

# RNA Modifications Meet Tumors

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**Abstract:** RNA modifications occur through the whole process of gene expression regulation, including transcription, translation, and post-translational processes. They are closely associated with gene expression, RNA stability, and cell cycle. RNA modifications in tumor cells play a vital role in tumor development and metastasis, changes in the tumor microenvironment, drug resistance in tumors, construction of tumor cell-cell “internet”, etc. Several types of RNA modifications have been identified to date and have various effects on the biological characteristics of different tumors. In this review, we discussed the function of RNA modifications, including *N*<sup>6</sup>-methyladenine (*m*<sup>6</sup>A), 5-methylcytosine (*m*<sup>5</sup>C), *N*<sup>7</sup>-methyladenosine (*m*<sup>7</sup>G), *N*<sup>1</sup>-methyladenosine (*m*<sup>1</sup>A), pseudouridine ( $\Psi$ ), and adenosine-to-inosine (A-to-I), in the microenvironment and therapy of solid and liquid tumors.

**Keywords:** tumor, RNA modification, non-coding RNA, tumor microenvironment, tumor therapy

## Introduction

According to the central principles of molecular biology, genetic information progressively flows from DNA to RNA to proteins. Epigenetics is a branch of genetics that studies heritable changes in gene expression with unchanged DNA sequences, including chromatin remodeling, DNA methylation, RNA methylation, histone modification, and other modifications.<sup>1,2</sup> These modifications, like nucleosome remodeling, can regulate the expression of genes, thereby determining cell state and influencing cell differentiation and development. The role of DNA modifications in regulating gene expression is well understood. In recent years, with the development of immunoprecipitation technology and second-generation sequencing technology, the diversity of RNA has been reflected, and the role of RNA in transcription and translation and the expression of other genes has been gradually understood.

More than 170 forms of modification are known to exist in various coding and non-coding RNA in cells, and most RNA species contain more than one chemical modification.<sup>3,4</sup> *m*<sup>6</sup>A, *m*<sup>5</sup>C, and *m*<sup>7</sup>G are the three most representative modifications in addition to *m*<sup>1</sup>A,<sup>5</sup>  $\Psi$ ,<sup>6</sup> and A-to-I,<sup>7</sup> among others. Different RNA modifications are connected and transformed through gene transfer processes and cell networks, forming dynamic regulation. Based on epigenetic modifications, the targeted regulation of RNA in tumors has gradually become a new method for understanding tumors' occurrence, development, and treatment. With bioinformatics entering the post-genomic era, Chinese scholars have established RMVar: a database of RNA modifications (RM) - associated variants that hosts existing RNA modifications as much as possible, which is a useful resource for researchers to understand the basic functions of RNA modifications and its relationship with diseases.<sup>8</sup>

The treatment and metastasis of tumors in clinical practice have always been the focus and difficulty. Recently, researchers established RMDisease: a genetic variation database that can influence RNA modifications, providing a research platform for clinical workers to explore the pathogenesis of various diseases, including tumors, at the extra-transcriptome level.<sup>9</sup> Tumors are difficult to be found in the early stage because of their limited volume and no metastasis. Most of the current tumor treatments are surgical resection, radiotherapy and chemotherapy. Such treatments

not only have many side effects, but also lead to tumor recurrence and tolerance to treatment, and ultimately failure. Research shows these modifications can affect tumor development, metastasis, and drug resistance and have a certain relationship with the tumor microenvironment, including immune cells, stromal cells, extracellular matrix (ECM), other secretory molecules, blood, and lymphatic networks.<sup>10–13</sup>

RNA modifications can improve the therapeutic prognosis of tumor patients by regulating the malignant biological behavior of tumor to achieve precise surgical resection and improve the sensitivity of radiotherapy and chemotherapy. Moreover, RNA modifications associated with the tumor microenvironment are especially becoming the current focus of the scientific community, offering hope for the targeted treatment of tumors.

In this review, we summarized the composition and function of RNA modifications in normal cells such as m<sup>6</sup>A, m<sup>5</sup>C, m<sup>7</sup>G, m<sup>1</sup>A, Ψ, and A-to-I and their association with the tumor microenvironment. Therefore, we can understand RNA modifications in the development and treatment of tumors in depth and provide scientists with ideas for future research on RNA modifications.

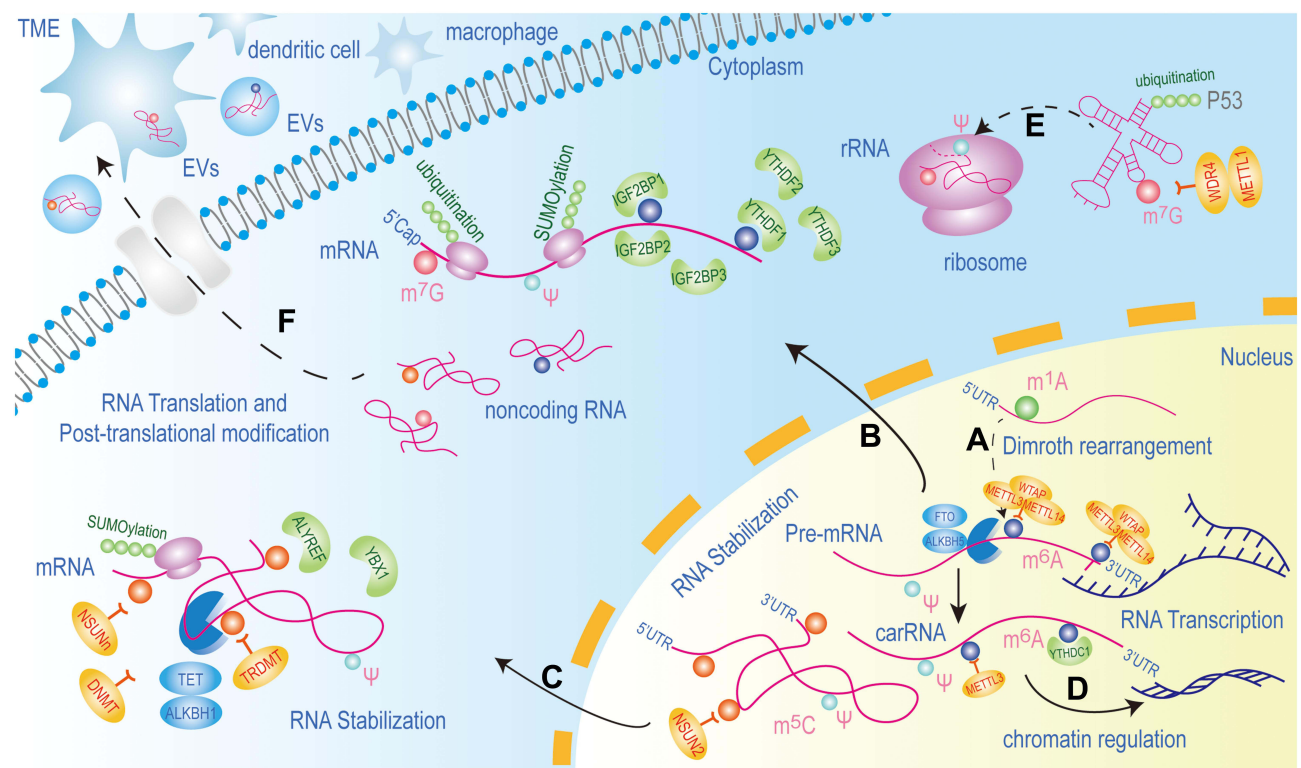
## The Function of RNA Modifications from Transcription to Translation

### N<sup>6</sup>-Methyladenosine (m<sup>6</sup>A)

In 1975, the concept of m<sup>6</sup>A modification in RNA was first reported.<sup>14</sup> m<sup>6</sup>A is one of the most common modifications in the messenger RNA (mRNA) of eukaryotic cells, with S-adenosyl-L-methionine (SAM) as the methylated donor.<sup>15</sup> m<sup>6</sup>A methylation can be catalyzed by methyltransferases such as methyltransferase-like 3/14/16 (METTL3/14/16) (“writers”), removed by demethylases such as fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5) (“erasers”), and interacts with m<sup>6</sup>A binding proteins. The m<sup>6</sup>A modification takes part in the shearing process of primary mRNA (pre-mRNA) and participates in the maturation of mRNA from the cell nucleus. The role of m<sup>6</sup>A modification in the downstream regulation of mRNAs, such as translation, export, and stability, is mainly determined by its reader, which recognizes target-modifying mRNA, such as YTH domain family proteins (YTHDCs and YTHDFs) and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) (“readers”)<sup>16,17</sup> (Figure 1B).

In order to better explore the function of m<sup>6</sup>A modification, researchers created an online database-DRUM, to combine the association between disease, gene, m<sup>6</sup>A-RNA methylation sites and gene expression, RNA methylation, disease similarity data of the Random Walk with Restart (RWR) algorithm through the method of multi-layer heterogeneous network, to support the query of disease related RNA m<sup>6</sup>A methylation points.<sup>18</sup> Another comprehensive online platform, m<sup>6</sup>A-TSHub, is used to reveal context specific m<sup>6</sup>A methylation and gene mutations that may regulate m<sup>6</sup>A epigenetic markers.<sup>19</sup> The establishment of these databases provides a convenient platform for researchers to study m<sup>6</sup>A mechanism in tumors.

With further study of m<sup>6</sup>A modification in mRNA, it was found that m<sup>6</sup>A modification can regulate the stability and translation of mRNA in various biological processes. However, RNA stability mediated by m<sup>6</sup>A modification is a complex process involving crosstalk with other mRNA modifications, RNA species, or decay pathways. The regulation of mRNA degradation is the main factor affecting the overall mRNA abundance in cells. As efficient transcription results in a relatively long poly (A) tail, m<sup>6</sup>A modification was not detected in the poly (A) tail; therefore, it may not be involved in polyadenylation-dependent mRNA degradation, which indirectly maintains mRNA stability.<sup>20</sup> Just as identified using high-throughput sequencing analysis, m<sup>6</sup>A modification is enriched in the 3'-UTR region, which contains several important functional domains required for mRNA degradation, such as AU-rich elements (ARE), iron reaction elements (IRE), and cytoplasmic polyadenylation elements (CPE). Moreover, the 3'-UTR is a region targeted by microRNAs (miRNAs); therefore, the possibility that m<sup>6</sup>A modification is involved in regulating mRNA stability cannot be ruled out.<sup>21,22</sup> This characteristic that the mRNA stability is maintained by m<sup>6</sup>A-dependent mode has been identified in tumors; for example, Wilms' tumor 1-like protein (WTAP) interacts with its m<sup>6</sup>A target, long non-coding RNA (lncRNA) DIAPH1-AS1, to promote the growth and metastasis of nasopharyngeal carcinoma in an m<sup>6</sup>A-dependent manner.<sup>23</sup> Another study on head and neck tumors found that the m<sup>6</sup>A reader-IGF2BP2 could maintain the mRNA stability of Slug in head and neck squamous cell carcinoma cells in an m<sup>6</sup>A-dependent manner, thereby promoting lymphatic metastasis and epithelial-to-mesenchymal transformation (EMT) of tumors.<sup>24</sup> In contrast to m<sup>6</sup>A enhancing mRNA stability, FTO,



**Figure 1** RNA modifications in tumor cells interact with each other to maintain the dynamic balance of the tumor microenvironment. (A) m<sup>1</sup>A is generally located in the 5'-UTR of mRNA and can be converted to m<sup>6</sup>A by Dimroth rearrangement. (B and C) m<sup>6</sup>A and m<sup>5</sup>C modifications mediate mRNA processing, stability of RNA, post-translational protein modification, etc. (D) m<sup>6</sup>A modification of carRNA reversely regulates chromatin. (E) Ψ in rRNA aggregated at the binding site of tRNA and mRNA and thus participated in RNA translation. m<sup>7</sup>G modification mainly affects tRNA and rRNA and mediates post-translational protein modification. (F) RNA modifications play an important role in the material exchange and information transmission between tumor cells and other cells through the cell-cell "internet" by EVs.

as an m<sup>6</sup>A demethylase, reduces the mRNA stability of apolipoprotein (APOE) by reducing its m<sup>6</sup>A modification, eventually inhibiting glycolysis and growth in papillary thyroid carcinoma.<sup>25</sup> Similarly, ALKBH5, another m<sup>6</sup>A demethylase, also reduces the mRNA stability of PKMYT1 by reducing its m<sup>6</sup>A modification, thereby inhibiting the invasion of gastric cancer.<sup>26</sup>

Precursor proteins are notoriously inactive and often undergo a series of post-translational processes before transforming into mature functional proteins. Studies on the post-translational modification of proteins and m<sup>6</sup>A in tumor cells have made some achievements. The relationship between the interaction, localization, and phosphorylation of the METTL3-METTL14-WTAP complex produced by m<sup>6</sup>A modification has been recognized.<sup>27</sup> Accordingly, phosphorylated-YTHDF2, mediated by EGFR/SRC/ERK signaling, is located at serine 39 and threonine 38 sites. In order to stabilize the YTHDF2 protein and promote the invasive growth of glioblastoma,<sup>28</sup> phosphorylation of AKT in prostate cancer has also been shown to be downstream of METTL3/YTHDF2/LHPP/NKX3-1 to induce tumor proliferation and migration.<sup>29</sup> The ubiquitination and SUMOylation of proteins are reversible post-translational modifications that play an important role in molecular regulation.<sup>30</sup> Furthermore, the roles of m<sup>6</sup>A and ubiquitin post-translational modifications have been demonstrated in different tumor subtypes, such as clear cell carcinoma of the kidney and stomach and ovarian cancer.<sup>31–33</sup> Moreover, m<sup>6</sup>A methylation promotes cancer development by ubiquitination of histones.<sup>34</sup> Also, the small ubiquitin-like modifier (SUMO) catalytic cycle includes maturation, activation, binding, linking, and modification. Disorders of the SUMO system are associated with many diseases, particularly tumors. SUMOylation is widely involved in carcinogenesis, DNA damage response, proliferation, metastasis, and apoptosis of cancer cells.<sup>35</sup> The roles of m<sup>6</sup>A modification and SUMOylation in tumors are also being studied. For example, METTL3 is modified by SUMO1 primarily at lysine residues, including K177, K211, K212, and K215, which the SUMO1-specific protease, SENP1, can reduce. SUMOylation of METTL3 significantly inhibits its m<sup>6</sup>A methyltransferase activity, thereby

decreasing m<sup>6</sup>A mRNA levels.<sup>36</sup> The influence of SUMOylation on the ability of YTHDF2 to bind m<sup>6</sup>A modified mRNA and the regulation of mRNA after binding have also been found. Therefore, a new mechanism by which the m<sup>6</sup>A reading protein, YTHDF2, promotes cancer development was revealed.<sup>37</sup> The SUMO-modified METTL3 made CirC\_0000677 promote proliferation and drug resistance in colorectal cancer (CRC)<sup>38</sup> (Figure 1B).

Finally, the one-way flow of genetic instructions from DNA to RNA to protein is now the dominant idea in many studies. However, in a recent study, we found that the knockout of m<sup>6</sup>A methylation-related enzymes, METTL3 or YTHDC1, in embryonic stem cells from mice increased chromatin openness and activated transcription through chromosome-associated regulatory RNA (carRNA) in an m<sup>6</sup>A-dependent manner. m<sup>6</sup>A acts as a switch that influences the abundance of carRNAs, thereby regulating nearby chromatin status and downstream transcription<sup>39</sup> (Figure 1D). Therefore, the process of methylation in cells is reversible and dynamic. None of the writers, the erasers, or readers are isolated from each other, which can be explored in terms of their functions.

There have been far fewer studies on m<sup>5</sup>C, m<sup>7</sup>G, m<sup>1</sup>A, Ψ, and A-to-I compared to those on m<sup>6</sup>A;<sup>40</sup> however, this does not mean that these RNA modifications are not important. Therefore, these RNA modifications are discussed in this review.

## 5-Methylcytosine (m<sup>5</sup>C)

The mRNA distribution characteristics of m<sup>5</sup>C modifications are highly conserved in mammals; however, the genes modified by m<sup>5</sup>C modifications in different tissues are specific. A recent study has suggested that m<sup>5</sup>C modification is mainly distributed in CG-enriched regions.<sup>41</sup> Studies have found that NOP2/Sun domain family member 2 (NSUN2) (“writer”) protein is the main mRNA m<sup>5</sup>C methyltransferase, and its activity depends on C271 and C321 sites. Loss of NSUN2 prevents mRNA from being transported from the cell nucleus.<sup>42</sup> The nucleation regulator protein, Aly/REF export factor (ALYREF) (“reader”), specifically binds to the m<sup>5</sup>C modified site through lysine 171, thereby promoting mRNA nucleation<sup>43</sup> (Figure 1C).

The m<sup>5</sup>C modification is distributed with mRNA, enriched around the 5'-UTR and 3'-UTR, and conserved in transfer RNA (tRNA) and ribosomal RNA (rRNA). It is dynamically regulated by related enzymes, including methyltransferases (members of the NSUN, DNMT, and TRDMT families), demethylases (the Ten-eleven translocation family and AlkB homolog 1, ALKBH1), and binding proteins (ALYREF and YBX1). Previous studies have indicated that the m<sup>5</sup>C modification is involved in multiple RNA metabolic processes, including mRNA output, RNA stability, and translation<sup>44,45</sup> (Figure 1C).

The role of high-throughput technology in m<sup>5</sup>C modification is also reflected. Researchers predicted the prognosis of m<sup>5</sup>C regulator-NSUN3 and NSUN4 on lung squamous cell carcinoma (LUSC) by combining the public LUSC data set of LUSC.<sup>46</sup> CIBERSORT tool and TIMER database were used to evaluate the relationship between the risk model of m<sup>5</sup>C-related lncRNA in lung adenocarcinoma and tumor infiltrating immune cells;<sup>47</sup> Scientists obtained the expression matrix of m<sup>5</sup>C lncRNA in breast cancer (BC) from the cancer genome atlas database, and finally constructed a BC-specific m<sup>5</sup>C lncRNA risk model.<sup>48</sup> What's more, researchers obtained triple negative breast cancer (TNBC) data from cancer genome map and gene expression summary, and analyzed the specificity and role of m<sup>5</sup>C regulator-NSUN2 and NSUN6 in tumor immune microenvironment.<sup>49</sup> Through TCGA database, NGS analysis and other means, the role of m<sup>5</sup>C modification in different types of tumors has been gradually understood.

Similar to m<sup>6</sup>A modification, m<sup>5</sup>C modification is also involved in the post-protein modification; ubiquitination and SUMOylation of m<sup>5</sup>C contribute to tumor development. The reaction between ubiquitin modification and m<sup>5</sup>C-modified mRNA in epithelial ovarian cancer (EOC) can lead to mRNA instability.<sup>50</sup> In a study of gastric cancer, the SUMO2/3 promoted the carcinogenic activity of NSUN2 by stabilizing NSUN2 and mediating its nuclear transport by directly interacting with NSUN2.<sup>51</sup> Moreover, the role of m<sup>5</sup>C modification in non-coding RNA has also been discovered by scientists. It was recently found that the lack of m<sup>5</sup>C in mitochondrial RNA (mtRNA) in oral cancer cells caused functional changes in the mitochondria, severely impairing their metabolic plasticity and promoting tumor progression. We believe that with technological progress, researchers will have a deeper understanding of m<sup>5</sup>C<sup>52</sup> (Figure 1C).

## $N^7$ -Methyladenosine( $m^7G$ )

$m^7G$  RNA methylation can regulate mRNA transcription, miRNA biosynthesis, biological functions, tRNA stability, and 18S rRNA nuclear processing and maturation<sup>53,54</sup> (Figure 1E).  $m^7G$  RNA methylation is present in various molecules, including the mRNA 5' cap, mRNA interior, pre-miRNA, tRNA, and rRNA. First, RNA phosphatase cuts off the last phosphate group at the 5' end of the mRNA, and then with the assistance of mRNA guanylyltransferase, GTP is linked to the 5' end of the mRNA in the form of a 5'-5' triphosphate bond. Subsequently, guanine- $N^7$ -methyltransferase transfers the methyl group on S-adenosine to the  $N^7$  position of guanine to complete the  $m^7G$  modification, and the 2'-O-ribose methylation modification of adjacent nucleotides is catalyzed by a specific methyltransferase.<sup>54,55</sup> Furthermore, RNA methyltransferase,  $m^7G$  methyltransferase-like 1 protein (METTL1), catalyzes  $m^7G$  modification of tRNA. METTL1 depletion leads to a decrease in the abundance and cell cycle of  $m^7G$  modified tRNA, especially for TCT-4-1-Arg,<sup>56,57</sup> and inhibition of carcinogenicity such as intrahepatic cholangiocarcinoma,<sup>58</sup> lung cancer<sup>59</sup> bladder cancer.<sup>60</sup> A recent study showed that increased  $m^7G$  modification of tRNA subsets by the METTL1/WD repeat domain 4 (WDR4) complex stabilizes these mRNAs to improve the efficiency of protein translation and reduce ribosomal dormancy, leading to higher malignancy in human cancers.<sup>61</sup> In hepatocellular carcinoma,  $m^7G$  methylation and ubiquitination of p53 lead to decreased expression of p53 and promote tumor progression<sup>62</sup> (Figure 1F). In addition, scientists recently found that  $m^7G$  methylation inhibits lung cancer cell migration by promoting the maturation of miRNA let-7,<sup>63</sup> thereby discovering the role of  $m^7G$  in non-coding RNA and providing new ideas for future research.

## $N^1$ - Methyladenosine ( $m^1A$ )

$m^1A$  is produced by adding methyl groups to the  $N^1$  position of adenosine. Under physiological conditions,  $m^1A$  is positively charged and may influence local RNA structures or protein-RNA interactions. Its methyl group is located at the Watson-Crick base-pairing interface, thus blocking normal base pairing with thymine nucleoside or uridine. Alternatively,  $m^1A$  can form hydrogen bonds with other nucleosides through Hoogsteen base pairing, which is relatively unstable compared to the normal A:U or A:T base pairing. In the case of chemical transformation,  $m^1A$  can undergo Dimroth rearrangement under alkaline conditions to form  $m^6A$ .<sup>5,40,64</sup> (Figure 1A). However, recent studies mainly focused on  $m^6A$ , unlike  $m^1A$ , which was relatively poorly studied.

$m^1A$  is distributed among mRNA, tRNA, rRNA, and mtRNAs. Unlike  $m^6A$ ,  $\Psi$ , and other RNA modifications,  $m^1A$  is mostly distributed in the 5'-UTR of mRNA (Figure 1A). The locus distribution of  $m^1A$  in tRNA was 9,14,22,57,58. The expression of  $m^1A$  modification was low at sites 14 and 22 and caused negligible biological effects. The modification of site 57 occurs as an intermediate of 1-methylinosine ( $m^1I$ ). The most abundant  $m^1A$  modifications are at sites 9 and 58, which play an important role in tRNA's tertiary structure and stability maintenance. There are three  $m^1A$  sites in the nuclear-coding rRNA, all located on the large subunit rRNA. Although mtRNA lacks the 5'-UTR,  $m^1A$  was detected in its CDS coding region. In addition, the mitochondrial methyltransferases TRMT61B and TRMT10C can target mtRNAs.<sup>5,65</sup>

As mentioned before,  $m^1A$  modification in tumors is rarely studied compared with other RNA modifications. One of the main reasons is that  $m^1A$  modification is rare in RNA.<sup>66</sup> Previous technical limitations were mainly based on the normal physiological effects of  $m^1A$  modifications in cells under cell culture conditions. However, with the progress of high-throughput sequencing technology, the role of  $m^1A$  in different types of tumors, such as hepatocellular carcinoma,<sup>67</sup> glioma<sup>68,69</sup> and bladder cancer<sup>70</sup> has been gradually clarified. It has been found that the upregulation of  $m^1A$  expression by TRMT6 and other methyltransferase family members promotes the malignant behavior of these tumors. Therefore,  $m^1A$  can be regarded as a new tumor marker for monitoring tumor development and the prognostic evaluation of tumor therapy in these tumors.<sup>67-70</sup>

## Pseudouridine ( $\Psi$ )

The ribosome is the site of protein synthesis, and rRNA is the most abundant type of RNA in cells.  $\Psi$ , the most abundant post-transcriptional modification of RNA, is the fifth nucleotide.  $\Psi$  is the C-C glycoside isomer of uridine (U). It binds the C5 atoms of the base to the glycoside bond, which allows  $\Psi$  to have an additional hydrogen bond donor at the non-Watson-Crick edge and

then contributes to maintaining the stability of its host RNA.<sup>6</sup> In addition,  $\Psi$  aggregates in important functional regions of rRNA, especially at the binding sites of tRNA and mRNA, and thus participates in RNA translation modifications<sup>71</sup> (Figure 1E).

With the development of high-throughput assays, thousands of  $\Psi$  sites have been dynamically distributed on the coding sequence and 3'-UTR of mRNA, and  $\Psi$  has been identified in the positions associated with the alternative splicing region in the newly born pre-mRNA. PUS1, PUS7, and RPUSD4, three tissue-specific pre-mRNA-modified  $\Psi$  synthases, control a wide range of changes in pre-mRNA splicing and 3'-terminal processing.<sup>72</sup> The increase in the expression of PUS7 inhibits pseudouridylation of tRNA in glioblastoma stem cells (CSCs) and leads to the generation of glioblastoma.<sup>73</sup> Similarly, HSP90 can rely on the overexpression of PUS7 to promote CRC metastasis.<sup>74</sup> Recent research on  $\Psi$  has revealed new findings. In neuroblastoma cells, SNHG25 promotes the accumulation of SNORA50C and the assembly of the associated small nucleolar ribonucleoprotein (snoRNP) through pseudouridine synthase 1 (DKC1), which ultimately promotes the growth and migration of neuroblastoma (NB) cells. Eventually, there will be more functions of  $\Psi$  in more RNA types that will be recognized.

## Adenosine-to-Inosine (A-to-I)

The conversion of adenosine to inosine by hydrolysis has become the most common RNA editing in higher eukaryotes, which can be considered a special type of RNA "modification" and plays a vital role in coding RNA and non-coding RNA.<sup>7</sup> Such irreversible adenosine deamination occurs in double-stranded RNA (dsRNA), which is highly conserved in humans and is mediated by the RNA-acting adenosine deamination enzyme family, ADAR.<sup>75</sup> A-to-I plays different roles in different organelles. When identified as guanosine, it can lead to recoding and alternative splicing in proteins or make some changes in the specificity of miRNA; when recognized by inosine-binding proteins, its transcripts can be retained in the nucleus or degraded. Recent studies have found that specific dsRNA sensors in cancers induce antiviral responses that inhibit cell division and promote apoptosis, a new addition to RNA-targeted therapy.<sup>75,76</sup> In addition, an increasing number of studies have focused on the RNA editing enzyme, ADARs, and found that ADAR1-mediated A-to-I editing can effectively maintain the stability of tumor stem cells in glioblastoma and cell immortalization in breast cancer as a proto-oncogene.<sup>77,78</sup> In addition, when the expression of ADAR1 is downregulated, some tumor suppressor miRNA are activated to inhibit the growth and invasion of triple-negative breast cancer cells.<sup>79</sup>

## RNA Modifications in Antisense RNA in Tumor Cells

Reviewing the above types of RNA modifications, we can clearly understand that these modifications exist in both coding and non-coding RNAs, playing their respective functions. Here, we discuss the RNA modifications of a more overlooked RNA, the antisense RNA.

An RNA molecule complementary to mRNA and other RNA antisense RNA in eukaryotes has been found.<sup>80,81</sup> Since ribosomes cannot translate double-stranded RNA, the specific complementary binding of antisense RNA to mRNA inhibits the translation of the mRNA.<sup>82</sup> Based on this principle, in recent years, antisense RNA genes have been synthesized artificially and transcribed into antisense RNA by introducing them into cells,<sup>82,83</sup> which can inhibit the expression of a specific gene and block the function of the gene, suggesting that the role of RNA modifications in antisense RNA is worth studying in tumors, such as lncABHD11-AS<sup>84</sup> and lncMAPKAPK5-AS.<sup>85</sup> For example, m<sup>6</sup>A reader YTHDF3 enhances its interaction with DICER1-AS1 and participates in the transcription of the sense gene DICER1, thereby regulating glycolysis and tumor development in pancreatic cancer.<sup>86</sup> Although there are few studies on RNA modifications in antisense RNA, and almost all of them focus on m<sup>6</sup>A, antisense RNA still needs to be given attention because it can suppress the expression and function of target genes like cancer-promoting genes. Moreover, RNA modifications can enhance the function mentioned above, providing the prospect for targeted tumor therapy in the future.<sup>82,83</sup>

## RNA Modifications in the Tumor Microenvironment

The tumor microenvironment refers to tumor cells' internal and external environments during tumorigenesis, growth, and metastasis. This finding is clinically significant for tumor prevention and treatment.<sup>87</sup> The complex tumor microenvironment contains various cells and components: (1) immune cells: T and B lymphocytes, tumor-associated macrophages (TAM), dendritic cells (DC), natural killer cells (NK), neutrophils, myeloid-derived inhibitory cells (MDSC), etc.; (2) stromal cells: cancer-

associated fibroblasts (CAF), pericytes, mesenchymal stromal cells, etc.; (3) extracellular matrix (ECM) and other secretory molecules: growth factors, cytokines, chemokines, and extracellular vesicles (EVs); (4) Blood and lymphatic vascular networks.<sup>10–13</sup> The relationship between RNA modifications and the tumor microenvironment, especially the role of m<sup>6</sup>A and m<sup>5</sup>C modifications, has been described in many kinds of cancer subtypes such as lung adenocarcinoma,<sup>88,89</sup> pancreatic carcinoma<sup>90,91</sup> and CRC;<sup>92,93</sup> however, these studies are not in-depth and very few in number (Figure 1).

Similar to solid tumors, studies of RNA modifications in hematologic malignancies have been conducted.<sup>94,95</sup> For example, lncRNA UCA1 can promote the progression of acute myeloid leukemia (AML) by increasing the expression of METTL14.<sup>96</sup> Furthermore, the level of m<sup>6</sup>A expression in follicular lymphoma and AML may be used to monitor the tumor microenvironment for targeted treatment. Similarly, detecting m<sup>6</sup>A modification levels in lncRNA helps evaluate the prognostic level of patients with acute and chronic myelogenous leukemia.<sup>97,98</sup>

## Tumor Hypoxia and Biotransformation

The main reason why carcinomas are difficult to cure is that tumor cells will continue to adapt to the adverse tumor microenvironment quickly. Tumor hypoxia is mainly caused by an imbalance between low oxygen supply caused by abnormal vascularization and high oxygen consumption of tumor cells.<sup>99</sup> The rapid proliferation of tumor cells accelerates oxygen consumption and prevents the amount of oxygen available for further diffusion into tumor tissues. For example, hypoxia-mediated reader-YTHDF2 overexpression of m<sup>6</sup>A results in the activation of the mTOR/AKT axis, thereby promoting the proliferation and invasion of lung squamous cell carcinoma.<sup>100</sup>

In hypoxic environments, tumor cells mainly absorb energy through glycolysis. Some recent studies have shown the role of RNA modifications in hypoxia and glycolysis in tumor cells. They also show that the dysregulation of energy metabolism caused by abnormal RNA modifications like m<sup>6</sup>A may be related to the malignant biological behavior of tumors.<sup>101</sup> Furthermore, among solid tumors, pyruvate kinase muscle isozyme M2 (PKM2) is involved in tumor metabolism and growth as a rate-limiting enzyme in glycolysis, while overexpression of ALYREF promotes bladder cancer cell proliferation through glycolysis mediated by indirect upregulation of PKM2 expression through activation of ALYREF and hypoxia-inducible factor-1  $\alpha$  (HIF-1 $\alpha$ ).<sup>102,103</sup> FTO can reduce the mRNA stability of APOE and inhibit glycolysis in thyroid papillary carcinoma (PTC) by reducing m<sup>6</sup>A modification.<sup>25</sup> Furthermore, RNA modifications also act on glycolysis in liquid tumors. For example, phosphofructokinase PFKP and lactate dehydrogenase B (LDHB), two key glycolytic genes, were effectively regulated by FTO/m<sup>6</sup>A/YTHDF2. R-2-hydroxyglutaric acid (R-2HG) restored glycolysis in AML cells by inhibiting the expression of PFKP/LDHB mediated by FTO/m<sup>6</sup>A/YTHDF2.<sup>104</sup>

Moreover, most studies on RNA modifications in the biotransformation of tumor cells have focused on the energy metabolism of tumors, especially glycolysis and lactic acid synthesis, in the anoxic environment of tumor cells. However, fat metabolism, deoxycholic acid metabolism, and other bio-transformations are equally important and can be regulated by RNA modifications. The increase in R-2HG produced by IDH1/2 inhibited adipogenesis and decreased the activity of the adipose-related protein, FTO, thereby increasing the level of m<sup>6</sup>A in leukemia cells. The MYC/CEBPA signaling pathway was then inhibited to prevent leukemia progression.<sup>105</sup> In addition, m<sup>6</sup>A modification can regulate deoxycholic acid in deoxycholic acid metabolism to inhibit gallbladder cancer.<sup>106</sup>

In summary, the studies of m<sup>6</sup>A modification in hypoxia and biotransformation have been considered for both solid and liquid tumors. However, it is undeniable that other RNA modifications, except m<sup>6</sup>A, have not been sufficiently reported to date, which needs to be considered by the scientists in future.

## Immune Escape and Cell Networks in Tumors

Currently, many studies on RNA modifications have focused only on tumor cells. However, tumor cells are not isolated, and their growth and metastasis are influenced by the assistance of other cells in the body or EVs in the intracellular environment. The complex interactions between cancer and immune cells are also important in researching new cancer treatments. Immune cells can also stimulate the growth of tumor cells instead of protecting the body. For example, neutrophils can promote the circulation of the cell cycle of circulating tumor cells in breast cancer.<sup>107</sup>

Recent studies have suggested that the deletion of METTL3 in macrophages reshaped the tumor microenvironment by enhancing tumor invasion by M1- and M2-like TAM and regulatory T Cell (Treg) and had a synergistic effect on the growth

and invasion of tumor cells, leading to high malignancy<sup>108</sup> However, deleting the mRNA m<sup>6</sup>A-binding protein YTHDF1 in dendritic cells enhanced anti-tumor immunity<sup>109,110</sup> Similarly, METTL3-mediated methylation of m<sup>6</sup>A RNA in NK cells promotes anti-tumor immunity.<sup>111</sup> Finally, ALKBH5 promotes the assembly of hypoxia-induced paraspeckles and secretion of IL8 to generate an immunosuppressive tumor microenvironment.<sup>112</sup> For example, intrinsic ALKBH5 inhibits T-cell proliferation and cytotoxicity by maintaining PD-L1 expression in tumor cells, which promotes immune escape.<sup>113</sup> In addition to m<sup>6</sup>A, METTL1 and the m<sup>5</sup>C modulator-NOP2 are associated with immune invasion in many tumor subtypes.<sup>114,115</sup> As a piece of evidence, upregulation of METTL1 enhances TGF- $\beta$ 2 translation by inducing myeloid-derived suppressor cells to form an immunosuppressive environment, thereby leading to HCC recurrence.<sup>116</sup> Also, the NSUN2 promotes the progression of NPC by regulating immune infiltration.<sup>117</sup> Therefore, we can clarify the role of RNA modifications in tumor immunity.

EVs are increasingly regarded as important mediators of intercellular communication and the transport of macromolecules. As a piece of evidence, cells communicate with each other using some miRNAs transported by EVs, which constitutes a cell-cell “internet”.<sup>118</sup> RNA modifications are efficiently delivered on such “internet.” Information and materials can be exchanged between tumor cells and immune cells through EVs.<sup>119</sup> Furthermore, M2-like TAM can secrete lncMAPKAPK5-AS1 (MAAS)-carrying exosomes (a type of EVs). These exosomes act as a medium for communication between TAM and tumor cells, which can be transferred to HBV + HCC cells and promote the proliferation of HCC cells<sup>85</sup> (Figure 1F).

Therefore, this provides a new idea for future studies on RNA modification in the tumor microenvironment.

## Tumor Invasion and Metastasis

### Epithelial-to-Mesenchymal Transformation (EMT)

EMT is an important biological process by which epithelial-derived malignant tumor cells acquire the ability to migrate and invade. Through EMT, epithelial cells lose their polarity and connection to the basement membrane and other epithelial phenotypes and acquire a higher ability to migrate, invade, resist apoptosis, and degrade the extracellular matrix. EMT is characterized by the decreased expression of cell adhesion molecules (such as E-cadherin), the transformation of the cytoskeleton from keratin to vimentin, and mesenchymal cell morphology.<sup>120,121</sup> The role of m<sup>6</sup>A modification in EMT has been extensively described in different tumors,<sup>122</sup> such as glioblastoma,<sup>123</sup> lung adenocarcinoma, breast cancer,<sup>124</sup> head and neck cancer,<sup>24</sup> etc. In addition, METTL3 is an important promoter of EMT and metastasis of gastric cancer cells. It is an important downstream target gene that plays an important regulatory role in the metastasis of gastric cancer cells and breast cancer.<sup>125</sup> m<sup>5</sup>C modification and m<sup>7</sup>G methyltransferase- WDR4 can enhance EMT in lung adenocarcinoma<sup>102</sup> and hepatocellular carcinoma cells.<sup>62,126</sup>

In addition to EMT, the extracellular matrix also plays an important role. It has been found that the upregulation of m<sup>5</sup>C regulatory factor- NSUN2 is closely related to spliceosome, RNA degradation, cell cycle signaling pathway, and RNA polymerase in TNBC.<sup>49</sup> Moreover, another m<sup>5</sup>C regulatory factor-NSUN6 downregulation is associated with extracellular matrix receptor interactions, metabolism, and cell adhesion. m<sup>5</sup>C-related-lncRNAs in pancreatic ductal adenocarcinoma and lung adenocarcinoma can regulate the tumor immune microenvironment,<sup>47,127</sup> and METTL1-mediated m<sup>7</sup>G tRNA modification promotes bladder cancer development through extracellular matrix regulation,<sup>60</sup> thereby inspiring subsequent studies on the role of RNA regulation in tumors.

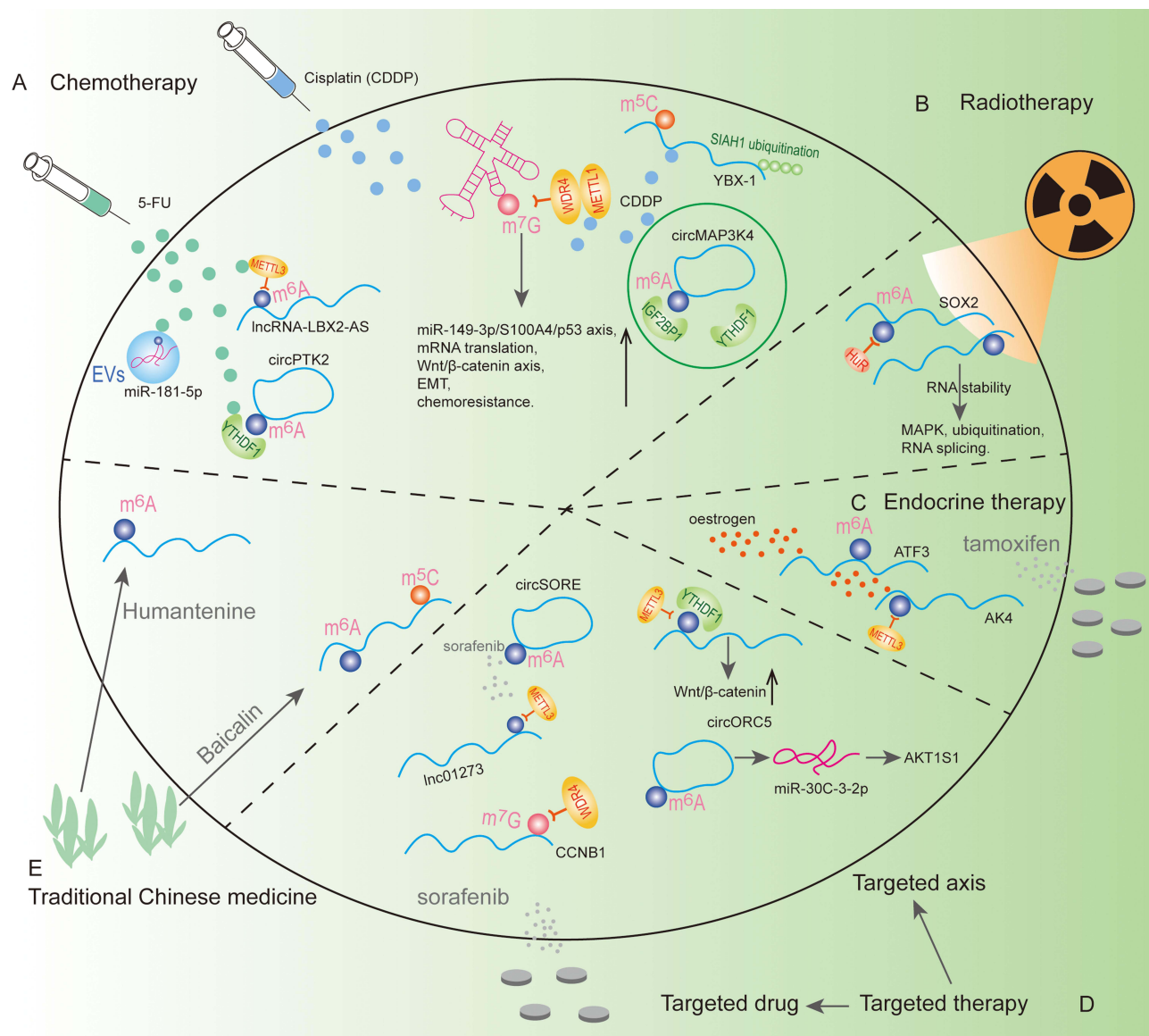
## Angiogenesis

Angiogenesis has been recognized as a marker of cancer. Newborn blood vessels can provide energy to tumors, promote tumor growth and metastasis, and lead to drug resistance and recurrence.<sup>128,129</sup> Moreover, the employment of anti-angiogenesis drugs is becoming a new method of tumor therapy, aiming to cause less harm to tumor patients and have a better prognosis than traditional therapy.<sup>130</sup> The role of RNA modifications in angiogenesis has also gradually been recognized. For example, the increased m<sup>6</sup>A can promote angiogenesis in glioblastoma and head and neck squamous cell carcinoma.<sup>123,131</sup> Furthermore, m<sup>7</sup>G Methyltransferase METTL1 promotes angiogenesis in peripheral vascular diseases.<sup>132</sup> However, the detailed mechanism of m<sup>6</sup>A in tumor angiogenesis is unclear, and the role of other RNA modifications in tumor angiogenesis has not been clarified. Therefore, these are areas that scientists should explore in the future.

In summary, RNA modifications in tumor cells are not isolated, static, and simple but occur in an interconnected, dynamic, and complex tumor microenvironment. Therefore, the existing research on RNA modifications and tumor microenvironment is insufficient, and future studies can be more detailed, systematic, and comprehensive to provide new ideas for tumor treatment.

## RNA Modifications Regulate Tumor Treatment Resistance

It is well known that drug resistance in tumor cells is an important factor leading to tumor treatment failure. Recently, RNA modifications have been found to play a unique role in regulating tumor drug resistance. Therefore, it is necessary to summarize the regulatory effects of RNA modifications on tumor treatment, such as 5-fluorouracil (5-FU), cisplatin, and other drugs, to improve tumor resistance and explore new options for tumor treatment in the future.<sup>133</sup> (Figure 2, Table 1).



**Figure 2** Overview of RNA modifications in different therapies. **(A)** Chemotherapy drugs-5-FU and CDDP regulate the signal pathways/axis of lncRNA, circRNA and miRNA by regulating the regulators of m<sup>6</sup>A, m<sup>5</sup>C and m<sup>7</sup>G (“Writer”-METTL1, METTL3, “Reader”-YTHDF1), thus inducing tumor chemotaxis. **(B)** Radiotherapy antagonizes the action of m<sup>6</sup>A modification by destroying the stability of mRNA in tumor cells. **(C)** ATF3 and AK4 regulated by m<sup>6</sup>A “Writer”-METTL3 can regulate the resistance of breast cancer cells to tamoxifen. **(D)** The signal pathways/target axis mediated by RNA modification can affect the biological behavior of different types of tumors; m<sup>6</sup>A, m<sup>7</sup>G “Writer”-METTL3, WDR4 can induce sorafenib resistance in HCC cells. **(E)** Some active components in traditional Chinese medicine have also been found to interact in RNA modification. In the figure, the upward black arrow represents “upward adjustment”, and the downward black arrow represents “downward adjustment”.

**Table 1** Comparison of Different Therapeutic Methods in RNA-Modified Tumors

Type	Specific Drug	Mechanisms	Advantage	Disadvantage
Chemo-therapy	5-fluorouracil (5-FU)	Inhibits thymidine synthase and blocks the formation of thymidine; m <sup>6</sup> A-related markers affect its efficacy	Used alone or combined with other chemotherapy drugs.	Short half-life, easy to pass through blood brain barrier. Decreased blood count, nausea, vomiting and phlebitis
	Cisplatin (CDDP)	Cross-link purine bases on DNA and interfere with DNA repair mechanism. m <sup>6</sup> A, m <sup>5</sup> C and m <sup>7</sup> G-related markers with signal pathway/axis and other ways affect its efficacy		
Radio-therapy		Damages DNA on targeted cancer cells. m <sup>6</sup> A relies on HuR, MAPK, ubiquitin and RNA splicing to promote radiotherapy resistance.	Reduce tumor range, create conditions for surgery, prevent recurrence.	Residual tumor cells patients with advanced tumor or patients with cachexia, radiotherapy is contraindicated
Endocrino-therapy	Tamoxifen	Regulate estrogen receptor	Make the tumor smaller/slow down the growth rate.	Related to hormone receptor, time too long, lead to hormone level imbalance.
Targeted therapy	Signal path/target axis	Signal pathways/axis involve p53, Wnt, $\beta$ -catenin and other genes affects the biological progress of tumor cells	Precise treatment of specific tumors	Expensive, cause the reaction of human autoimmune system
	Sorafenib	Inhibits tumor growth and angiogenesis by targeting RAF/MEK/ERK pathway and receptor tyrosine kinase. m <sup>6</sup> A, m <sup>7</sup> G-related mRNA, lncRNA and circRNA affect its efficacy.	Clearly locate the carcinogenic site without damaging the surrounding normal tissues	
Traditional Chinese medicine	Humantenine, Baicalin	m <sup>6</sup> A modification can affect the Efficacy with epigenetic modification	Good supplement to tumor treatment	Mechanism is still unclear and needs further study

## Chemotherapy

### 5-Fluorouracil (5-FU)

5-FU is commonly used to treat squamous cell carcinomas.<sup>134</sup> As an anti-metabolite that prevents cell proliferation, 5-FU mainly inhibits thymidine synthase and blocks the formation of thymidine required for DNA synthesis. Although it has a relatively short half-life (< 30 min), it can easily enter the brain through passive diffusion. Clinically, it can be used either as a single agent or in combination with other chemotherapeutic therapies.<sup>135</sup>

lncRNA -LBX2 antisense RNA1 (LBX2-AS1) is an important regulator of cancer progression. The increase in LBX2-AS1 expression in CRC is mediated by METTL3-dependent m<sup>6</sup>A methylation, which promotes CRC progression and leads to resistance to 5-FU in CRC.<sup>136</sup> Similarly, circPTK2 can mediate the m<sup>6</sup>A “reader” protein YTHDF1, leading to the 5-FU resistance on CRC.<sup>137</sup> Exosomes are naturally occurring EVs that carry biomolecules such as proteins, miRNAs, and metabolites.<sup>138</sup> Its properties suggest special effects for the treatment of tumors. Exosomes secreted by CAF from CRC inhibit the efficacy of 5-FU by transporting miRNA-miR-181D-5p, which m<sup>6</sup>A modifies. Therefore, a new discovery has been made regarding the mechanism of chemotherapeutic resistance in CRC.<sup>139</sup>

Furthermore, METTL3 is an effective target for enhancing the therapeutic effects in patients with pancreatic cancer. METTL3-depleted pancreatic cancer cells showed higher sensitivity to anti-cancer agents than those without the regulation of METTL3, such as gemcitabine, 5-FU, cisplatin, and radiation.<sup>140</sup> In addition to m<sup>6</sup>A modification, other

RNA modifications such as m<sup>5</sup>C and m<sup>7</sup>G have not been studied in relation to 5-FU, which provides a new idea for future research on RNA modifications such as m<sup>5</sup>C and m<sup>7</sup>G and tumor chemotherapy resistance. (Figure 2A)

### Cisplatin (CDDP)

Cisplatin is another chemotherapy drug that has also been commonly used and has good efficacy in treating tumors, with poor efficacy after radiotherapy and surgical resection, especially in head and neck tumors.<sup>141</sup> Its mode of action is associated with its ability to cross-link purine bases on DNA. Furthermore, it can interfere with DNA repair mechanisms, leading to DNA damage and the subsequent apoptosis of cancer cells.<sup>142,143</sup>

The combined effect of RNA modifications and cisplatin showed that increased METTL1 results in increased modification and expression of m<sup>7</sup>G-modified tRNA, which leads to enhanced codon recognition during mRNA translation, upregulation of the WNT/β-catenin signaling pathway, promotion of EMT, and chemoresistance to cisplatin and docetaxel in vitro and in vivo.<sup>144</sup> The combined role of cisplatin and RNA modifications in tumors other than head and neck tumors is also widely recognized. The overexpression of METTL1 in m<sup>7</sup>G regulation makes colon cancer cells sensitive to cisplatin by regulating the miR-149-3p /S100A4/p53 axis.<sup>145</sup> m<sup>5</sup>C-related lncRNA can regulate the micro-environment of low-grade glioma;<sup>146</sup> m<sup>5</sup>C-modified mRNA can also be unstable owing to YBX-1 ubiquitination by SIAH1 at Lys304, thus making EOC cells sensitive to intracellular cisplatin (CDDP). In addition, the overexpression of SIAH1 enhances the anti-tumor efficacy of cisplatin in vitro and in vivo.<sup>50</sup> Certainly, there has been some progress in studying m<sup>6</sup>A modifications and drug resistance in tumors. m<sup>6</sup>A demethylase-ALKBH5 leads to drug resistance in EOC, inhibits bladder cancer proliferation through glycolysis, and enhances sensitivity to cisplatin.<sup>147,148</sup> IGF2BP1 and YTHDF1, as m<sup>6</sup>A readers, are both vital in cisplatin's resistance. CircMAP3K4 modified by IGF2BP1 can protect HCC cells from cisplatin.<sup>149</sup> Similarly, YTHDF1 can also mediate m<sup>6</sup>A modifications in breast cancer cells, leading to cisplatin resistance<sup>150</sup> (Figure 2A).

### Radiotherapy

Radiotherapy, as an important treatment of tumor, targets cancer cells by damaging DNA, which has been found to be related to tumor immune microenvironment.<sup>151</sup> It has been shown that radiation in GBM (glioblastoma) cells enhances the expression of METTL3, thereby enhancing the m<sup>6</sup>A level. By recruiting HuR (human antigen R), m<sup>6</sup>A modification can improve the stability of SOX2, then resisting radiotherapy.<sup>152</sup> Similarly, in pancreatic cancer (PC), MAPK, ubiquitin and RNA splicing pathways can rely on m<sup>6</sup>A modification to promote radio-resistance.<sup>140</sup> The point that m<sup>6</sup>A antagonizes the maintenance of mRNA stability and the effect of radiotherapy has been gradually recognized by researchers, which has an impact on the improvement of tumor treatment.<sup>153</sup> (Figure 2B).

### Endocrine Therapy

Some specific tumors have been proved to be related to hormone levels, for example, breast cancer. Tamoxifen (TAM) is the most prescribed selective estrogen receptor modulator (SERM) for hormone receptor positive breast cancer patients.<sup>154</sup> A recent study found that the protein expression level of ATF3 in tamoxifen resistant (TamR) MCF-7 cells was significantly higher than that in corresponding parent cancer cells. Further research found that m<sup>6</sup>A-modified ATF3 could regulate the resistance of breast cancer cells to tamoxifen.<sup>155</sup> Similarly, another study found that the protein levels of adenylate kinase 4 (AK4) and m<sup>6</sup>A “writer” METTL3 in tamoxifen resistant (TamR) MCF-7 cells were significantly higher than those in their parent cells, and found a new m<sup>6</sup>A-mediated external transcriptome mechanism regulating AK4.<sup>156</sup> Through RNA modifications, tamoxifen, a traditional chemotherapy drug for breast cancer, has achieved better efficacy (Figure 2C).

### Targeted Therapy

Increasing tumor therapies can be reflected in targeted therapy owing to the increasingly thorough study of the role of RNA modifications. Various signaling pathways have been further studied, except for the above traditional treatment methods, whose role has gradually been recognized. Esophageal squamous cell carcinoma (ESCC) cells downregulate APC by METTL3/YTHDF coupling, thus increasing the activity of the Wnt/β-catenin pathway.<sup>157</sup> CircRNA can act as

miRNA sponges to regulate cancer progression. For example, circORC5-mediated m<sup>6</sup>A modification regulates the miR-30C-2-3p /AKT1S1 axis to inhibit gastric cancer tumor growth.<sup>158</sup> Moreover, several known molecularly targeted drugs are involved in RNA modifications, mainly m<sup>6</sup>A modification.<sup>159</sup> For example, sorafenib, a multi-kinase inhibitor, is a first-line targeted agent approved by the US Food and Drug Administration for advanced HCC.<sup>160</sup> Sorafenib can prolong the survival of patients with HCC by inhibiting tumor growth and angiogenesis by targeting the RAF/MEK/ERK pathways and receptor tyrosine kinases.<sup>161</sup> However, drug resistance limits their efficacy. The m<sup>6</sup>A methyltransferase METTL3 promotes m<sup>6</sup>A modification of the lncRNALINC01273, resulting in sorafenib resistance.<sup>162</sup> In sorafenib-resistant HCC, the increased level of circRNA-SORE is caused by increased m<sup>6</sup>A. These results revealed a new mechanism of sorafenib resistance and provided evidence for circRNA-SORE as a new drug target for sorafenib treatment in patients with advanced HCC.<sup>163</sup> m<sup>7</sup>G methyltransferase-WDR4 promotes mRNA stability and translation of CCNB1 to enhance HCC progression and contribute to sorafenib resistance.<sup>62</sup> However, the role of sorafenib in regulating m<sup>5</sup>C has not yet been studied (Figure 2D).

## Traditional Chinese Medicine

In addition to traditional chemotherapy drugs and molecular targeted drugs, some effective components extracted from traditional Chinese medicine have also been proved to have multiple targets, slight side effects and good tumor treatment effects.<sup>164,165</sup> Recently, some scholars found that Chinese herbal extracts can be regulated by m<sup>6</sup>A to play a role in the treatment of tumors.<sup>159</sup> Humantenine, an alkaloid isolated from *Gelsemium elegans*, was found to have an impact on the m<sup>6</sup>A-modified colon cancer cell line HCT116, through bioinformatics analysis.<sup>166</sup> Another study on liver cancer patients with type-2 diabetes (T2D) found that Baicalin significantly inhibited the epigenetic modification of m<sup>6</sup>A-modified HKDC1 in HepG2 tumors, thereby inhibiting T2D induced liver tumors.<sup>167</sup> These studies not only proved the anti-tumor effect of these traditional Chinese medicine preparations, but also improved their efficacy by exploring the influence of RNA modifications on their anti-tumor effect (Figure 2E).

In conclusion, these recent studies have highlighted the important role of RNA modifications in cancer therapy.

RNA modifications play different roles in various tumors. For example, regarding m<sup>6</sup>A modification, METTL14 plays the role of tumor inhibitor in CRC,<sup>168,169</sup> bladder cancer,<sup>170</sup> and breast cancer.<sup>171</sup> It is a carcinogenic factor in cervical cancer,<sup>172</sup> EOC,<sup>173</sup> pancreatic cancer<sup>174</sup> and leukemia<sup>175,176</sup> during their development and incidence.<sup>177,178</sup> Therefore, studies on RNA modifications should be carried out extensively and comprehensively in various types of tumors.

## Discussion

Tumor growth and development are complex processes. Under hypoxic conditions, tumor cells mediated by RNA modifications can still obtain energy through glycolysis to satisfy their growth needs.<sup>25,101,104,105,179</sup> When the surrounding nutrients are exhausted, tumors can generate blood vessels under the regulation of RNA modifications, which can connect them with the vascular system (blood vessels and lymph vessels) and membrane blood vessels in the human body to obtain energy and other materials elsewhere or be carried to obtain a better living environment in the distance.<sup>123,128–132</sup> Furthermore, tumor and immune cells in the tumor microenvironment can form a cell-cell “internet”, and immune cells that should protect the human body help tumor cells grow and metastasize well with the participation of RNA modifications. Therefore, RNA modifications are vital in many aspects of tumor cell growth and development.<sup>107–115,180</sup>

Of course, it is undeniable that although RNA modifications have received unprecedented attention, the role of DNA and Histone modifications as members of epigenetic modifications in tumor growth and development cannot be ignored. Tumor cells are in the proliferation phase of the cell cycle for a long time, and explosive growth after cell dormancy makes tumor treatment difficult.<sup>181,182</sup> It was recently found that histone modification could inhibit the transcription of lncRNA miR100HG, thereby inhibiting its role in inducing cell cycle G0-G1 arrest in CRC and promoting cell proliferation.<sup>183</sup> Similar to RNA modifications, m<sup>6</sup>A modifications are also present in DNA. N6AMT1, a functional methyltransferase modified by m<sup>6</sup>A in genomic DNA, inhibits tumor proliferation through the transcription of cell cycle inhibitors.<sup>184</sup> However, unlike RNA, DNA, as the source of gene expression, is particularly “unstable” in the cell cycle.

DNA damage can cause genomic instability, threatening the maintenance of cellular homeostasis and allowing cells to escape programmed death and immortalize.<sup>185</sup>

RNA modifications occur through the entire process of transcription, translation, and post-translational modification. The relationship between RNA and DNA modifications is a direction for future research. A recent study on leukemia revealed that m<sup>6</sup>A readers in RNA modifications could regulate DNA replication and play a key role in the occurrence and development of leukemia.<sup>186</sup> As mentioned earlier, m<sup>6</sup>A modification occurs in both DNA and RNA. Both are of great significance in the occurrence and development of tumors. However, research has not clarified the relationship between the two to date.<sup>184</sup> Currently, scientists have found that m<sup>6</sup>A, as a multifunctional checkpoint, can couple different levels of gene regulation through non-coding RNA as an intermediary.<sup>187</sup> Furthermore, changes in DNA, such as base modification and mutation, will cause relevant changes in the activity and function of corresponding transcription factors.<sup>188</sup> As a piece of evidence, p53, as a tumor suppressor gene in common transcription factors, can effectively maintain genomic stability. Post-translational modification is the most effective way to regulate its activity.<sup>189,190</sup> Activated p53 can quickly be recruited at damaged DNA sites to guide DNA repair,<sup>191</sup> and the post-translational modification of p53 involves m<sup>6</sup>A modification.<sup>176</sup> In conclusion, RNA modifications can affect DNA modifications through non-coding RNA, transcription factors, and other factors. Scientists have focused on studying the repair effect of tumor suppressor genes in DNA to treat tumors. Therefore, many signal transduction pathways have been explored, and many studies have proposed RNA-modified pathways to provide tumor-specific therapeutic strategies.

However, studying RNA modifications in tumors is bound to be a long way off for several reasons. First, the dynamic expression patterns of writers, readers, and eraser proteins complicate the identification of the precise functional consequences of modified abnormal deposition in RNA metabolism and tumor cell fate determination. Previous studies have been limited to the role of individual writers, readers, or eraser proteins in RNA modification in specific tumor subtypes. Currently, it is not clear how specific RNA modifications affect different populations of tumor cells. The relationship between different RNA modifications, and even between different writers, readers, and eraser proteins within specific RNA modifications, is not completely clear. So far, only studies on cholangiocarcinoma and CRC have combined m<sup>5</sup>C and m<sup>6</sup>A modifications, with the exception of the m<sup>7</sup>G modification.<sup>192,193</sup> Furthermore, the combined effect of METTL3 and METTL14 on oral squamous cell carcinoma was studied.<sup>194</sup> Moreover, in addition to the several types of RNA modifications discovered to date, there must be other RNA modifications that have not been discovered. Therefore, developing more advanced and accurate tools for determining RNA modifications is crucial to explore further the role of RNA modifications at different stages of tumor development and discover new RNA modifications.

## Conclusion

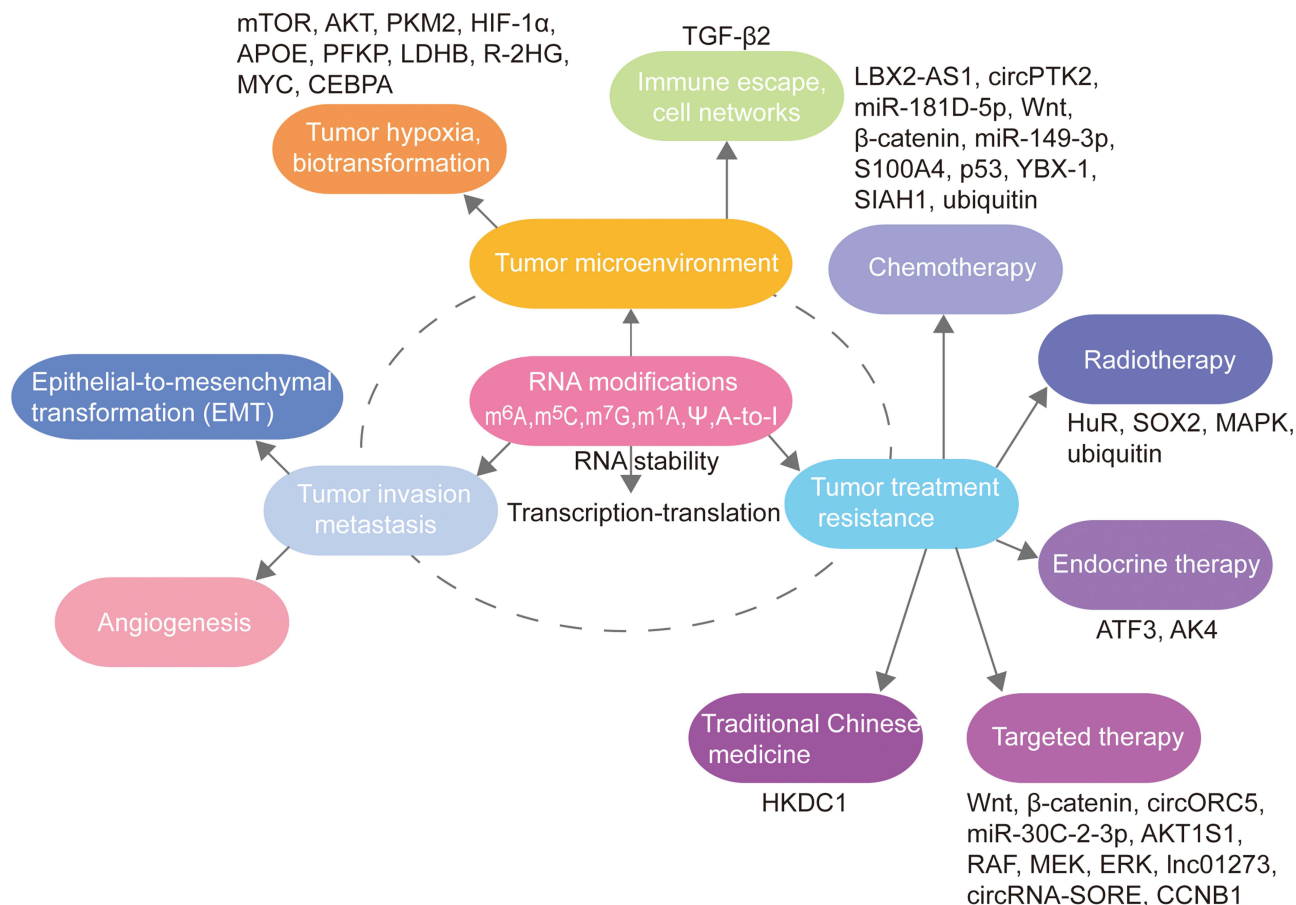
With the development of high-throughput sequencing technology and bioinformatics, researchers found that the regulation of RNA modifications in tumors runs through the whole process from transcription to translation of tumor cells, including m<sup>6</sup>A, m<sup>5</sup>C, m<sup>7</sup>G, m<sup>1</sup>A, Ψ, A-to-I, etc.

Tumor microenvironment contains various components of cells, which plays an important role in both solid tumors and liquid tumors. RNA modifications can change the malignant progression of tumor by influencing tumor hypoxic environment and biotransformation. Moreover, RNA modifications can affect the properties of immune cells, participate in the formation of intercellular communication network through EVs, and ultimately affect the prognosis of tumors.

The migration and metastasis of tumor is the main cause for the failure of tumor treatment. EMT and angiogenesis are two main ways of tumor metastasis. The effect of RNA modifications on both of them has also been gradually known by researchers.

In addition to surgical treatment, chemotherapy, radiotherapy, targeted therapy, endocrine therapy and traditional Chinese medicine are all effective treatments for tumors. The effect can be improved by regulating RNA modifications in treatment (Figure 3).

However, RNA modifications found so far is not comprehensive, and the target specificity of RNA modifications and its various action modes in different tumor microenvironments, migration and metastasis, and different therapies are still unclear.



**Figure 3** Biological function of RNA modification in tumors. RNA modifications regulate the differential expression of genes at the post-transcriptional level by maintaining RNA stability during the whole process from transcription to translation, which contributes to the process of tumor development, including the impact on the tumor microenvironment (biological metabolism, immune escape, cell networks), invasion and metastasis, and therapeutic resistance (chemotherapy, radiotherapy, endocrine therapy, and traditional Chinese medicine treatment).

## Abbreviations

m<sup>6</sup>A, N<sup>6</sup>-methyladenine; m<sup>5</sup>C, 5-methylcytosine; m<sup>7</sup>G, N<sup>7</sup>-methyladenosine; Ψ, pseudouridine; A-to-I, adenosine-to-inosine; RM, RNA modification; ECM, extracellular matrix; mRNA, messenger RNA; SAM, S-adenosyl-L-methionine; METTL3, methyltransferase-like 3; METTL14, methyltransferase-like 14; METTL16, methyltransferase-like 16; FTO, fat mass and obesity-associated protein; ALKBH5, AlkB homolog 5; YTHDCs and YTHDFs, YTH domain family proteins; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; RWR, Random Work with Restart; ARE, AU-rich elements; IRE, iron reaction elements; CPE, cytoplasmic polyadenylation elements; miRNAs, microRNAs; WTAP, Wilms' tumor 1-like protein; lncRNA, long non-coding RNA; EMT, epithelial-to-mesenchymal transformation; APOE, apolipoprotein; SUMO, small ubiquitin-like modifier; SENP1, SUMO1-specific protease; CRC, colorectal cancer; carRNA, chromosome-associated regulatory RNA; NSUN2, NOP2/Sun domain family member 2; ALYREF, Aly/REF export factor; ALKBH1, AlkB homolog 1; EOC, epithelial ovarian cancer; tRNA, transfer RNA; rRNA, ribosomal RNA; LUSC, lung squamous cell carcinoma; BC, breast cancer; TNBC, triple negative breast cancer; mtRNA, mitochondrial RNA; METTL1, methyltransferase-like 1; WDR4, WD repeat domain 4; m<sup>1</sup>I, 1-methylinosine; CSCs, glioblastoma stem cells; snoRNP, small nucleolar ribonucleoprotein; DKC1, pseudouridine synthase 1; NB, neuroblastoma; dsRNA, double-stranded RNA; ADAR, adenosine deamination enzyme family; GBM, glioblastoma; HuR, human antigen R; PC, pancreatic cancer; TAM, tumor-associated macrophages; tamoxifen; DC, dendritic cells; NK cell, natural killer cells; MDSC, myeloid-derived inhibitory cells; CAF, cancer-associated fibroblasts; ECM, extracellular matrix; EVs, extracellular vesicles; AML, acute myeloid leukemia; PKM2, pyruvate kinase muscle isozyme M2; HIF-1α, hypoxia-inducible factor-1 α; PTC, thyroid papillary carcinoma; LDHB, lactate dehydrogenase

B; R-2HG, R-2-hydroxyglutaric acid; Treg, regulatory T Cell; 5-FU, 5-fluorouracil; CDDP, Cisplatin; ESCC, esophageal squamous cell carcinoma; SERM, selective estrogen receptor modulator; TamR, tamoxifen resistance; AK4, adenylate kinase 4.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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