Molecular Therapy
Oncolytics
Review

Novel roles of METTL1/WDR4 in tumor via m^7G methylation

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As one of the prevalent posttranscriptional modifications of RNA, N^7-methylguanosine (m^7G) plays essential roles in RNA processing, metabolism, and function, mainly regulated by the methyltransferase-like 1 (METTL1) and WD repeat domain 4 (WDR4) complex. Emerging evidence suggests that the METTL1/WDR4 complex promoted or inhibited the processes of many tumors, including head and neck, lung, liver, colon, bladder cancer, and teratoma, dependent on close m^7G methylation modification of tRNA or microRNA (miRNA). Therefore, METTL1 and m^7G modification can be used as biomarkers or potential intervention targets, providing new possibilities for early diagnosis and treatment of tumors. This review will mainly focus on the mechanisms of METTL1/WDR4 via m^7G in tumorigenesis and the corresponding detection methods.

INTRODUCTION

RNA modifications affect all of the RNA processes, including splicing, stability, and localization.[1] Currently, there are more than 160 kinds of distinct RNA modifications,[2] of which N^7-methylguanosine (m^7G) has existed in various species. m^7G is positively charged and produced by the addition of a methyl group at position N^7 of ribo-guanosine,[3] which is the most ubiquitous mRNA cap modification[4,5] and is also present in internal mRNA, microRNA (miRNA), tRNA and rRNA.[6–9] As one of the most prevalent posttranscriptional modifications of RNA, m^7G functions in regulating gene expression and has critical roles in RNA processing, metabolism, and function,[10] mainly modified by the methyltransferase-like 1 (METTL1) and WD repeat domain 4 (WDR4) complex.[11]

Emerging evidence has recently suggested that the METTL1/WDR4 complex regulates the initiation and progression of various tumors, tightly dependent on m^7G methylation modification, which may be the new candidate target for the prevention and treatment of tumors.[12] METTL1 and m^7G can be used as biomarkers or potential intervention targets, providing new possibilities for early diagnosis and treatment of tumors. This review will focus on the detailed mechanisms of METTL1/WDR4 regulation, the association with m^7G in tumors, and the corresponding detection methods.

m^7G modification, the METTL1/WDR4 complex, and other methyltransferases

m^7G cap modification and its function

m^7G cap modifications have existed in nearly all eukaryotic cells and viral mRNAs.[5] It is installed at the 5′ cap during transcription initiation, forming the first co-transcriptional modification of RNA polymerase II transcribed RNA.[13] Capping of the 5′ end for nascent RNA is presented in eukaryotic cells and most viruses with three sequentially catalytic steps, including removal of the gamma phosphate by RNA triphosphatase, the addition of GMP from GTP by RNA guanylyl-transferase via a phosphoramide-linked GMP-enzyme intermediate, and N^7 methylation of the added GMP by RNA cap methyltransferase.[14] And then, three types of cap structures have been formed at different levels of methylation, containing caps 0, I, and II separately. The RNA cap methyltransferase adds a methyl group to N^7 amine of the guanosine cap to form m^7GPPPN as a cap 0 structure.[15] m^7GPPPN is methylated on the ribose 2′-hydroxyl (2′-O) of the first nucleoside by RNA 2′-O-ribose methyltransferase to produce m^7GPPPNm as cap I. Further methylation of cap I at the ribose 2′-O position of the second nucleoside results in the formation of m^7G-PPPNmNm as cap II.[16] The RNA cap methyltransferase in mammalians is known as RNA guanine-7 methyltransferase (RNMT).

The m^7G cap is necessarily required for efficient pre-mRNA splicing,[17] recruiting, and binding to the nuclear cap-binding complex (CBC) consisting of CBP80 and CBP20 and then co-transcribing together with a CBP80/20 heterodimer, which orchestrates processes such as spliceosome assembly, 3′ end processing, RNA export, miRNA biogenesis, and nonsense-mediated decay.[18] Moreover, once exported into the cytoplasm, m^7G-capped mRNAs recruit a second m^7G CBC, composed of eukaryotic translation initiation factors such as eukaryotic translation initiation factor 4E (eIF4E), for the steady-state rounds of translation.[15] Besides, m^7G is not only restricted to the caps of mRNAs but also occurred internally in mRNAs. METTL1/WDR4 mediates m^7G

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methylation to install in the inner mRNAs at the 5′ UTR region and in AG-rich contexts.[8–10] Thus, the translation efficiency of internal m^7G-modified mRNAs is enhanced compared with that of unmodified ones.[10]

Besides, m^7G also has modified sites in miRNA at G-rich regions, modulated by RNA methyltransferase of the METTL1/WDR4 complex.[19] m^7G methylation affects non-canonical base pairing in primary miRNA (pri-miRNA), changing the stability of the secondary structure G-quadruplex. The m^7G modification destabilizes G-quadruplexes, promoting the procession efficiency of the pri-miRNA transcript into pre-miRNA and matured miRNA.[19]

Meanwhile, m^7G widely occurs in the tRNA variable loop of eubacteria, eukaryotes, and a few archaea,[20,21] most of which are frequently located at position 46 in its variable region, forming a tertiary base pair with C13-G22 in the three-dimensional core to stabilize the structure of tRNA.[20,22] The m^7G tRNA modification is modulated by the METTL1/WDR4 complex in mammalians, essentially, for proper expression under normal growth conditions.[23] In addition, the m^7G tRNA modification also regulates the translation process of mRNA and ribosome biogenesis.[11,24]

METTL1/WDR4 complex and other methyltransferases associated with m7G

METTL1 serves as the m^7G catalytic enzyme, while WDR4 plays a stabilizing role in the complex,[9,24,25] which are required for the introduction of the m^7G at position 46 of tRNA and the appropriate translation.[26] *METTL1* mapping to 12q13[26] is transcribed in a large variety of organs and tissues and regulated by protein kinase B (Akt) and ribosomal S6 kinase (RSK) under growth-factor stimulation,[27] playing important roles in self-renewal and differentiation of embryonic stem cells and cancer.[24,28–30] *WDR4* is a candidate gene for some of the Down syndrome phenotypes with mental retardation, located at human chromosome 21q22.3,[31] serving as an important supporting role of METTL1 to be essential for m^7G modification on tRNA. The depletion of WDR4 would obviously decrease *METTL1* expression, suggesting that WDR4 was indispensable for maintaining normal METTL1 protein levels and the function of the METTL1/WDR4 complex.[32] The mutation in *WDR4* would cause a distinct form of microcephalic primordial dwarfism characterized by facial dysmorphism, brain malformation, and severe encephalopathy with seizures, of which the potential mechanisms might relate to the reduced level of tRNA m^7G modification.[33–36] The reduction of m^7G tRNA levels by depletion of METTL1 or WDR4 affected tRNA function, increasing ribosomes pausing at m^7G tRNA-dependent codons and declining the expression of genes associated with a wide range of biological functions. Those genes were selectively enriched in abnormality of forebrain morphology, cerebrum, and skull size, which was consistent with microcephalic primordial dwarfism described in *WDR4*-mutated patients.[24] Moreover, m^7G tRNA was involved in human stem cell renewal and differentiation by affecting the translation of the cell-cycle genes and multipotent transcription factor translation in the same codon-dependent manner.[24,29] Therefore, m^7G tRNA modification is widespread in affecting proper expression, essentially for normal biological functions in mammalian cells.

m^7G is conserved in 18S rRNA at G1639 of human eukaryotic cells and mediated by metastasis-related methyltransferase 1 (MERM1), which is also identified as Williams-Beuren syndrome chromosome region 22 (WBSCR22). The methyltransferase WBSCR22 partners with its metabolic stabilizer tRNA methyltransferase activator subunit 11-2 (TRMT112) and has two important functions in the biogenesis of small ribosomal subunits in human cells: efficient processing of nuclear 18S rRNA precursors and nuclear export of pre-40S ribosomal subunits. Ribosome biogenesis requires the presence of the WBSCR22/TRMT112 complex rather than its m^7G-modifying catalytic activity, but the function of the 18S rRNA m^7G methylation in ribosome biogenesis and translation needs to be understood further.[37,38]

Therefore, m^7G methyltransferases have contained RNMT, METTL1/WDR4, and WBSCR22/TRMT122 in humans so far. RNMT mediated m^7G cap modification and increased mRNA stability. METTL1/WDR4 controlled interior mRNAs, miRNAs, and tRNA m^7G modifications to regulate mRNA translation, while WBSCR22/TRMT122 regulated rRNA m^7G modification to conduct a potential effect on ribosomal biogenesis.

Different RNA modifications by specific m^7G methyltransferases should be related to their conserved domains. RNMT, METTL1, and WBSCR22 contain the conserved domain of the S-adenosyl-L-methionine (AdoMet) methyltransferase, which plays a major role in the methylation reaction, but their binding motifs were slightly different. The AdoMet binding motifs are VL(D/E)LGCGKG on RNMT, DIGCGYGGLLVELSPLFPDTLILGLEIR on METTL1, and MAGRALELLYLPENKPCYLLDIGCG on WBSCR22.[4,26,39] Besides, different methyltransferases also have their own special structures and functions. RNMT has an N-terminal domain, negatively regulating the methyltransferase activity and mediating recruitment to transcription initiation sites, which is necessary for transcript expression, translation, and cell proliferation.[40] Meanwhile, the RNMT-activating mini protein, as an activating subunit of RNMT, stabilizes the structure and ensures optimal positioning of the RNMT lobe and its adjacent α-helix hinge in the active sites.[41] The RNA substrates of METTL1/WDR4 could have clues from the yeast homologs Trm8/Trm82. The major recognition sites of Trm8/Trm82 were the D- and T-stem structures of tRNA, and the Py48 sequence in the variable region was required for efficient methylation.[42] In terms of WBSCR22, there has been no idea to identify their binding sites or substrates on precursor ribosomes at present, but m^7G synthesis was a late event that occurred specifically in small subunits, whereas WBSCR22/TRMT112 association with pre-ribosomes was an early step on nascent nucleolar transcripts.[38]

Thus, the differences among these enzymes mentioned above have constituted different domains and specific binding sites, supporting m^7G methyltransferases to recognize special RNA substrates in the corresponding biological stages. Different kinds of m^7G methyltransferases

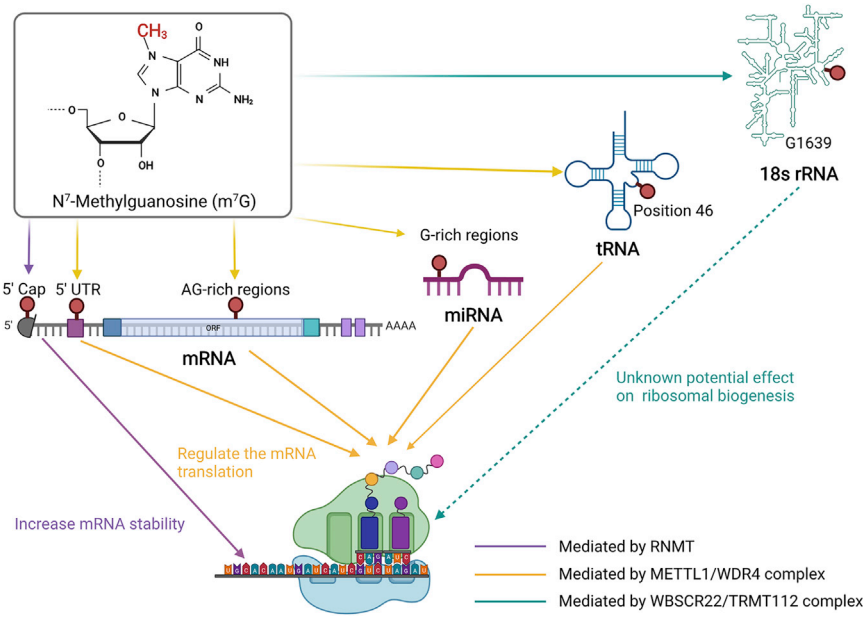

Figure 1. Diverse m^{7}G sites and bio-effects mediated by RNA methyltransferases

The m^{7}G modification presents in 5′ cap of mRNA, 5′ UTR, and AG-rich regions of internal mRNA, G-rich regions of miRNA, position 46 of tRNA, and G1639 of 18s rRNA in humans. The bio-effects are mediated by different RNA methyltransferases, including RNMT, the METTL1/WDR4 complex, and the WBSCR22/TRMT112 complex, acting on mRNA stability, translation, and ribosomal biogenesis.

participate in protein synthesis via m^{7}G modification, as shown in Figure 1.

Overall, m^{7}G has critical roles in RNA processing, metabolism, and function, whose abnormal changes cause cellular pathological features. The METTL1/WDR4 complex regulates the modification abundance of m^{7}G, affecting the occurrence and progression of diseases, including tumors.

Roles of METTL1/WDR4 via m^{7}G in tumors

Subsequently, we focused on the one of the m^{7}G methyltransferases, METTL1/WDR4 complex, which is significantly associated with the initiation, progression, and prognosis of tumors relying on the changes in the m^{7}G modification level.

Head and neck cancer

Otorhinolaryngology, oral, maxillofacial, and neck cancer belong to head and neck cancer. Head and neck squamous cell carcinoma was the most common malignancy in the head and neck, developed from the mucosal epithelium in the oral cavity, pharynx, and larynx.[43] The upregulation of the METTL1/WDR4 complex would increase m^{7}G modification of tRNA, activating the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin complex (mTORC) signaling pathway in head and neck squamous cell carcinoma and the regulatory associated protein of mTOR complex 1 (RPTOR)/unc-51 like autophagy activating kinase 1 (ULK1)/autophagy axis in esophageal squamous cell carcinoma via a codon-dependent manner decoded by m^{7}G-tRNA, contributing to tumorigenesis.[44,45]

Nasopharyngeal carcinoma had a high incidence in East and Southeast Asia, and terminal patients had a poorer prognosis.[46] High-level METTL1 selectively promoted mRNA levels depending on m^{7}G-tRNA codons and activated the Wnt/β-catenin pathway and increased the cyclin D1 level in nasopharyngeal carcinoma, promoting the proliferation and migration of cancer cells.[47]

Therefore, the METTL1/WDR4 complex can increase the m^{7}G modification level of tRNA via a codon-dependent manner decoded by m^{7}G tRNA to promote the translation of cyclin and associated oncogenes, accelerating the occurrence and development of head and neck cancer.

Lung cancer

As one of the most common malignant tumors, lung cancer had an overexpressed level of METTL1 and WDR4 to promote the proliferation, migration, and invasion capacities of cancer cells.[32,48] Just like head and neck squamous cell carcinoma (HNSCC), the METTL1/WDR4 complex played a carcinogenic role via a codon-dependent manner decoded by m^{7}G tRNA, selectively promoting the translation of oncogenes and modulating the processes of cell-cycle-related mRNAs including cyclin D3 and cyclin E1 in lung cancer.[32]

However, there was a study that found that the level of m^{7}G modification had not been dramatically affected in tRNAs after reducing the level of METTL1.[19] It pointed out that METTL1 inhibited the progression of lung cancer. The oncogene high-mobility group AT-hook 2 (*HMGA2*) promoted epithelial-to-mesenchymal transition and accelerated cancer progression with poor survival of cancer.[49,50] The pri-let-7e miRNA was directly methylated by the METTL1/WDR4 complex, promoting the processes of its transcript into precursor pre-let-7e miRNA and matured let-7e miRNA, which regulated HMGA2 negatively and then inhibited the proliferation of A549 cells.

Liver cancer

Hepatocellular carcinoma (HCC), one of the most common malignant tumors, is one of the leading causes of cancer deaths worldwide,[51] with upregulated METTL1 and WDR4. METTL1/WDR4-mediated m^{7}G tRNA modification could raise the translation of cyclin A2, epidermal growth factor receptor (*EGFR*), and vascular endothelial growth factor A (*VEGFA*), which were decoded by m^{7}G

Table 1. METTL1 regulated tumor progression by confirmed association with m^7G

Tumors	Role in tumors	m^7G target	Mechanisms	Reference
Head and neck cancer	accelerator	tRNA	activated the PI3K/Akt/mTORC signaling pathway, RPTOR/ULK1/autophagy axis, and Wnt/β-catenin pathway, as well as promoted the cyclin D1 translation	44,45
Lung cancer	accelerator	tRNA	promoted translation of cell-cycle genes including cyclin D3 and cyclin E1	32
	suppressor	miRNA	promoted transcription of let-7e miRNA and inhibited expression of *HMGA2*	19
Liver cancer	accelerator	tRNA	promoted the translation of cell-cycle genes including cyclin A2, cyclin D2, *CDK6*, and *CDK8* as well as activated EGFR, VEGFA, and MAPK signaling pathways	52,54
Colon cancer	suppressor	miRNA	promoted transcription of let-7e miRNA and inhibited expression of *HMGA2*	56
Bladder cancer	accelerator	tRNA	promoted the translation of *EGFR* and *EFEP1* and activated EGFR pathway	59
Teratoma	suppressor	tRNA	promoted translation of pluripotency genes, including *Oct4*, Nanog, and *Sox2*, as well as activated cell-cycle signaling pathway	29

tRNA in a codon-dependent manner and then activated Akt and mitogen-activated protein kinase (MAPK) in EFGR and VEGFA signaling pathways, promoting cell proliferation and migration of HCC.[52]

Intrahepatic cholangiocarcinoma (ICC) currently accounts for 10%–20% of primary hepatic tumors.[53] m^7G tRNA modification and the METTL1/WDR4 complex were significantly upregulated in ICC and associated with a poor prognosis. m^7G tRNA modification could selectively promote the translation of oncogenic transcripts, including EGFR, VEGFA, and MAPK signaling pathways and the corresponding downstream targets, as well as cell-cycle-related mRNAs of cyclin A2, cyclin D2, cyclin-dependent kinases 6 (*CDK6*), *CDK8*, and *EFGR* via a codon-dependent manner decoded by m^7G tRNA.[54]

METTL1 and WDR4 promote tumor cell growth by stimulating the translation of mRNAs related to the cell cycle and activating oncogenic signaling pathways such as EGFR in HCC and ICC. Therefore, the mechanisms of METTL1/WDR4 promoting tumorigenesis in HCC and ICC were similar. METTL1/WDR4-complex-mediated m^7G tRNA modification selectively promotes the translation of oncogenic transcripts and the relative genes via a codon-dependent manner decoded by m^7G tRNA, affecting the occurrence and development of liver tumors.

Colon cancer

Colon cancer is also a common malignant tumor of the human digestive tract with high morbidity and mortality, seriously degrading the quality of human life.[55] let-7e miRNA regulated the expression of *HMGA2* negatively and then inhibited the proliferation, migration, and invasion of colon cancer cells.[56] In the meantime, the METTL1/WDR4 complex promoted the let-7e miRNA process in an m^7G-dependent manner and overexpressed *METTL1*-decreased HMGA2 by upregulating let-7e miRNA via m^7G, inhibiting the progression of colon cancer.[19,57]

Bladder cancer

Bladder cancer, a grave urogenital malignancy worldwide, was one of the most frequent malignancies in males of developed countries.[58] Overexpression of METTL1 would mediate m^7G tRNA modification, upregulating levels of EGFR and EGF-containing fibulin extracellular matrix protein 1 (EFEMP1) in an m^7G tRNA codon-dependent manner to activate the EFGR pathway and promote bladder tumorigenesis.[59]

Teratoma

Downregulation of m^7G tRNA methylation enhanced teratoma formation *in vivo* by promoting human induced pluripotent stem cell proliferation and angiogenesis in nude mice.[29] Knockdown of *Mettl1* decreased the mRNA translation of stem cell transcription factors recombinant octamer binding transcription factor 4 (*Oct4*), Nanog, and sex-determining region Y (*Sox2*) by downregulating m^7G tRNA, thus increasing the differentiation, inhibiting the cell-cycle signaling pathway, and impairing self-renewal of human induced pluripotent stem cells, which enhanced teratoma formation in mice.[24,29,60–62]

The functions of METTL1/WDR4 in tumors via m^7G methylation are shown in Table 1.

Detection methods of m^7G modification

To test the m^7G modification level, the most common methods currently include quantitative detection and high-throughput sequencing. The quantitative detection method could get the overall m^7G level of RNA, including high-performance liquid chromatography and coupling of liquid chromatography to mass spectrometry,[8,63] while the high-throughput sequencing method could identify the exact m^7G sites based on antibodies or chemicals.

Methylated RNA immunoprecipitation sequencing (MeRIP-seq) was used for the whole-transcriptome analysis of m^7G by immunoprecipitation of the specific antibody.[8] With a high resolution of m^7G localization on fragmented RNA, individual-nucleotide-resolution cross-linking and immunoprecipitation with sequencing (miCLIP-seq) was adopted to detect m^7G at the single-base resolution induced by an antibody cross-linked to ultraviolet.[10]

However, these antibody-based m^7G immunoprecipitation sequencing techniques would have the issue of false positives because of inevitable non-specific binding.[64] So chemical-based sequencing technologies

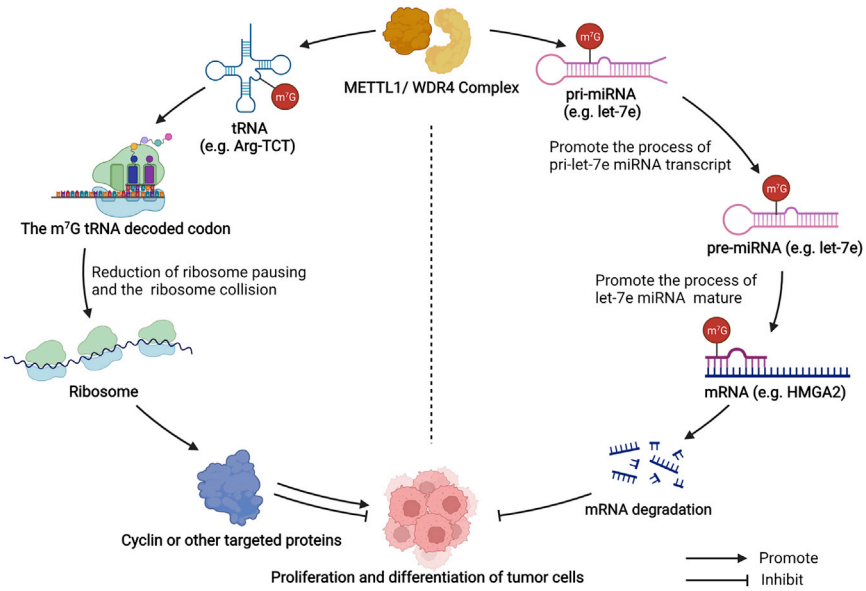

Figure 2. Mechanisms of METTL1/WDR4-m^{7}G modification affecting tumorigenesis

METTL1/WDR4-complex-mediated m^{7}G regulates the processes of the tumor by targeting tRNA or miRNA. The m^{7}G-modified tRNA causes the reduction of ribosome pausing and the elimination of ribosome collision-mediated translation inhibition, selectively promoting the translation of certain cell-cycle regulatory mRNAs, which are enriched in corresponding m^{7}G-tRNA cognate codons, regulating the proliferation and differentiation of tumor cells. m^{7}G modifies pri-miRNA directly to mature miRNA efficiency, inhibits the expression of oncogene, and then inhibits the proliferation and differentiation of tumor cells.

relying on borohydride reduction were applied, including AlkAniline-seq,[65,66] m^{7}G mutational profiling sequencing (m^{7}G-MaP-seq),[67] and tRNA reduction and cleavage sequencing (TRAC-seq),[68] which not only could identify m^{7}G modification at the single-base resolution but also were more specific than the antibody-based sequencing technique.[65,67–69] Moreover, chemical-based sequencing technologies have higher specificity and better resolution power than those that are antibody based.

Conclusion

RNA methylation contributes to revealing the underlying mechanisms of many aspects of tumors, involving initiation, development, invasion, infiltration, and so on. m^{7}G methylation is a double-edged sword to tumors, needing appropriate level boundaries. The excessive m^{7}G modification of certain genes leads to the acceleration of tumor development, whereas deficient m^{7}G modification might also accelerate tumor progression. METTL1/WDR4-complex-mediated m^{7}G acts on different RNA targets, affecting the processes of tumorigenesis.

METTL1/WDR4-complex-mediated m^{7}G tRNA methylation selectively promotes the translation of certain cyclin and oncogenic transcripts and its downstream pathway-related mRNAs, regulating cell proliferation and apoptosis with affluent homologous codons of m^{7}G tRNAs correspondingly.[70] The upregulation of m^{7}G abundance would cause the reduction of ribosome pausing and the elimination of ribosome collision-mediated translation inhibition.[71] m^{7}G modification targets are Arg-TCT tRNAs responsible for decoding AGA codons, promoting the stabilization and increasing the translation of mRNAs of enriched AGA, including cell-cycle-related genes.[72]

However, abnormal m^{7}G modification will bring about different tumor outcomes to promote the formation and progression of head and neck, and liver as well as bladder cancer while inhibiting teratoma by METTL1/WDR4-mediated m^{7}G tRNA changes. Differentially targeted cells might also be one of the intrinsic reasons. For head and neck, liver, and bladder cancer, the epigenetic mutations occur in somatic cells, while it was reported in human induced pluripotent stem cells to occur in teratoma with higher pluripotency levels.

m^{7}G miRNA methylation shows the role of the suppressor in tumors. m^{7}G methylation promotes the process of pri-miRNA transcript into pre-miRNA and accelerates the maturation efficiency of miRNA, inhibiting the expression of targeted genes in colon and lung cancers. The roles of m^{7}G modification modulated by the METTL1/WDR4 complex in tumorigenesis are concluded in Figure 2.

Perspectives and challenges

The critical role of METTL1 and m^{7}G RNA methylation in tumor initiation and progression provides new possibilities for early diagnosis and treatment. A remarkable upregulation of METTL1 or m^{7}G might suggest the tumor progression in head and neck, liver, or bladder cancer, but downregulation would connect with teratoma or colon cancer. Cells need normal expressions of METTL1 and m^{7}G, and once they are imbalanced, the associated tumors would more likely occur and proceed.

Additionally, METTL1-mediated m^{7}G is also crucial for tumor chemoresistance. The regulators or inhibitors of m^{7}G methylation may have prospects for tumor treatment. Cisplatin was an ordinary chemotherapeutic drug for colon cancer treatment clinically, but its continuous chemotherapy would induce the drug resistance of cancer cells, and overexpressed METTL1 could increase the chemosensitivity of colon cancer cells to cisplatin by regulating the miR-149-3p/S100A4/p53 axis.[73] Besides, 5-fluorouracil (5-FU) was a pyrimidine analog, most widely used as a chemotherapeutic agent for varieties of solid cancers. Interfering with m^{7}G tRNA methylation by knocking down METTL1 in HeLa cells could potentiate the sensitivity to 5-FU, providing a new idea to improve 5-FU chemotherapy effects on cancer.[74]

However, there are still numerous challenges in the field of m^7G RNA methylation research. The molecular mechanism is bidirectional of METTL1/WDR4-complex-mediated m^7G during tumor progression. Especially in lung cancer, m^7G-tRNA promoted progression, while m^7G-miRNA showed the opposite effect, indicating different m^7G modification targets had differential results sometimes.

Furthermore, whether m^7G methylation exists in internal mRNA and miRNA or not still needs to be studied further because of controversial results from different current detection methods. Some studies reported no evidence for internal m^7G modifications presented in other small RNAs and mRNAs using chemical-based sequencing technologies,[65,67,69] while other research showed the m^7G methylation was identified to exist in internal mRNA and miRNA using mostly antibody-based sequencing technologies.[8,10,19] Additionally, another study using the chemical-based technique identified m^7G existing in miRNAs, but it doubted the observation of m^7G-dependent enrichment because of the sequencing protocol rather than special pull-down.[19,69] Thus, more reliable methods are eagerly needed to prove the exact existence of m^7G modification in internal mRNA and miRNA, with good repeatability and verification.

Besides, the links between m^7G RNA modification and other tumors are still waiting to be discovered and verified apart from the mentioned tumors above. Some studies revealed that METTL1 contributed to the initiation and progression of gastric cancer and glioma with poor prognosis, offering a good foundation for relations to the m^7G methylation.[75–77] The associations between the METTL1/WDR4 complex and m^7G modification in tumors need to be explored further to obtain more interesting discoveries in the future.

Moreover, m^7G also has a crucial role in vasculogenesis, possibly with the occurrence of hemangioma.[29,78] A critical angiogenic factor for angiogenesis, *VEGF* was highly expressed in hemangioma, contributing to proliferation and abnormal angiogenesis of vascular endothelial cells because METTL1 promoted its m^7G modification by upregulating the mRNA translation.[79,80]

Therefore, METTL1 and m^7G have dual roles of tumor promotion and suppression. METTL1 would act as an oncogene in cancers of the head and neck and liver as well as bladder but as a tumor suppressor in colon cancer and teratoma, which may also induce the formation of other types of cancers or other diseases via specific m^7G regulation accordingly. The clinical application of m^7G in human tumors needs to be assessed further for targeted therapy and precise intervention in future studies.

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AUTHOR CONTRIBUTIONS

W.C. finished the manuscript, A.G. updated the literature search and revision, H.L. reviewed and edited the revision, and W.Z. completed critical revisions and proofread the manuscript. All authors have read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare that they do not have any conflicts of interest related to this study. This manuscript has been read and approved by all the authors and has not been submitted to or is not under consideration for publication elsewhere.

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