutations were highly associated with the decreased methyltransferase activity of DNMT2 and the reduction of tRNA [151]. Similarly, NSUN3 is an RNA methyltransferase to regulate the level of 5-formylcytidine (f^5C), a downstream analogue of m^5C. The reduction of NSUN3 decreases the level of both m^5C and f^5C in tRNA, which is also linked with cancer [152].

Mcm^5u_{34} in tRNA

The modification on tRNA and their related enzymes has long shown significance in the regulation of cancer pathogenesis [140,153,154]. In addition to the whole tRNA, the modified tRNA fragments or derivatives (tRFs/tsRNAs), which are cleaved by angiogenin, Dicer or RNase Z at different positions of the mature tRNA [94,155], also play crucial roles in RNA silencing, microenvironment monitoring and diseases like cancers [156]. The genome-wide tRNA profiling data revealed that the nuclear and mitochondrial encoded tRNAs were usually upregulated in pathogenic cells compared to healthy ones [157–160]. The disease-related tRNA modifications have been well summarized very recently [161]. We highlight here some discovery on cancer-associated wobble uridine modification, mcm^5U_{34} in tRNA.

It is known that the modification at wobble position of tRNA affects the translational efficiency [162,163]. The 5-carbonylmethyluridine (cm^5U) was methylated by ALKBH8 and

tRNA methyltransferase 9-like (*hTRM9L)* to generate 5-methoxycarbonylmethyluridine (mcm^5U) at wobble position [164]. In human breast cancer, the expression of U_{34}-modifying enzymes, namely elongator complex protein 3 (Elp3) and cytoplasmic tRNA 2-thiolation protein 1 and 2 (Ctu1/2), which further catalysed the formation of mcm^5s^2-U_{34}, promoted the translation of oncoprotein DEK and increased the translation of the oncogenic LEF-1 mRNA via binding to the LEF1-IRES sequence, leading to the invasion and metastasis of breast cancer cells [154]. Another study reported the high level of tRNA methyltransferase homolog 12 (TRMT12) in several breast cancer cell lines and tissues [153], although its molecular mechanisms were unclear. On 2016, it was reported that the *methyltransferase* ALKBH8, the Trm9 homologs in mammals, was highly expressed in bladder cancer and the absence of ALHBH8 promoted cell apoptosis due to the reduction of the anti-apoptotic protein surviving level [165,166].

In addition to sustaining the metastasis of breast and bladder cancers, U_{34}-tRNA modifiers were shown to be the key regulators of the survival of malignant melanoma cells [154,166,167]. The elevated levels of ELP1, ELP3, CTU1 and CTU2 were observed in $BRAF^{V600E}$ cells which is the most common mutation among human melanoma patients and believed to be responsible for resistance to targeted therapy [161]. In addition, the development of $BRAF^{V600E}$ melanoma in a zebrafish model was compromised by the inactive ELP3 [167]. The depletion of ELP1, ELP3, ELP5 or ELP6 in melanoma cells contributed to the reduction of the migration and oncogenesis [168]. The high level of ELP3 was shown to link to the phosphorylation level of protein kinase B (AKT) in human hepatocellular carcinoma (HCC) cells [169].

The Elongator complex induced the radical SAM-dependent pathway for modification on position 5 of U_{34} with the involvement of Kti11/Dph3-Kti13 complex [170,171]. Kti11 (also known as Dph3) and Kti13 (also known as Ats1) were shown to influence in Elongator regulation process [172]. A hetero-dimer of Kti11 and Kti13 affected Elongator's of U_{34} modification process by precipitating the Elongator subunits (Elp1, Elp2, Elp3, Elp5) [170,171,173–176]. Depletion of Kti11 diminished the U_{34} modification activity of Elongator while the loss of Kti13 reduced 20% of the tRNA modification [174,175,177].

Diphthamide is a posttranslational modification on histidine residue (His699 in yeast; His715 in humans) found on translation elongation factor 2 (EF2), which is an essential translation factor that mediates the translocation of the ribosome during elongation process. Diphthamide-EF2 was catalysed by a group of Dph family Dph1, Dph2, Dph4, Dph5, Dph6 and Dph7 including Kti11/Dph3 [178,179]. It has been found that Dph1 and Dph5 activity is associated with the proliferation of intestinal stem cell in Drosophila melanogaster [180]. Diphtheria toxin (DT) introduced cell death via inactivation of the translation factor through adenosine diphosphate (ADP)-ribosylation. It has been found that the loss of Kti11/Dph3 let to the cell resistance to DT suggesting that diphthamide-EF2 is the target of DT [170,174,178,179,181]. These data supported that diphthamide post-translation modification regulates cell growth and proliferation via stabilizing the reading frame and reducing the ribosomal errors [161,181–185]. In contrary, the methylation enzyme, hTRM9L, was reported to be down-regulated in breast, bladder, colorectal, cervix and testicular carcinomas and diminished in more aggressive SW620 and HCT116 colon carcinoma cell lines. Interestingly, the restored methylation dramatically suppressed tumour growth *in vivo* via LIN9 and HIF1-α-dependent mechanisms [164]. Therefore, the dysregulation of $mcm^5s^2U_{34}$ modification seems to be regulated by many layers of protein-RNA complex chain interactions, which affect the level of modification on U_{34} of tRNA. The presence of modification on U_{34} may also be subjected to tRNA fragmentation formation leading to the cancer cell progression or inhibition of oncogene as showed in Fig. 3.

2′-O-Me modification in rRNA

An increasing body of evidence links the alteration of rRNA modification levels and the defect in components of the rRNA modification machinery to development, genetic diseases and cancer [186]. For example, as stated previously, pseudouridine modification is regulated by the pseudouridine synthase 1 (DKC1) gene, which played critical roles in dyskeratosis congenita (DC) and its associated cancers.

2′-O-Me modification in rRNA was reported to depend on the methylation level of rRNA. Ribosome expression is upregulated in most of cervical intraepithelial neoplasia (CIN) when compared to healthy tissue. The methylation level at cytosines in the CpG islands was significantly reduced in rDNA promoter region of CIN tissues together with the decondensation of rDNA chromatin. The methylation inhibition experiment by 5-aza-2′-deoxycytidine (DAC) suggested the negative correlation between methylation level in rDNA promoter region and 45S-rDNA. The data indicated that the decreasing of methylation in rDNA promoter results in the development of human cervical cancer through an increasing of rRNA synthesis [187].

Studies showed the correlation of modulation function of FBL gene and 2′-O-Me patterns. Downregulation of FBL led to rRNA 2′-O-Me patterns, with a direct impact on ribosome function, in neurogenesis and stem cell differentiation [188,189]. In addition, maintaining the expression of FBL in stem cells prolonged their pluripotent state in mouse embryos [189]. In breast cancer cells, changes in FBL expression, which altered the level of 2′-O-Me in rRNA, affected translational accuracy and translational initiation efficiency of mRNAs containing internal ribosome entry site (IRES) elements [190–192]. Diminishing the rRNA 2′O-methyltransferase, fibrillarin, by FBL knocked down affected the ribosome biogenesis and global 2′-O-Me-rRNA in human cells [193]. The overexpression of FBL in tumours and cancer cells upregulated 2′-O-Me modification [190]. Fibrillarin stimulates the cancer-promoting protein translation; IGF1R [194], c-Myc [195], FGF1/2 [196], and VEGFA [190,197]. Mutated p53 associated with tumorigenesis was reported to promote methylation level in rRNA and thus increased their translation fidelity and rate (Fig. 4A) [117].

On the contrary, the FBL knockdown resulted in the accumulation of p53, increasing IRES-driven de novo synthesis,

possibly through the effect of UTR of the p53_mRNA [192]. Elimination of the methylation function affected translation from globin and GAPDH 5′UTR in the *in vitro* translation assay. However, 2′-O-Me does not significantly modulate the ability of ribosomes to initiate m^7G-Cap-dependent translation. However, due to the dysregulation of FBL on the cancer cell growth and the interplay of p53, more studies are required to fully understand the mechanism of FBL modulation on the level of 2′-O-Me and its effect on translational activity.

P53 is the key mediator [198] of the abolishing of cell differentiation and proliferation in mice liver caused by deletion of gene encoding 40S ribosomal protein S6 (RpS6 or eS6) [199]. During the impairment of 60S ribosome biogenesis, many precursor complexes newly synthesized 60S ribosomal protein L5 (RPL5, uL18), L11 (RPL11, uL5) and 5S rRNA. They target the E3 ubiquitin-protein ligase HDM2 (also known as MDM2 in mice) thereby preventing the ubiquitylation and degradation of p53 [200–205]. The free pre-ribosomal RPL5–RPL11–5S rRNA complex that binds to HDM2 has been termed 'asimpaired ribosome biogenesis checkpoint' (IRBC) complex [23]. The IRBC regulated p53–HCM2 interactions through stress-activated responses [206]. Among several ribosomal proteins (RPs), the studies showed that RPL5 and RPL11 are the main RPs that involved in stabilizing p53 in a mutually dependent manner (Fig. 4C) [204,207]. A crystal structure of HDM2-RPL11 complex revealed the binding site in the acidic region of HDM2 [208], which was hypothesized to mimic the 28S rRNA binding site for RPLL in the 60S subunit [23,208]. Additional analyses are needed to elucidating the HDM2-IRBC binding mechanism to facilitate the HDM2 inhibition therapeutic.

The IRBC was also reported to involve in hyperactive ribosome biogenesis. When MDM2 (HDM2) of Eμ-*Myc* mice failed to bind to IRBC because of the mutation on *Mdm2*^{C305F} knock-in, the higher rate of lymphomagenesis than the expression in wild-type *Mdm2* was observed [209]. A number of studies hypothesized that the upregulation of MYC translation would increase the number of RPL5 and RPL11 for HDM2-inhibition leading to an intrinsic tumour suppressor response [209–212]. It was also reported that RPL5 and RPL11 destabilize MYC-mRNA through the inhibition of MYC transcription (Fig. 4C) [213–216] which was supported by the observation of increasing the level of MYC protein on primary mouse embryonic fibroblasts with heterozygous deletion of *Rpl11* [217]. The cellular senescence was induced by many stress signals including telomere shortening, oxidative stress and DNA damage, generally in a p53-dependent manner [218]. IRBC could activate cellular senescence as a barrier against tumour formation by preventing proliferation or by inducing immune-mediated clearance of pre-malignant cells [218] which supported that IRBC mediates tumour suppression [219].

lncRNAs with cancer

In the end, we think it is worthwhile highlighting the research progress of the three most studied cancer-related lncRNAs, which contain various of chemical modifications: the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), the Hox transcript antisense intergenic RNA (HOTAIR), and the X-inactive specific transcript (XIST). MALAT1 bears m^6A and pseudouridine modifications and was reported to function as a regulator of metastasis to control cancer cell proliferation, migration and apoptosis in pancreatic, hepatic and ovarian cancers. HOTAIR which bears cytosine methylation can promote metastasis in gastric, colorectal, pancreatic, hepatic, breast and skin cancers. XIST has all three types of chemical modifications, including m^6A, m^5C and ψ, and can act either as oncogene or as a suppressor in leukaemia and colorectal cancers (Fig. 5) [59].

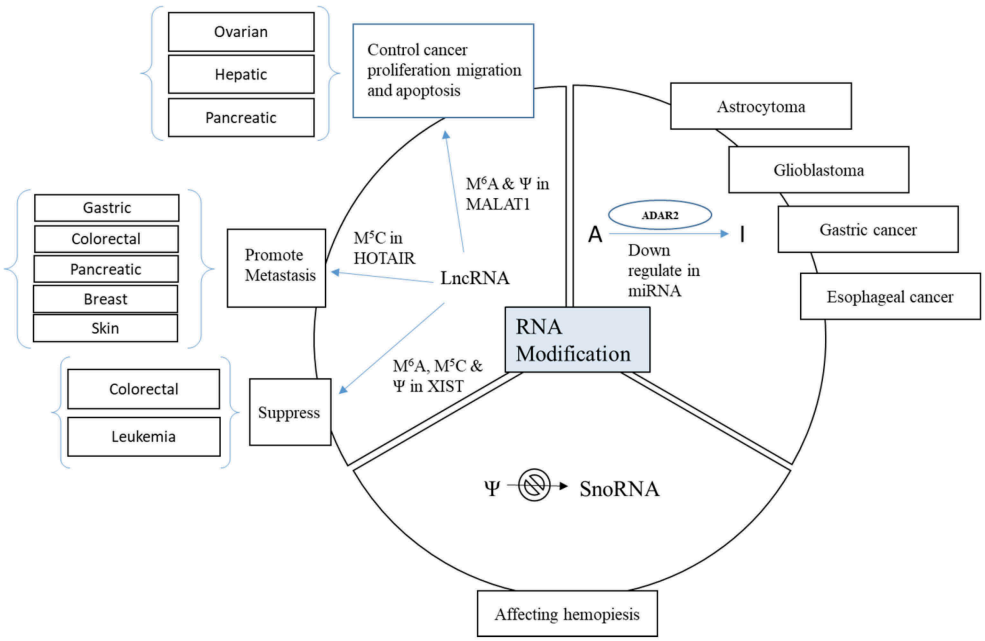

Figure 5. Examples of aberrant RNA modifications in cancer-related lncRNAs. M^6A and Ψ in MALAT1 were reported to function as a regulator of metastasis to control cancer cell proliferation, migration and apoptosis in pancreatic, hepatic and ovarian cancers. M^5C in HOTAIR can promote metastasis in gastric, colorectal, pancreatic, hepatic, breast and skin cancers.

Concluding remarks

As summarized above, epitranscriptomic levels and dynamic changes of RNA modifications may hold promise as new diagnostic biomarkers of clinical values. More importantly, the enzymes involved in regulating RNA metabolism may function as oncogenic regulators and serve as novel therapeutic targets. In the future, precision medicine based on epitranscriptomic signatures may be tailored to the diagnosis and treatment of specific tumour types within individual patients. However, the functionality of these chemical modifications in both coding and non-coding RNAs is not yet fully understood and still require collaborative endeavour to draw a clear connection between modifications in RNAs and cancer. Further improvements in sequencing sensitivity and functional validation methods are urgently needed to achieve this loft goal.

Acknowledgments

This work was supported by grants from NSF (CHE-1845486 MCB-1715234 to JS), Cancer Prevention and Research Institute of Texas (RP170660 to YZ), National Institute of Health grants (R01HL134780 to YH, R01HL146852 to YH, R01GM112003 to YZ), the Welch Foundation (BE-1913-20190330 to YZ), the American Cancer Society (RSG-18-043-01-LIB to YH; RSG-16-215-01-TBE to YZ). Ya Ying Zheng is currently supported by NIH training grant T32GM132066.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the American Cancer Society [RSG-18-043-01-LIB]; American Cancer Society [RSG-16-215-01-TBE]; National Institutes of Health [R01HL134780, R01HL146852]; National Institutes of Health [R01GM112003]; National Science Foundation [1845486]; Welch Foundation [BE-1913-20190330].

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