Novel roles of METTL1/WDR4 in tumor via m7G methylation

Wenli Cheng,1 Aili Gao,2 Hui Lin,3 and Wenjuan Zhang1

As one of the prevalent posttranscriptional modifications of RNA, N7-methylguanosine (m7G) 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 m7G methylation modification of tRNA or micro-RNA (miRNA). Therefore, METTL1 and m7G 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 m7G in tumorigenesis and the corresponding detection methods.

INTRODUCTION

RNA modifications affect all of the RNA processes, including splicing, stability, and localization. Currently, there are more than 160 kinds of distinct RNA modifications, of which N7-methylguanosine (m7G) has existed in various species. m7G is positively charged and produced by the addition of a methyl group at position N7 of ribo-guanosine, which is the most ubiquitous mRNA cap modification and has critical roles in RNA processing, metabolism, and function, mainly modified by the methyltransferase-like 1 (METTL1) and WD repeat domain 4 (WDR4) complex.

Emerging evidence has recently suggested that the METTL1/WDR4 complex regulates the initiation and progression of various tumors, tightly dependent on m7G methylation modification, which may be the new candidate target for the prevention and treatment of tumors. METTL1 and m7G 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 m7G in tumors, and the corresponding detection methods.
methylase to install into the inner mRNAs at the 5’ UTR region and in AG-rich contexts.8–10 Thus, the translation efficiency of internal m7G-modified mRNAs is enhanced compared with that of unmodified ones.10

Besides, m7G also has modified sites in miRNA at G-rich regions, modulated by RNA methyltransferase of the METTL1/WDR4 complex.19 m7G methylation affects non-canonical base pairing in primary miRNA (pri-miRNA), changing the stability of the secondary structure G-quadruplex. The m7G modification destabilizes G-quadruplexes, promoting the process efficiency of the pri-miRNA transcript into pre-miRNA and matured miRNA.19

Meanwhile, m7G 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 three-dimensional core to stabilize the structure of tRNA.20,22 The m7G tRNA modification is modulated by the METTL1/WDR4 complex in mammalians, essentially, for proper expression under normal growth conditions.23 In addition, the m7G 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 m7G catalytic enzyme, while WDR4 plays a stabilizing role in the complex,9,24,25 which are required for the introduction of the m7G at position 46 of tRNA and the appropriate translation.26 METTL1 mapping to 12q13 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 WDR4 is a candidate gene for some of the Down syndrome phenotypes with mental retardation, located at human chromosome 21q22.3,29 serving as an important supporting role of METTL1 to be essential for m7G 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.30 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 m7G modification.33–36 The reduction of m7G tRNA levels by depletion of METTL1 or WDR4 affected tRNA function, increasing ribosomes pausing at m7G 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, m7G 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.24,25 Therefore, m7G tRNA modification is widespread in affecting proper expression, essentially for normal biological functions in mammalian cells.

m7G 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 m7G-modifying catalytic activity, but the function of the 18S rRNA m7G methylation in ribosome biogenesis and translation needs to be understood further.37,38

Therefore, m7G methyltransferases have contained RNMT, METTL1/WDR4, and WBSCR22/TRMT112 in humans so far. RNMT mediated m7G cap modification and increased mRNA stability. METTL1/WDR4 controlled interior mRNAs, miRNAs, and tRNA m7G modifications to regulate mRNA translation, while WBSCR22/TRMT112 regulated tRNA m7G modification to conduct a potential effect on ribosomal biogenesis.

Different RNA modifications by specific m7G 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, DIGCGYGGLLVELSPDPDTLILGLEIR on METTL1, and MAGRAELLYLPENKPCYLLDGCG on WBSCR22.5,26,39 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 m7G 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 m7G methyltransferases to recognize special RNA substrates in the corresponding biological stages. Different kinds of m7G methyltransferases...
participate in protein synthesis via m^7G modification, as shown in Figure 1.

Overall, m^7G 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^7G, affecting the occurrence and progression of diseases, including tumors.

Roles of METTL1/WDR4 via m^7G in tumors
Subsequently, we focused on the one of the m^7G methyltransferases, METTL1/WDR4 complex, which is significantly associated with the initiation, progression, and prognosis of tumors relying on the changes in the m^7G 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. The upregulation of the METTL1/WDR4 complex would increase m^7G 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^7G-tRNA, contributing to tumorigenesis.

Nasopharyngeal carcinoma had a high incidence in East and Southeast Asia, and terminal patients had a poorer prognosis. High-level METTL1 selectively promoted mRNA levels depending on m^7G-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.

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. 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^7G 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.

However, there was a study that found that the level of m^7G modification had not been dramatically affected in tRNAs after reducing the level of METTL1. The oncogene high-mobility group AT-hook 2 (HMGA2) promoted epithelial-to-mesenchymal transition and accelerated cancer progression with poor survival of cancer. 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, with upregulated METTL1 and WDR4. METTL1/WDR4-mediated m^7G 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^7G.
tRNA in a codon-dependent manner and then activated Akt and mitogen-activated protein kinase (MAPK) in EGFR 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 m7G tRNA modification and the METTL1/WDR4 complex were significantly upregulated in ICC and associated with a poor prognosis. m7G 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 m7G 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 m7G tRNA modification selectively promotes the translation of oncogenic transcripts and the relative genes via a codon-dependent manner decoded by m7G 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 m7G-dependent manner and overexpressed METTL1-decreased HMGA2 by upregulating let-7e miRNA via m7G, 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 m7G tRNA modification, upregulating levels of EGFR and EGF-containing fibulin extracellular matrix protein 1 (EFEMP1) in an m7G tRNA codon-dependent manner to activate the EFGFR pathway and promote bladder tumorigenesis.29

**Teratoma**

Downregulation of m7G tRNA methylation enhanced teratoma formation in vivo by promoting human induced pluripotent stem cell proliferation and angiogenesis in nude mice.59 Knockdown of Mettl1 decreased the mRNA translation of stem cell transcription factors re-combinant octamer binding transcription factor 4 (Oct4), Nanog, and sex-determining region Y (Sox2) by downregulating m7G 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 m7G methylation are shown in Table 1.

| Tumors                  | Role in tumors | m7G 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 | 52        |
|                        | suppressor     | miRNA      | promoted transcription of let-7e miRNA and inhibited expression of HMGA2     | 56        |
| 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 EFEMP1 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        |
relying on borohydride reduction were applied, including AlkAniline-seq, m7G mutational profiling sequencing (m7G-MaP-seq), tRNA reduction and cleavage sequencing (TRAC-seq), which not only could identify m7G modification at the single-base resolution but also were more specific than the antibody-based sequencing technique. 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. m7G methylation is a double-edged sword to tumors, needing appropriate level boundaries. The excessive m7G modification of certain genes leads to the acceleration of tumor development, whereas deficient m7G modification might also accelerate tumor progression. METTL1/WDR4-complex-mediated m7G acts on different RNA targets, affecting the processes of tumorigenesis.

METTL1/WDR4-complex-mediated m7G 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 m7G tRNAs correspondingly. The upregulation of m7G abundance would cause the reduction of ribosome pausing and the elimination of ribosome collision-mediated translation inhibition. m7G 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.

However, abnormal m7G modification will bring about different tumor outcomes to promote the formation and progression of head and neck, liver as well as bladder cancer while inhibiting teratoma by METTL1/WDR4-mediated m7G 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.

m7G miRNA methylation shows the role of the suppressor in tumors. m7G 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 m7G modification modulated by the METTL1/WDR4 complex in tumorigenesis are concluded in Figure 2.

Perspectives and challenges
The critical role of METTL1 and m7G RNA methylation in tumor initiation and progression provides new possibilities for early diagnosis and treatment. A remarkable upregulation of METTL1 or m7G 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 m7G, and once they are imbalanced, the associated tumors would more likely occur and proceed.

Additionally, METTL1-mediated m7G is also crucial for tumor chemoresistance. The regulators or inhibitors of m7G 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. Besides, 5-fluorouracil (5-FU) was a pyrimidine analog, most widely used as a chemotherapeutic agent for varieties of solid cancers. Interfering with m7G 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.

Figure 2. Mechanisms of METTL1/WDR4- m7G modification affecting tumorigenesis
METTL1/WDR4-complex-mediated m7G regulates the processes of the tumor by targeting tRNA or miRNA. The m7G-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 m7G-tRNA cognate codons, regulating the proliferation and differentiation of tumor cells. m7G modifies pri-miRNA directly to mature miRNA efficiency, inhibits the expression of oncogene, and then inhibits the proliferation and differentiation of tumor cells.
However, there are still numerous challenges in the field of m7G RNA methylation research. The molecular mechanism is bidirectional of METTL1/WDR4-complex-mediated m7G during tumor progression. Especially in lung cancer, m7G-tRNA promoted progression, while m7G-miRNA showed the opposite effect, indicating different m7G modification targets had differential results sometimes.

Furthermore, whether m7G 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 m7G modifications presented in other small RNAs and mRNAs using chemical-based sequencing technologies. Additionally, another study using the chemical-based technique identified m7G existing in miRNAs, but it doubted the observation of m7G-dependent enrichment because of the sequencing protocol rather than special pull-down. Thus, more reliable methods are eagerly needed to prove the exact existence of m7G modification in internal mRNA and miRNA, with good repeatability and verification.

Besides, the links between m7G 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 m7G methylation. The associations between the METTL1/WDR4 complex and m7G modification in tumors need to be explored further to obtain more interesting discoveries in the future.

Moreover, m7G also has a crucial role in vasculogenesis, possibly with the occurrence of hemangioma. 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 m7G modification by upregulating the mRNA translation.

Therefore, METTL1 and m7G 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 m7G regulation accordingly. The clinical application of m7G 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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