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REVIEW

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N7-methylguanosine modification in cancers: from mechanisms to therapeutic potential

Qihui Wu[1†], Xiaodan Fu[2†], Guoqian Liu[2†], Xiaoyun He[3*†], Yimin Li[4*†] and Chunlin Ou[1,2,5*†]

Abstract

N7-methylguanosine (m7G) is an important RNA modification involved in epigenetic regulation that is commonly observed in both prokaryotic and eukaryotic organisms. Their influence on the synthesis and processing of messenger RNA, ribosomal RNA, and transfer RNA allows m7G modifications to affect diverse cellular, physiological, and pathological processes. m7G modifications are pivotal in human diseases, particularly cancer progression. On one hand, m7G modification-associated modulate tumour progression and affect malignant biological characteristics, including sustained proliferation signalling, resistance to cell death, activation of invasion and metastasis, reprogramming of energy metabolism, genome instability, and immune evasion. This suggests that they may be novel therapeutic targets for cancer treatment. On the other hand, the aberrant expression of m7G modification-associated molecules is linked to clinicopathological characteristics, including tumour staging, lymph node metastasis, and unfavourable prognoses in patients with cancer, indicating their potential as tumour biomarkers. This review consolidates the discovery, identification, detection methodologies, and functional roles of m7G modification, analysing the mechanisms by which m7G modification-associated molecules contribute to tumour development, and exploring their potential clinical applications in cancer diagnostics and therapy, thereby providing innovative strategies for tumour identification and targeted treatment.

Keywords N7-methylguanosine, RNA modification, Immune evasion, Energy metabolism, Cell death, Biomarkers, Targeted therapy

[†]Qihui Wu, Xiaodan Fu and Guoqian Liu are contributed equally to this work and should be considered as co-first authors.

[†]Xiaoyun He, Yimin Li and Chunlin Ou are jointly supervised this work.

*Correspondence:
Xiaoyun He
hexiaoyun@csu.edu.cn
Yimin Li
lym12999@rjh.com.cn
Chunlin Ou
ouchunlin@csu.edu.cn
[1] Department of Gynecology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China
[2] Department of Pathology, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China
[3] Departments of Ultrasound Imaging, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China
[4] Department of Pathology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China
[5] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China

Introduction

Cancer is a malignant disease characterised by uncontrolled proliferation of transformed cells, invasion of surrounding tissues, and eventual organ failure, resulting in high morbidity and mortality [1]. Despite notable advances in the understanding and treatment of cancer in recent years, tumour recurrence and metastatic potential remain high, contributing to persistently elevated mortality rates [2]. One major challenge in cancer treatment is the incomplete understanding of the mechanisms underlying tumourigenesis, compounded by the lack of cancer-specific clinical trials, which hampers drug development [3]. Therefore, a deeper exploration of the mechanisms driving cancer initiation and progression as well as the identification of potential diagnostic biomarkers and therapeutic targets is crucial to improve our understanding of targeted cancer therapy and facilitate the design of more effective treatments.

In recent years, rapid advancements in next-generation sequencing have highlighted the importance of post-transcriptional modifications as critical players in numerous physiological and pathological processes. Dynamic RNA modifications are pervasive across all nucleotides. To date, over 170 distinct types of RNA modifications have been identified [4, 5]. Various RNA species undergo modifications, most of which involve more than one type of chemical modification [6–8]. RNA methylation is the most common and abundant form of RNA modification, with studies spanning over 60 years [9–11]. RNA methylation is fundamental for the regulation of several biological processes, including RNA transcription, splicing, structural integrity, stability, and translation. To date, over 70 types of RNA methylation have been identified, with extensive studies conducted on modifications such as N6-methyladenosine (m6A), N7-methylguanosine (m7G), 5-methylcytosine (m5C), N1-methyladenosine (m1A), N3-methylcytosine (m3C), and pseudouridine (ψ) [12–14]. Among these, m6A is the most common and extensively studied modification [15]. However, in recent years, other types of RNA methylation, particularly m7G methylation, have garnered increasing attention [9, 16, 17].

m7G methylation is one of the most prevalent and evolutionarily conserved RNA modifications, involving N-methylation at the seventh position of guanosine in RNA, which is catalysed by specific methyltransferases [9, 18, 19]. This modification primarily occurs at the 5' cap of mRNA, targeting the nitrogen 7 of guanosine [20–23]. Additionally, m7G modifications are found internally within messenger RNA (mRNA), in primary microRNA (pri-miRNA), ribosomal RNA (rRNA) and transfer RNA (tRNA) across various species [24, 25]. This modification regulates numerous biological processes including mRNA transcription, tRNA stability, microRNA (miRNA) biosynthesis and function, and the processing and maturation of 18S rRNA [26, 27]. m7G modification through the regulation of multiple molecular expressions participates in various physiological and pathological processes, contributing to the onset of diseases such as cardiovascular diseases, developmental disorders, neurological diseases, metabolic-related disorders, and especially cancers. A growing body of evidence demonstrates that m7G methylation is closely associated with cancer development and progression, and affects various cancer-related biological functions [28–31]. In cancers, m7G methyltransferases are often aberrantly expressed, altering m7G modifications in mRNA, tRNA, rRNA, and miRNA, which in turn affects the expression of target genes and modulates cancer-related biological processes [32, 33].

This review summarises the molecular mechanisms underlying m7G modifications in cancer development, and their potential applications in cancer therapy. Additionally, we discuss the potential of m7G modification-associated molecules as biomarkers for cancer diagnosis, disease monitoring, and prognostic evaluation, thereby offering new strategies for cancer diagnosis and targeted therapy.

Function and role of the N7-methylguanosine (m7G) modification

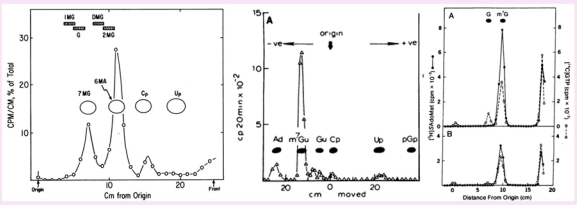
Discovery, definition, and biological function of the m7G modification

m7G is a crucial and evolutionarily conserved RNA modification involved in epigenetic regulation that is widely present in both prokaryotic and eukaryotic organisms [8, 32–36]. The m7G modification involves the methylation of nitrogen at the seventh position of guanosine in RNA, which is catalysed by specific methyltransferases. These modifications affect the synthesis and processing of mRNA, rRNA, miRNA, and tRNA, contributing to various physiological and pathological cellular processes [9, 18, 19].

The discovery and definition of the m7G modification has evolved progressively over time (Fig. 1). In 1965, Holley et al. [37] determined the sequence of yeast $tRNA^{Ala}$, which marked an early milestone in RNA research. In 1975, m7G modifications were first reported in viral RNA, mRNA, tRNA, and rRNA [38, 39]. That same year, Hefti et al. [40] became the first to identify the m7G cap at the 5' end of sindbis virus RNA, and Ensinger et al. successfully solubilised m7G methyltransferase from vaccinia virus [41]. In 1977, the presence of m7G caps and internal m7G modifications in various RNA molecules was further elucidated [42, 43]. The development of m7G-specific antibodies in 1978 greatly accelerated

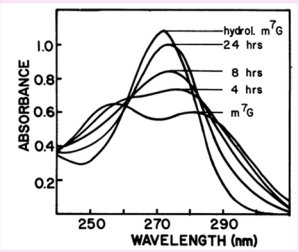
1975

- D T Dubin et al. and S Muthukrishnan et al. reported m7G modification in viral RNA, mRNA, tRNA, and rRNA.
- E. Hefti et al. identified the m7G cap at the 5' end of Sindbis virus RNA.
- M J Ensinger et al. solubilized m7G methyltransferase from vaccinia virus.



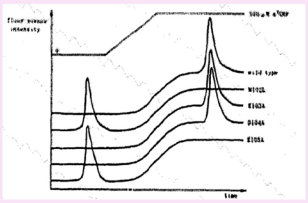
1978

- L. Rainen et al. developed m7G-specific antibodies.



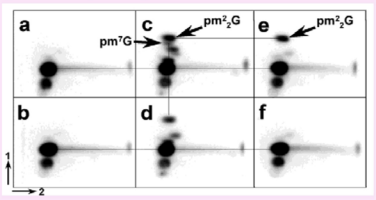
1991

- H. Ueda et al. identified eIF4E as the m7G reader.



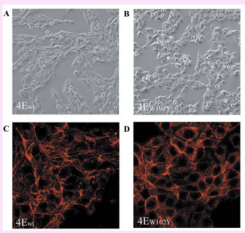
2002

- A. Alexandrov et al. discovered m7G modification at the G46 position in yeast tRNA, mediated by the Trm8p/Trm82p complex.



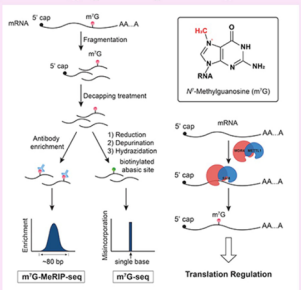
2007

- T.M. Goldson et al. first linked eIF4E with various malignancies, highlighting the role of m7G modification in cancer research.



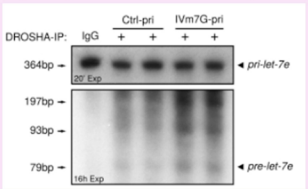
2019

- L.-S. Zhang et al. identified m7G in mature mRNA using high-throughput sequencing.



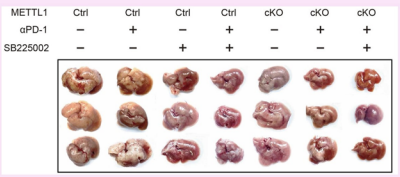
2019

- L. Pandolfini et al. localized m7G modifications to specific miRNAs, including let-7e-5p, using BoRed-seq, RNA immunoprecipitation, and mass spectrometry.



2023

- H. Liu et al. showed in a mouse model of intrahepatic cholangiocarcinoma that METTL1 depletion, combined with CXCR2 inhibition, enhanced PD-1 blockade therapy efficacy.



2024

- Y. Luo et al. proposed the RMscore model, linking m7G modification to immunotherapy resistance in breast cancer via PD-1/PD-L1 expression correlation.

Fig. 1 Milestone events in the field of m7G RNA modification

research in this field [44]. In 1991, the m7G reader, eukaryotic initiation factor 4E (eIF4E), was identified, revealing its binding mechanism to the m7G group via hydrogen bonding and clarifying the role of m7G modification in RNA metabolism [45]. In 2002, Alexandrov et al. [25] discovered an m7G modification at the G46 position in yeast tRNA, mediated by the Trm8p/Trm82p heterodimer complex, providing further insights into its

biological significance. In 2007, the association between eIF4E and various malignancies opened new avenues for cancer research focusing on m7G modifications [46]. In 2019, researchers used high-throughput sequencing to detect m7G modifications in mammalian mRNA and tRNA and identified m7G in mature miRNA and miRNA precursors [24, 47]. By combining BoRed-seq and RNA immunoprecipitation, researchers have localised m7G modifications to miRNAs involved in suppressing cell migration, pinpointing m7G on a specific guanosine in miRNA let-7e-5p using mass spectrometry [47]. In 2020, a debate arose between Vinther and Pandolfini regarding methodologies for detecting m7G in miRNA let-7e in colorectal cancer (CRC) using m7G-RIP-seq, BoRed-seq, and MS/MS analysis. This has stimulated further methodological advancements in the detection of epigenetic modifications in RNAs [48, 49]. In 2021, the regulatory role of m7G in cancer progression, particularly within the tumour immune microenvironment, gained increasing recognition. In 2023, Liu et al. [50] reported that the depletion of methyltransferase-like 1 (METTL1), a key methyltransferase responsible for m7G modifications of RNA, combined with CXCR2 (a receptor for CXCL8) inhibition, enhanced the efficacy of PD-1 blockade therapy in a mouse model of intrahepatic cholangiocarcinoma (ICC). In 2024, Luo et al. [51] proposed the RMscore model, which links m7G modification to immunotherapy resistance in breast cancer by correlating PD-1/PD-L1 expression in patient samples.

Although our understanding of the m7G-modified regulators remains limited, several key methyltransferases responsible for the formation of m7G modifications have been identified. These enzymes catalyse the transfer of a methyl group to the N7 position of guanosine in RNA, thereby affecting RNA function. Major methyltransferases include METTL1/WD repeat domain 4 (WDR4), Williams–Beuren syndrome chromosome region 22 (WBSCR22)/methyltransferase activator subunit 11–2 (TRMT112), and RNA guanine-7 methyltransferase (RNMT)/RNMT-activating mini-proteins (RAM) [36]. The METTL1/WDR4 complex is among the best-known m7G methyltransferase systems and is composed of METTL1 and its partner WDR4. METTL1, a tRNA methyltransferase, transfers a methyl group from S-adenosylmethionine to the N7 position of guanosine in tRNA, thereby stabilising the tRNA tertiary structure. WDR4 stabilises METTL1, enhancing its methyltransferase activity [25, 32]. Additionally, the METTL1/WDR4 complex mediates high levels of m7G modification in mRNA, particularly in the 5'-UTR, coding sequence, and 3'-UTR, suggesting broad involvement in RNA regulation [52, 53]. The WBSCR22/TRMT112 complex mediates the m7G modification at position G1639 in human 18S rRNA, which is essential for ribosome maturation and function. WBSCR22 acts as a catalytic subunit, whereas TRMT112 serves as a coactivator, supporting ribosome biogenesis by stabilising the complex. Lack of this modification impairs ribosome maturation and nuclear export, thus reducing overall translation efficiency [54–57]. The RNMT/RAM complex methylates the guanosine residue of the first transcribed nucleotide in capped mRNA, thereby contributing to m7G cap formation [58]. By modifying the mRNA cap, RNMT can influence pre-mRNA export, translation initiation, and stability [59, 60].

In summary, the m7G modification plays a significant role in regulating gene expression, RNA processing, and translation by modulating RNA structure, stability, and interactions with proteins. These regulatory mechanisms represent potential therapeutic targets for diseases, including cancer, underscoring the importance of m7G modification in various physiological and pathological contexts.

Mechanisms of m7G modification

Research on RNA modifications has advanced our understanding of m7G and has revealed its critical role in various biological processes. The m7G modification is widely distributed in RNA molecules and influences key functions, including mRNA stability, nuclear export, translation, tRNA stability and translation, regulation of ribosome synthesis by influencing 18S rRNA maturation, and modulation of non-coding RNAs (ncRNAs) (Fig. 2).

Regulation of mRNA stability, nuclear export, and translation

The m7G cap structure at the 5' end of mRNA, such as m7GpppX, enhances RNA stability by reducing exonuclease-mediated degradation, thus increasing RNA half-life and maintaining integrity [60]. The m7G cap interacts with eIF4E to form a cap-eIF4E-RNMT complex, which regulates RNA nuclear export and enhances translation efficiency [18]. eIF4E competes with RNMT for m7G cap binding, thereby modulating RNA transport and translation. Cowling [59] demonstrated that the RNMT/RAM complex enhanced cyclin D1 mRNA cap methylation and translation, thereby regulating the cell cycle and promoting cell proliferation and transformation. In addition, Yu et al. [61] reported that Mettl1 stabilises and upregulates serine and arginine rich splicing factor 9 mRNA via m7G modification, which promotes the selective splicing of nuclear factor of activated T cells 4, contributing to cell enlargement.

Regulation of tRNA stability and translation

m7G modification also affects tRNA stability and protein translation. m7G modifications in specific tRNA regions, such as the D-arm, T-arm, and variable loop, influence

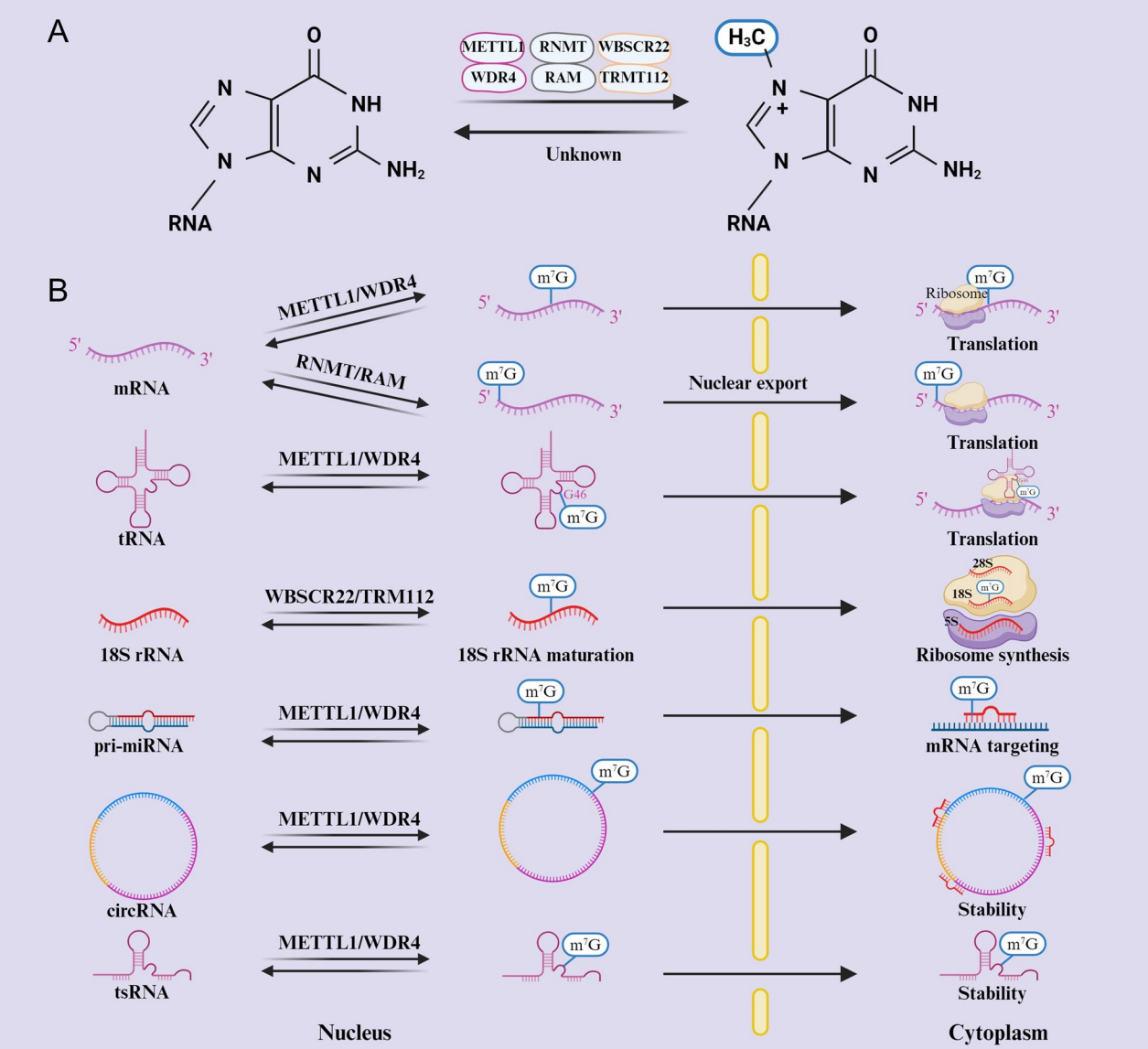


Fig. 2 m7G modifications mediated by RNA methyltransferases and their biological mechanisms in various RNA types. **A** The m7G methyltransferase complexes, including METTL1/WDR4, RNMT/RAM, and WBSCR22/TRMT112, catalyse the insertion of the m7G modification at the N7 position of guanosine in target RNA molecules. **B** Under the action of m7G methyltransferase complexes, m7G modifications occur in mRNA, tRNA, 18S rRNA, and ncRNA, influencing transcript stability, maturation, nuclear export, and translation

tRNA stability and function. For instance, m7G46 modification affects tRNA folding and functionality [62]. Furthermore, METTL1 knockdown reduces m7G46 levels in yeast tRNAs, impairing their transport and translational functions [17, 25].

Role in ribosome synthesis via influencing 18S rRNA maturation

The WBSCR22/TRMT112 complex mediates m7G modifications in rRNA that are critical for ribosome biogenesis. This complex is involved in the maturation of 18S rRNA precursors and facilitates nuclear export of the 40S ribosomal subunit [63]. The inhibition of WBSCR22 leads to the accumulation of immature ribosomal subunits in the nucleus, disrupting ribosome synthesis [54, 55]. Interestingly, the catalytic activity of these methyltransferases is not always required for processing and export of the precursor 18S rRNA, indicating a conserved quality-control mechanism in rRNA maturation.

Regulating the production of ncRNAs

The m7G modification also plays a role in regulating the production of ncRNAs, including miRNA, circular RNA (circRNA), and tRNA-derived small RNAs (tsRNA). In miRNAs [64–66], m7G modification stabilises G-quadruplex structures within the pri-miRNA, facilitating DROSHA-mediated cleavage and miRNA maturation [35]. METTL1 regulates miRNAs, such as let-7, through m7G modification, thereby influencing miRNA maturation and function [47]. m7G modification also stabilizes circRNAs [67, 68]. METTL1 promotes the stability of circKDM1A through GG-dependent m7G modification [69]. tsRNAs are short RNA fragments produced by the cleavage of mature tRNAs or precursor tRNAs and are involved in diverse regulatory processes [70, 71]. The knockdown of METTL1 reduces m7G levels, leading to tRNA destabilization and increased tsRNA biogenesis, and this disruption affects translation efficiency and contributes to altered cell behavior [72]. Interestingly, other study reported that altering METTL1 levels does not affect the total abundance of tsRNAs but influences the expression of m7G-modified tRNA-derived stress-induced small RNAs (tiRNAs) and tsRNAs [73].

In summary, as a critical post-transcriptional modification, the m7G modification is integral to RNA metabolism. It stabilises RNA molecules, regulates RNA transport and translation, controls gene expression, contributes to ribosome biogenesis, and influences ncRNA function. These mechanisms underscore the pivotal role of m7G in RNA function and regulation and highlight its importance in diverse biological processes.

M7G Modification and human diseases

m7G modification is present across various RNAs, impacting gene expression and cellular functions, thereby participating in diverse biological processes, including protein synthesis, translational regulation, and signal transduction [31]. When dysfunction of m7G modification occurs, it may lead to multiple human diseases, such as cardiovascular diseases, developmental and neurological disorders, inflammation-related diseases, metabolism-related diseases, and tumours [61, 72, 74–82] (Table 1).

The m7G Disease Database highlights that cardiovascular diseases have the highest frequency of m7G site variations. METTL1- and WDR4-mediated m7G methylation play key roles in maintaining embryonic stem cell self-renewal and regulating angiogenesis [83, 84]. Specifically, METTL1 deletion enhances the expression of genes related to cardiovascular development [83]. Additionally, METTL1 knockout affects angiogenesis and mesoderm differentiation via multiple signalling pathways [83]. Zhou et al. demonstrated that METTL1 promoted post-ischaemic injury angiogenesis by enhancing vascular endothelial growth factor (VEGF) mRNA translation, suggesting its therapeutic potential in peripheral artery disease [74]. In mouse cardiac tissue, transverse aortic constriction or angiotensin II stimulation induces METTL1 expression, whereas METTL1 knockout alleviates pressure overload-induced cardiac hypertrophy by influencing NFATc4 splicing through SRSF9 mRNA m7G modification, thus affecting cardiac function [61]. These findings indicate that targeting METTL1-mediated m7G modifications may be a therapeutic strategy for vascular diseases [27].

The m7G modifications have been implicated in various developmental and neurological conditions. METTL1 silencing disrupts neuroectoderm formation and causes neurodevelopmental abnormalities [75]. In Alzheimer's disease models, METTL1 downregulation has been observed in excitatory neurones, astrocytes, and microglia within the cortex and hippocampus [78, 85]. In multiple sclerosis, an autoimmune demyelinating disorder of the central nervous system, METTL1 mutations are observed [86]. WDR4 mutations are associated with developmental disorders, including Galloway–Mowat syndrome [87], a unique form of primordial dwarfism with microcephaly [76, 88], and potentially Down syndrome, where WDR4 overexpression in mice has been shown to rescue Down syndrome phenotypes [89]. Mechanistically, dysregulation of let-7 miRNA owing to disturbances in m7G methylation caused by METTL1 or WDR4 mutations may contribute to these neurodevelopmental disorders [76, 88]. Collectively, mutations in METTL1 and WDR4 and aberrant m7G methylation have been linked to a range of neurodegenerative and developmental disorders [77, 89].

Especially, the m7G modification is increasingly associated with cancer progression [32]. The expression levels of m7G regulators such as METTL1 and WDR4 are often abnormally elevated in carcinomas such as acute myeloid leukaemia (AML) [72], ICC [81] and prostate cancer [82], where they enhance m7G tRNA expression [72], activate downstream oncogenic signalling pathways such as PI3K/AKT/mTOR [81], and inhibit the biogenesis of tsRNAs to control the synthesis of key regulators of tumour growth suppression, interferon pathway, and immune effectors [82].

M7G sequencing techniques and tools

In the 1970s, researchers employed a series of biochemical and analytical techniques, including enzymatic digestion, thin-layer chromatography, and mass spectrometry, to uncover modified nucleotides in RNA molecules, such as the m7G modification in tRNA [39, 90, 91]. With the advent of high-throughput sequencing

Table 1 Biological functions and role of m7G methyltransferases in human diseases

Disease type	Disease	m7G methyltransferase	Mechanism	References
Cardiovascular diseases	Heart failure (HF)	METTL1	METTL1 drives cardiac hypertrophy by regulating SRSF9-mediated splicing of NFATc4, serving as a critical modulator of myocardial hypertrophy and offering a novel therapeutic target for HF	[61]
	Peripheral arterial disease (PAD)	METTL1	METTL1 promotes post-ischaemic angiogenesis by enhancing the translation of VEGFA mRNA, presenting significant therapeutic potential for PAD	[74]
Developmental and neurological disorders	Teratoma	METTL1	METTL1-mediated m7G methylation maintains pluripotency in human stem cells, limits mesodermal differentiation, and restricts vascular development. METTL1 silencing alters the global m7G profile in human-induced pluripotent stem cells, reduces the translation efficiency of stem cell markers, slows the cell cycle, and skews differentiation toward mesodermal fates while inhibiting neuroectodermal differentiation in vitro and in vivo	[75]
	Microcephalic primordial dwarfism	WDR4	Mutations in WDR4 disrupt tRNA m7G46 methylation, causing a unique form of microcephalic primordial dwarfism. Patients with a WDR4-R170L missense mutation exhibit defective m7G levels on tRNA, implicating additional human disease-related modification genes	[76]
	Down syndrome	WDR4	WDR4 has been identified as a candidate gene for Down syndrome. Overexpression of Wdr4 in Ts1Yah mouse models enhances learning and memory in the hippocampus	[77]
	Alzheimer's disease (AD)	METTL1	METTL1 expression is downregulated in excitatory neurons, astrocytes, and microglia within the cortex and hippocampus in AD models	[78]
Inflammatory-related diseases	Pneumonia	TrmB	Deletion of the m7G tRNA methyltransferase TrmB significantly alleviates lung infections caused by the pathogen *Acinetobacter baumannii* in mice	[79]
Metabolic-related diseases	Osteoarthritis	METTL1	Elevated METTL1 expression and m7G levels in osteoarthritis chondrocytes upregulate mt-tRF3b-LeuTAA expression, exacerbating chondrocyte degeneration and inducing osteoarthritis progression	[80]
Tumours	Acute myeloid leukaemia	METTL1/WDR4	METTL1 knockdown reduces tRNA m7G modification, destabilizes tRNA, increases tsRNA production, and disrupts global translation efficiency in AML cells	[72]

Table 1 (continued)

Disease type	Disease	m7G methyltransferase	Mechanism	References
	Intrahepatic cholangiocarcinoma	METTL1	METTL1 knockout inhibits the PI3K/AKT/mTOR signaling pathway, reducing proliferation and lymphatic metastasis in ICC mouse models	[81]
	Prostate cancer	METTL1	METTL1 depletion disrupts m7G tRNA methylation, promoting 5′ tsRNAs that enhance tumor growth suppression, the interferon pathway, and immune effectors	[82]

technologies, researchers have gained the ability to comprehensively identify and quantify RNA modifications at the transcriptome level, particularly m7G modifications [92–94]. These integrated techniques provide valuable insights into the prevalence, distribution, and functions of m7G modifications in various cellular contexts.

Currently, the methods for detecting m7G modifications in RNA can be broadly classified into molecular biology experiments and sequencing-based approaches. The main detection methods fall into three categories: antibody-based RNA immunoprecipitation sequencing (e.g., m7G-MeRIP-seq), chemical reaction- and reverse transcription-based methods (e.g., m7G-seq), and immunoprecipitation-based m7G-miCLIP-seq. The latter two methods can achieve single-nucleotide resolution, enabling the identification of specific m7G modification sites in mRNA. For instance: (1) High-performance liquid chromatography and liquid chromatography-tandem mass spectrometry (LC–MS/MS) are commonly used to measure total m7G levels in RNA [95]. LC–MS/MS quantifies the overall modification level by analysing RNA hydrolysis products but cannot reveal modification sites on individual RNA molecules [96]. Antibody-based sequencing techniques, such as MeRIP-seq and miCLIP-seq, ptimiz specific antibodies for immunoprecipitation to capture and identify m7G-modified RNA molecules [24, 83, 94]. However, these methods may produce false positives owing to antibody quality and non-specific binding. (2) Chemical reaction-based sequencing methods, such as AlkAnilineseq, BoRed-seq, m7G-MaP-seq, and TRAC-seq, use chemical reactions (e.g., borohydride reduction) to detect m7G modifications at single-nucleotide resolution [47, 92, 93]. Compared with antibody-based methods, these approaches offer higher specificity and resolution [93, 97]. (3) The chemical-assisted m7G-seq approach does not require antibody enrichment; it selectively converts m7G sites to abasic sites and induces mutations via reverse transcriptase to achieve single-nucleotide resolution [98]. M7G-miCLIP-seq combines anti-m7G antibody immunoprecipitation with UV-crosslinking to capture internal m7G modifications in mRNA and track their dynamic changes [94]. The m7G-quant-seq technique, by screening reverse transcriptases and ptimizing conditions, accurately detects m7G sites in tRNA at a single-nucleotide resolution, enhances sensitivity to mutational signals, and shows promise for other RNA modification studies [99].

In summary, various methods are available for detecting m7G modifications, ranging from traditional molecular biology techniques to advanced high-throughput sequencing technologies. Conventional methods such as northern blotting and immunodot blotting lack single-nucleotide resolution, whereas sequencing-based technologies allow transcriptome-wide mapping of RNA modifications. Chemical approaches such as m7G-seq offer nucleotide-level precision for studying highly methylated sites. Although challenges remain in quantification yield and measurement accuracy, these techniques provide powerful tools for investigating the function and regulation of m7G modifications [100]. In addition to these sequencing techniques, several online tools have been developed to predict m7G sites in RNA molecules [87, 101–115] (Table 2). Using machine learning algorithms and other computational methods, tools such as PREDMOD, MeT-DB, and RDMAS estimate the probability of m7G modification at various RNA sites. These databases and web servers have greatly facilitated research on m7G methylation, including studies on conservation across species, the effects of genetic mutations on m7G methylation, the physiological and pathological roles of known and predicted m7G modifications, and the discovery of novel internal m7G sites. As our understanding of m7G methylation and its regulatory mechanisms deepens, the predictive accuracy of these web servers for m7G sites and associated diseases is expected to improve.

Table 2 Methods and tools for predicting m7G modification

Tool	Function	Website	References
m7GHub	A comprehensive online platform for decoding m7G positions, regulatory mechanisms, and pathogenesis within mRNA	www.xjtlu.edu.cn/biologicalsciences/m7ghub	[87]
m7GDisAI	A tool for exploring m7G-associated diseases, providing a list of the top 20 predicted m7G sites related to 177 diseases, along with detailed information on specific m7G-disease association	http://180.208.58.66/m7GdisAI/	[101]
iRNA-m7G	Identifies m7G modification sites in the human transcriptome using a feature fusion strategy that combines sequence-based and structure-based characteristics	http://lin-group.cn/server/iRNA-m7G/	[102]
XG-m7G	Differentiates m7G modification sites by applying the XGBoost algorithm in combination with six sequence encoding schemes	http://flagship.erc.monash.edu/XG-m7G/	[103]
m7G-IFL	A machine learning-based tool that uses an iterative feature representation algorithm to accurately identify m7G modification sites	http://server.malab.cn/m7G-IFL/	[104]
m7G-DPP	Encodes RNA sequences by leveraging dinucleotide physicochemical properties and extracts features like Pearson correlation, dynamic time warping, and distance correlation. Utilises LASSO feature selection and an SVM classifier to identify m7G modification sites	https://figshare.com/articles/online_resource/m7G-DPP/15000348	[105]
m7GPredictor	A machine learning model designed to predict internal m7G modification sites in RNA based on sequence features	https://github.com/NWAFU-LiuLab/m7Gpredictor	[106]
THRONE	A computational predictor that integrates multiple sequence-based features with machine learning classifiers to accurately identify m7G sites in the human genome	http://thegleelab.org/THRONE/	[107]
SVM-based model	Utilises optimal sequence features to predict n7-methylguanosine sites in human RNA	https://github.com/MapFM/m7g_model.git	[108]
m7GHub V2.0	An updated resource collection for m7G modifications across various RNA types and 23 species, containing 430,898 predicted m7G sites identified using NGS and ONT technologies	www.rnamd.org/m7GHub2	[109]
TMSC-m7G	A prediction model based on variational autoencoders and contrastive learning for accurate identification of m7G sites	http://39.105.212.81/	[110]
m7GRegpred	A bioinformatics framework integrating multiple features to predict substrates of m7G modification enzymes and readers	http://modinfor.com/m7GRegpred/	[111]
HN-CNN	A convolutional neural network-based model designed to predict disease associations with m7G sites within a heterogeneous network	–	[112]
BRPCA	A computational method that predicts potential associations between m7G sites and various diseases using advanced predictive techniques	–	[113]
BERT-m7G	A deep learning-based model using the BERT architecture to identify m7G modification sites in RNA sequences with high accuracy	–	[114]
Moss-m7G	An interpretable, motif-based deep learning method for predicting m7G modification sites in RNA sequences	–	[115]

m7G modifications involving in the hallmarks of cancer

Tumour development is a complex process defined by 14 hallmark biological features [116, 117]. Recent studies have increasingly indicated that m7G modification plays a significant role in tumourigenesis by regulating malignant behaviours, such as sustained proliferative signalling, resistance to cell death, invasion and metastasis, metabolic reprogramming, genomic instability, and immune evasion (Fig. 3).

Sustained proliferation signalling

To maintain sustained proliferation, cancer cells disrupt the signalling pathways that regulate cell growth and division in normal tissues. This can be achieved by producing growth factor ligands or stimulating normal cells in the tumour microenvironment to secrete growth factors [118, 119]. Additionally, cancer cells may increase surface receptor levels or modify receptor structures, making them abnormally responsive to growth factors [120] or bypass ligand-mediated

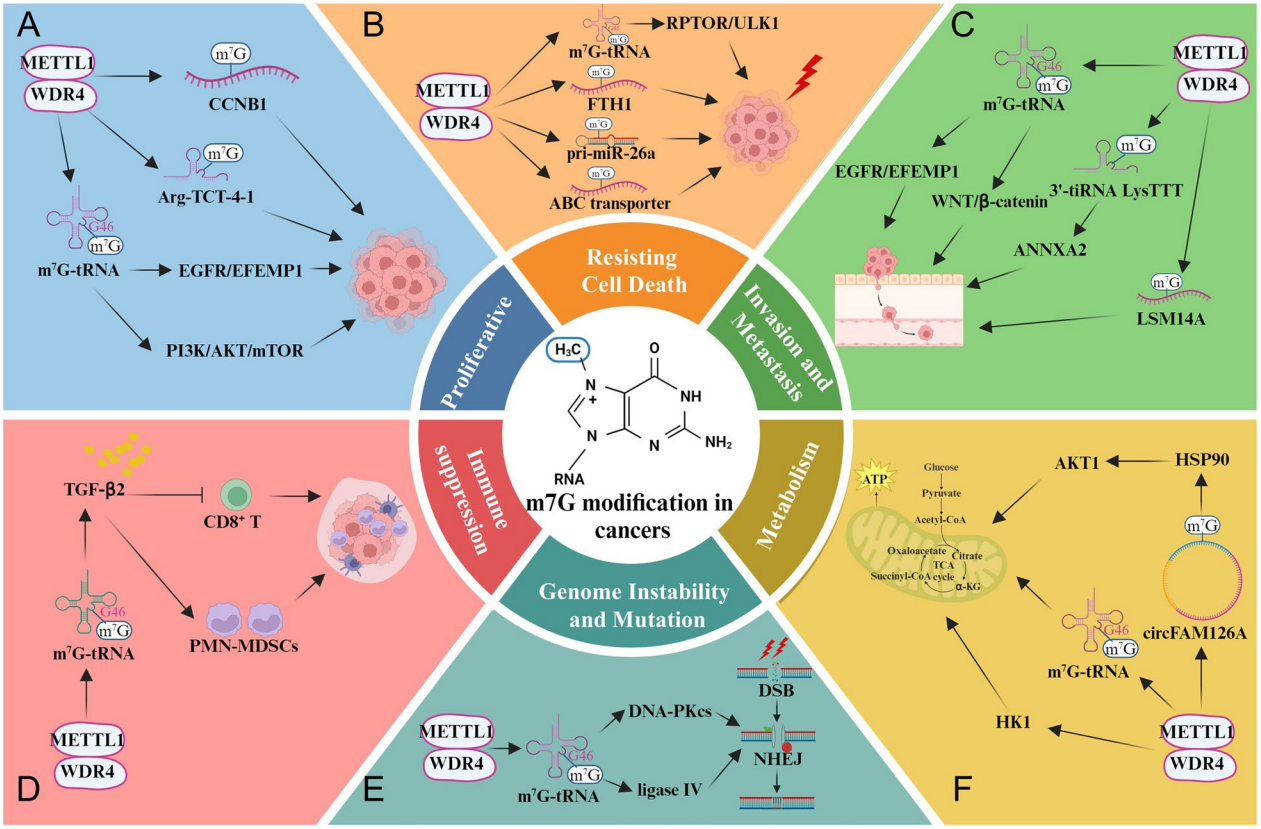


Fig. 3 Roles of m7G modification in tumour biology. **A**–**F** As an m7G RNA methyltransferase, METTL1/WDR4 regulates various tumour-related biological processes, including proliferation (**A**), resistance to cell death (**B**), invasion and metastasis (**C**), immune evasion (**D**), genomic instability (**E**), and metabolic reprogramming (**F**)

receptor activation by activating downstream signalling pathways [121].

Research shows that METTL1 is frequently amplified and overexpressed in various cancers. Its deletion decreases the number of m7G-modified tRNAs, disrupts the cell cycle, and inhibits tumourigenesis [29, 30, 72, 122, 123]. Conversely, overexpression of METTL1 induces cancer cell transformation and proliferation, promoting tumour progression [69, 124–128]. This indicates that METTL1 plays a pivotal role in sustaining tumour cell proliferation. In hepatocellular carcinoma (HCC) studies, METTL1 is highly expressed, which correlates with advanced staging and poor prognosis [28, 129]. METTL1 overexpression increases the expression of m7G-modified tRNAs, especially Arg-TCT-4–1, which in turn enhances the translation of mRNAs rich in AGA codons, including those encoding cell cycle regulators [130]. Thus, METTL1-mediated tRNA modification can drive oncogenic transformation by increasing the levels of growth-promoting proteins. Arg-TCT is elevated in various tumours and is associated with a poor prognosis [130]. Furthermore, METTL1/WDR4-mediated m7G-tRNA modification promotes head and neck squamous cell carcinoma (HNSCC) progression and metastasis by regulating oncogenic transcripts related to the PI3K/AKT/mTOR pathway [123]. Chemical modulators of this pathway can reverse the effects of METTL1 in HNSCC mouse models [123].

In summary, m7G modification is closely related to sustained proliferative signalling in cancer cells. METTL1-mediated m7G modification increases the tRNA abundance and translation efficiency of specific mRNAs, thus promoting cancer cell proliferation, transformation, and progression.

Resisting cell death

Cell death can be initiated by accidental cell death or by regulated cell death (RCD). RCD includes both programmed cell death (PCD) and nonprogrammed cell death [131]. There are eleven main PCD pathways: apoptosis [132], necroptosis [133], pyroptosis [133], ferroptosis [134], autophagy [135], parthanatos [136], entotic cell death [137], lysosome-dependent cell death [138], alkaliptosis [139], and oxeiptosis [140]. These pathways play

critical roles in physiological and pathological processes and are essential for maintaining tissue homeostasis and health [131].

Autophagy is a key mechanism of cell death and survival and maintains homeostasis under adverse conditions. Autophagy may promote cell survival or death in cancer cells [135, 141]. m7G RNA modification regulates autophagy by affecting translation of transcripts involved in the RPTOR/ULK1/autophagy pathway. Targeting METTL1 or WDR4 reduces m7G-modified tRNAs, thus downregulating mTORC1-mediated autophagy activation in oesophageal squamous cell carcinoma (ESCC) [142]. Subsequent studies confirmed that the disruption of m7G modification hyperactivates autophagy, leading to cell death in ESCC, suggesting that dysregulated m7G modification affects autophagy and cell survival in ESCC [143].

Necrosis, previously viewed as uncontrolled, is now recognised as a regulated form of cell death with potential pro-inflammatory and pro-tumour effects [144]. Tumour cell resistance to regulated cell death remains a hallmark of cancer and a challenge in therapy [145]. Evidence suggests that m7G modification of RNA plays a critical role in cell death resistance [146]. METTL1-mediated m7G tRNA modification is associated with radioresistance in HCC. In AML, transcriptomic analysis reveals significant differences in m7G mRNA modifications between AML and drug-resistant AML cells, including mRNAs related to ATP-binding cassette transporters, which are critical for multidrug resistance [147]. Furthermore, significant differences in the m7G methylation patterns are observed between drug-resistant and non-resistant AML cells, with drug-resistant cells exhibiting upregulated methylation. Pathway analyses have indicated that genes associated with lncRNA m7G sites are involved in drug resistance mechanisms in AML [148]. Interestingly, METTL1 increases osteosarcoma sensitivity to ferroptosis via m7G modification [149]. In CRC, METTL1 knockdown also affects sensitivity [150].

Overall, the m7G modification of tRNA plays a significant role in cancer cell resistance to death. Dysregulated m7G modification influences autophagy, DNA repair, and other processes, thereby affecting tumour progression and treatment responses. Insights into the m7G-mediated resistance to cell death may provide new strategies for counteracting cancer treatment resistance.

Activating invasion and metastasis

As cancer progresses towards greater malignancy, it exhibits local invasion and distant metastasis, where cancer cells often undergo morphological changes and alter their adhesion properties with other cells and the extracellular matrix [151, 152]. The invasion-metastasis cascade involves multiple steps that have been increasingly elucidated using advanced research tools, experimental models, and the discovery of key regulatory genes. Notable advances include an understanding of how the epithelial-mesenchymal transition (EMT) program extensively regulates invasion and metastasis, the role of stromal cells, and the complex mechanisms of metastatic seeding in various cancers [153].

Dysregulated m7G tRNA modifications, particularly through the upregulation of METTL1 and WDR4, have been implicated in promoting tumourigenesis and progression in several cancers, including bladder cancer, nasopharyngeal carcinoma (NPC), and lung cancer [146]. Ji et al. [30] demonstrated that METTL1 overexpression in bladder cancer correlates with poor patient prognosis and facilitates cancer progression through the METTL1-m7G-EGFR/EFEMP1 axis. Silencing of METTL1 inhibits the proliferation, migration, and invasion of bladder cancer cells both in vitro and in vivo.

In lung cancer, METTL1/WDR4-mediated m7G tRNA modifications enhance mRNA translation and cancer progression. Elevated levels of METTL1 and WDR4 have been observed in human lung cancer samples and correlate with poor patient prognosis. Deletion of METTL1/WDR4 impairs m7G tRNA modifications, reduces proliferation, colony formation, and invasion in lung cancer cells, and diminishes tumorigenic capabilities [29]. Similarly, METTL1 and WDR4 are upregulated in HCC, which correlates with advanced tumour stage and adverse patient outcomes. METTL1-mediated m7G tRNA modifications promote HCC cell proliferation, migration, and invasion [28]. WDR4 affects the PI3K/AKT and p53 pathways through the MYC/WDR4/CCNB1 signalling axis, enhancing CCNB1 translation and promoting HCC cell proliferation and metastasis [129].

Functional assays have indicated that METTL1-mediated m7G tRNA modifications support oncogene translation and promote proliferation, apoptosis, and migration in neuroblastoma cells and mouse models [154]. Dysregulation of this modification process can affect mRNA translation and signalling, contributing to enhanced cell proliferation, invasion, and metastasis. For instance, in NPC, METTL1/WDR4 induces EMT by upregulating the WNT/β-catenin signalling pathway, promoting NPC growth and metastasis in vitro and in vivo [125]. Silencing or inhibition of METTL1/WDR4 reduces cancer cell growth and invasion, highlighting their potential therapeutic targets [125].

In summary, m7G tRNA modifications critically influence cancer progression by regulating mRNA translation and key pathways like WNT/β-catenin, particularly by promoting invasion and metastasis.

Reprogramming energy metabolism

Malignant cells reprogram their metabolism in response to diverse extracellular and intracellular signals to support their rapid growth and survival. Some metabolic adaptations initiate the transformation process, whereas others sustain tumour growth, making cancer cells particularly vulnerable to inhibitors that target crucial metabolic pathways [155]. Emerging bioinformatics studies have identified dysregulated m7G-related genes across various cancers, suggesting that m7G modification may contribute to altered energy metabolism in tumour cells. For instance, Liu et al. [156] discovered that m7G-related lncRNAs exhibit significantly different expression in breast cancer tissues and developed a prognostic marker based on these lncRNAs. Gene enrichment analysis revealed associations with metabolic pathways.

Cancer cells often favour glycolysis over mitochondrial oxidative phosphorylation (OXPHOS), even under oxygen-rich conditions, a phenomenon known as "aerobic glycolysis" or the Warburg effect [157]. Zhao et al. [158] reported that m7G-modified circFAM126A regulates glycolysis in lung cancer cells by promoting the ubiquitination of HSP90 and inhibiting AKT1 expression, which influences disease progression. Furthermore, overexpression of METTL1 in adrenal cortical carcinoma (ACC) cells stimulates proliferation, migration, and invasion, and western blotting analysis showed that METTL1 positively regulates the glycolytic enzyme HK1 [159]. METTL1 is upregulated in anlotinib-resistant oral squamous cell carcinoma cells, facilitating a metabolic shift from glycolysis to OXPHOS by enhancing global mRNA translation and m7G tRNA modifications [127].

These studies suggest that m7G modification may influence tumour cell energy metabolism by modulating metabolic pathways. However, direct evidence linking m7G to reprogrammed energy metabolism in cancer remains limited, highlighting the need for further research to clarify this relationship.

Genome instability

Cancer progression often relies on ongoing genomic alterations in tumour cells. This process involves mutations that confer selective advantages, allowing certain cellular sub-clones to expand and dominate the local tissue environment. Normally, genomic maintenance systems detect and repair DNA defects and maintain low spontaneous mutation rates. However, cancer cells often have elevated mutation rates, and accumulate mutations that support tumourigenesis [160]. Recurring genetic variations and specific genomic abnormalities suggest that certain genes actively contribute to tumour development by facilitating the rapid accumulation of oncogenic mutations that promote cancer traits [161].

Polymorphisms in METTL1 and WDR4 may increase susceptibility to specific cancers such as hepatoblastoma in children [162, 163]. Although individual polymorphisms may have a limited impact, combinations of multiple risk genotypes can significantly increase the disease risk [162, 163]. Similarly, polymorphisms in these genes have been associated with paediatric glioma risk, with the rs15736 variant of WDR4 notably reducing the risk of glioma [164]. The rs15736 polymorphism also correlates with expression levels of WDR4 and the neighbouring gene, cystathionine β-synthase [164].

In addition to these polymorphisms, METTL1 and WDR4 may influence genomic stability through m7G modifications, thereby affecting tumour initiation and progression. After UVC whole-genome irradiation, m7G RNA levels increase in the cytoplasm within 10–12 min, reaching peak nuclear positivity at approximately 80 min [165]. In HCC, METTL1-mediated m7G modifications have been shown to selectively regulate the translation of DNA repair proteins, such as DNA-dependent protein kinase catalytic subunits and DNA ligase IV, following IR. This regulation increases the frequency of m7G-associated codons, thereby improving the efficiency of NHEJ-mediated DNA DSB repair [166]. These findings suggest that m7G-modifying genes play a significant role in maintaining genomic stability and mutation rates, thereby contributing to tumour formation and progression.

Evading immune destruction

Cancer cells have developed mechanisms to evade immune destruction, which is a fundamental hallmark of cancer [116]. This evasion is achieved through multiple strategies, including avoiding immune recognition, suppressing immune responses, and creating an immunosuppressive tumour microenvironment [167, 168]. Understanding these mechanisms is crucial for designing therapies that boost the immune activity against cancer. Recent advances in immunotherapy, including immune checkpoint inhibitors, chimeric antigen receptor T cell therapy, and cancer vaccines, have demonstrated the efficacy of targeting immune evasion to improve patient outcomes [169].

Research has highlighted a connection between m7G modifications and immune evasion. For example, in HCC, elevated METTL1 expression enhances the translation of TGF-β2, fostering an immunosuppressive microenvironment characterised by an increase in polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) and a decrease in CD8 + T cells. Blocking the METTL1-TGF-β2-PMN-MDSC axis has shown promise in restoring anti-tumour immunity [170].

Multiomics analysis of 33 cancer types further underscores m7G's impact on tumour immunity. This analysis

found that the m7G score negatively correlates with microsatellite instability and TMB, but positively correlates with immune suppression and exclusion, as measured by the tumour immune dysfunction and exclusion score. These findings suggest that m7G may serve as a biomarker for predicting immune checkpoint inhibitor responses. Moreover, an m7G-related lncRNA prognostic model has been developed to differentiate "hot" (immune-inflamed) from "cold" (immune-excluded) tumours, aiding in systemic treatment decisions [171].

In summary, m7G modifications play a substantial role in modulating tumour immune responses. The dysregulation of m7G regulatory genes can influence immune cell behaviour within the tumour microenvironment, providing valuable insights for future research and personalised cancer treatment strategies that focus on enhancing immune responses.

Potential clinical applications of m7G-associated molecules in cancer

M7G-Associated molecules as novel biomarkers in cancer

As a prevalent post-transcriptional RNA modification, m7G plays a significant role in RNA processing, metabolism, and function and is primarily regulated by enzymes related to m7G modification, such as METTL1 and its cofactors WDR4, WBSCR22/TRMT112, and RNMT/RAM. METTL1/WDR4 and WBSCR22 are abnormally expressed in various cancers (Fig. 4) including lung, breast, liver, prostate, and bladder cancers. High METTL1 expression has been observed in lung cancer, correlating with tumour, node, and metastasis staging [124]. Similarly, WDR4 is overexpressed in patients with lung cancer, where elevated levels are associated with a poor prognosis [29]. Protein tyrosine phosphatase non-receptor type 23, a substrate for WDR4-based ubiquitin ligase, is downregulated in lung cancer, with reduced expression correlating with higher WDR4 levels and worse prognostic outcomes [172]. Furthermore, in patients with breast cancer, both METTL1 and WDR4 are downregulated, and their expression levels are linked to tumour stage [126]. In HCC, both METTL1 and WDR4 show elevated expression levels, which correlate with poor patient prognosis [173]. In prostate cancer, high METTL1 expression is associated with unfavourable prognostic outcomes [174]. In bladder cancer, METTL1 is upregulated and its expression correlates with the tumour stage [175]. In clear cell renal cell carcinoma (ccRCC), METTL1 is upregulated, with its expression correlating with the M stage; Cox regression analysis shows that METTL1 is associated with poor prognosis in ccRCC [176].

Interestingly, m7G methyltransferases may function as potential tumour markers, and their modified molecules are closely associated with the clinicopathological characteristics of cancer patients [29, 69, 73, 81, 123–126, 142, 158, 172–175, 177–184] (Table 3). For example,

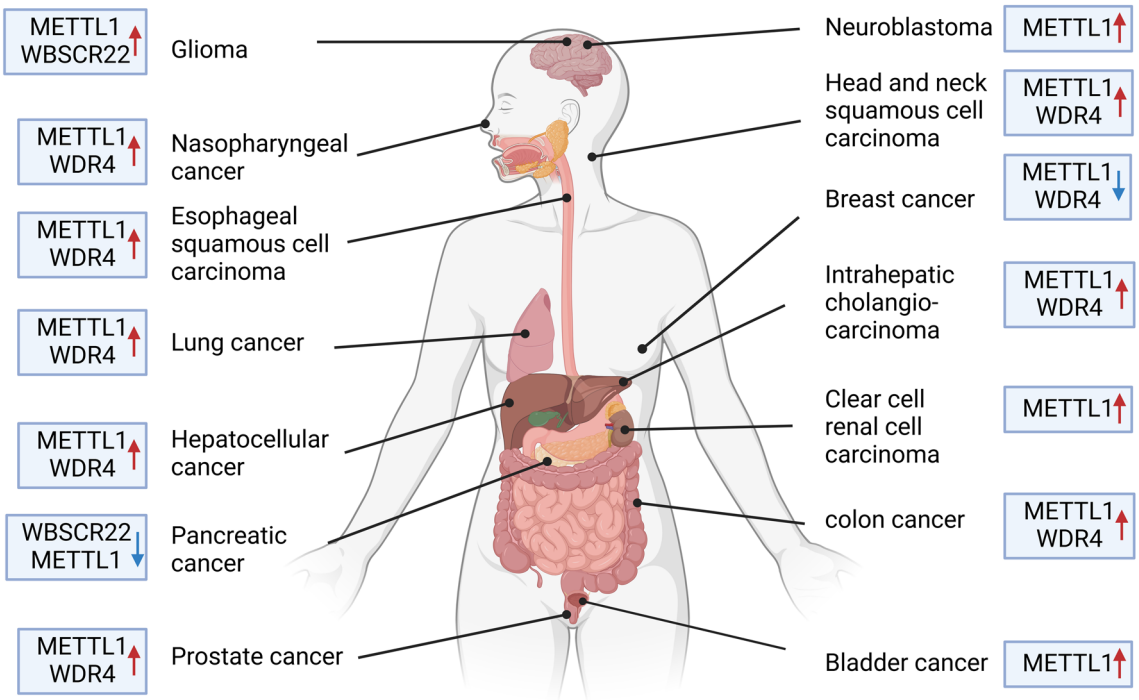


Fig. 4 Expression of m7G methyltransferases in human cancers

Table 3 Correlation between m7G-associated molecules and clinicopathological features of patients with cancer

Type of cancer	m7G-associated molecule	Expression	Relationship with clinicopathologic features	References
Intrahepatic cholangio-carcinoma	METTL1/WDR4	Upregulation	Survival	[81]
Head and neck squamous cell carcinoma	METTL1	Upregulation	Clinical stage, tumour stage, and differentiation grade	[123]
	WDR4		Tumour stage	
Nasopharyngeal cancer	METTL1	Upregulation	TNM stage and survival	[125]
Breast cancer	METTL1	Downregulation	Clinical stage	[126]
	WDR4			
Esophageal squamous cell carcinoma	METTL1/WDR4	Upregulation	Tumour grade, stage and survival	[142]
Lung cancer	WDR4	Upregulation	Survival	[29]
	METTL1		TNM stage	[124]
	circFAM126A	Downregulation	Survival	[158]
	PTPN23		Clinical stage and tumour size	[172]
Prostatic cancer	METTL1	Upregulation	Survival	[174]
	CDK14			
Clear cell renal cell carcinoma	METTL1	Upregulation	M stage	[176]
Hepatocellular carcinoma	WDR4	Upregulation	Survival	[173]
	METTL1			[177]
Colorectal cancer	METTL1	Upregulation	–	[178]
	WDR4		–	
	circKDM1A		Survival	[69]
	tsRNA-GlyGCC		Tumour metastasis	[179]
Bladder cancer	METTL1	Upregulation	Clinical stage	[175]
	miR-760			
	mtiRL	Downregulation	–	[73]
Glioblastoma	LSM14A	Upregulation	Clinical grade and survival	[180]
Glioma	METTL1	Upregulation	WHO grade and survival	[181]
	WBSCR22		Tumour grade and survival	[182]
Pancreatic cancer	METTL1	Downregulation	Survival	[183]
	WBSCR22			[184]

Zhao et al. [158] used m7G-circRNA epitranscriptome microarray analysis and identified circFAM126A as being downregulated in lung cancer, with low expression levels associated with tumour stage and size. Receiver operating characteristic curve analysis further indicated that circFAM126A has considerable diagnostic potential in lung cancer. In CRC, Sun et al. [69] revealed that METTL1 catalyses the m7G modification in circKDM1A, protecting it from degradation, and that high levels of m7G-modified circKDM1A are associated with poor prognosis. Xu et al. [179] demonstrated that tsRNA-GlyGCC is regulated by METTL1-mediated tRNA m7G modification and that its overexpression is linked to tumour metastasis. Similarly, Wang et al. [180] reported that METTL1 is upregulated and regulates the expression of Sm-like protein 14 homologue A (LSM14A) through mRNA m7G methylation. LSM14A expression correlates with tumour grade and poor prognosis of glioblastoma. Additionally, Ying et al. [73] discovered a novel m7G-modified tsRNA, m7G-3'-tiRNA LysTTT (mtiRL), exhibiting high expression in patients with bladder cancer. Another study by Xie et al. [175] demonstrated that METTL1 is upregulated, and its expression correlates with the tumour stage. It has been identified as a target of METTL1 among METTL1-mediated miRNAs in bladder cancer, where METTL1 directly methylates pri-miR-760, facilitating its processing, and miR-760 expression correlates with tumour stage.

Consequently, m7G methyltransferases, along with m7G modification-associated molecules, might serve as tumour markers, offering valuable insights for clinical practices such as early cancer detection, disease monitoring, prognostic assessment, and targeted cancer therapy.

Therapeutic potential of m7G-associated molecules in cancer

The close link between m7G modification and cancer progression highlights m7G-associated enzymes and

related molecules as promising biomarkers for cancer diagnosis and as potential therapeutic targets [50, 82, 123, 170] (Fig. 5 and Table 4).

METTL1 is associated with m7G modification and is notably elevated in recurrent HCC after complete radiofrequency ablation (RFA). This increase corresponds to higher levels of CD11b + CD15 + PMN-MDSCs and a decrease in the number of CD8 + T cells. Although complete RFA effectively eliminates tumours, incomplete RFA (iRFA) in mice leads to enhanced tumour growth, increased PMN-MDSC levels, and reduced CD8 + T cells. Inhibition of the METTL1-TGF-β2-PMN-MDSC axis—either through anti-Ly6G antibodies or by downregulating METTL1 expression—significantly reduces iRFA-induced tumour growth and restores CD8 + T cell populations. These findings underscore the critical role of METTL1 in fostering an immunosuppressive environment and suggest that targeting this pathway may restore antitumour immunity and prevent HCC recurrence after RFA [170].

In HNSCC, METTL1-mediated m7G tRNA modification regulates mRNA translation and activates the PI3K/AKT/mTOR signalling pathway. In METTL1 knockin mice treated with BKM120 (an anti-PI3K agent), there was a significant reduction in lesion size, invasive cancer, and lymph node metastasis, indicating that targeting the METTL1-PI3K/AKT/mTOR axis may be a promising therapeutic strategy for HNSCC [123].

METTL1-mediated m7G tRNA modification promotes PMN-MDSC recruitment via CXCL8. In a cholangiocarcinoma mouse model, METTL1 deficiency or combined treatment with SB225002 (a CXCR2 inhibitor) and anti-PD-1 therapy shows more substantial anticancer effects than anti-PD-1 therapy alone. This combined approach significantly reduces PMN-MDSC levels and increases CD4 + T cell counts. Furthermore, blocking METTL1, CXCR2, and PD-1 nearly completely eradicates liver tumours. These findings suggest that the inhibition of METTL1-mediated m7G tRNA modification reduces immune suppression and enhances the efficacy of anti-PD-1 treatment in ICC [50].

In prostate cancer, METTL1 deficiency leads to increased cytokine production, which is associated with an improved response to immune checkpoint blockade (ICB). In METTL1-deficient mouse tumours, ICB treatment with anti-PD1 and anti-CTLA4 antibodies is more effective. Additionally, elevated METTL1 expression has been linked to poor ICB responses in patients with breast cancer, CRC, ovarian cancer, and glioblastoma, indicating that high METTL1 levels may predict poor responses to ICB therapy [82]. This highlights METTL1's potential role in immunotherapy, where targeting METTL1, either alone or in combination with other immunotherapies, could improve treatment outcomes [82].

The oncogenic properties of eIF4E arise from its ability to bind m7G caps to mRNA, thereby selectively promoting the export and translation of cancer-associated mRNAs. Clinical trials with ribavirin, an analogue of the m7G cap, in patients with M4/M5 AML demonstrated the benefits of targeting eIF4E [185]. The eIF4F complex (which includes eIF4E) is associated with both innate and acquired drug resistance, making it a promising therapeutic target. Drug combinations that target both BRAF/MEK and eIF4F can overcome several resistance mechanisms in BRAF-mutated cancers [186]. In melanoma, CRC, and thyroid cancer, the eIF4E cap-binding protein forms complexes with eIF4G and eIF4A, reducing the efficacy of anti-BRAF and anti-MEK therapies. The inhibition of eIF4E-eIF4G interactions can prevent translation activation and address drug resistance [186]. In conclusion, m7G-associated proteins, particularly METTL1 and eIF4E, are potential therapeutic targets. Their inhibition can enhance cancer treatment efficacy, boost immune response, and overcome drug resistance, opening new avenues for cancer therapy.

Conclusions and perspectives

This review provides a comprehensive summary of the effects of m7G modifications on the structure and function of various types of RNA. This clarifies the relationship between the m7G modification and multiple diseases, highlighting its regulatory role in cancer progression. Additionally, this review outlines cancer-related m7G modifications, identifies m7G-associated tumour biomarkers, and proposes potential therapeutic targets. These findings suggest that m7G modification and its

(See figure on next page.)

Fig. 5 m7G modification plays an important role clinically as biomarkers and therapeutic targets for tumours. **A** m7G modification occurs in different RNAs, including mRNAs, tRNAs,18S rRNA, pri-miRNAs, circRNAs, and tsRNAs. **B** m7G-associated molecules may serve as diagnostic and prognostic biomarkers. **C**–**F** m7G-associated molecules are potential cancer therapeutic targets. In HCC mouse models, interrupting the METTL1-TGF-β2-PMN-MDSC axis restores anti-tumour immunity and prevents HCC recurrence after RFA therapy (**C**). In HNSCC mouse models, METTL1 knockin mice treated with anti-PI3K drugs show inhibition of tumour metastasis and reduction of lesion size (**D**). In ICC mouse models, METTL1 deletion or the reduction of CXCL5/CXCL8 translation reduces the accumulation of PMN-MDSCs in tumour cells and enhances anti-PD-1 treatment sensitivity (**E**). In prostate cancer mouse models, METTL1-deficient mice show induction of cytokine (such as IL-10, IFN-γ, CXCL1/5, and IL-6) secretion, and ICB treatment with anti-PD1 and anti-CTLA4 antibodies inhibits tumour volume in mice (**F**)

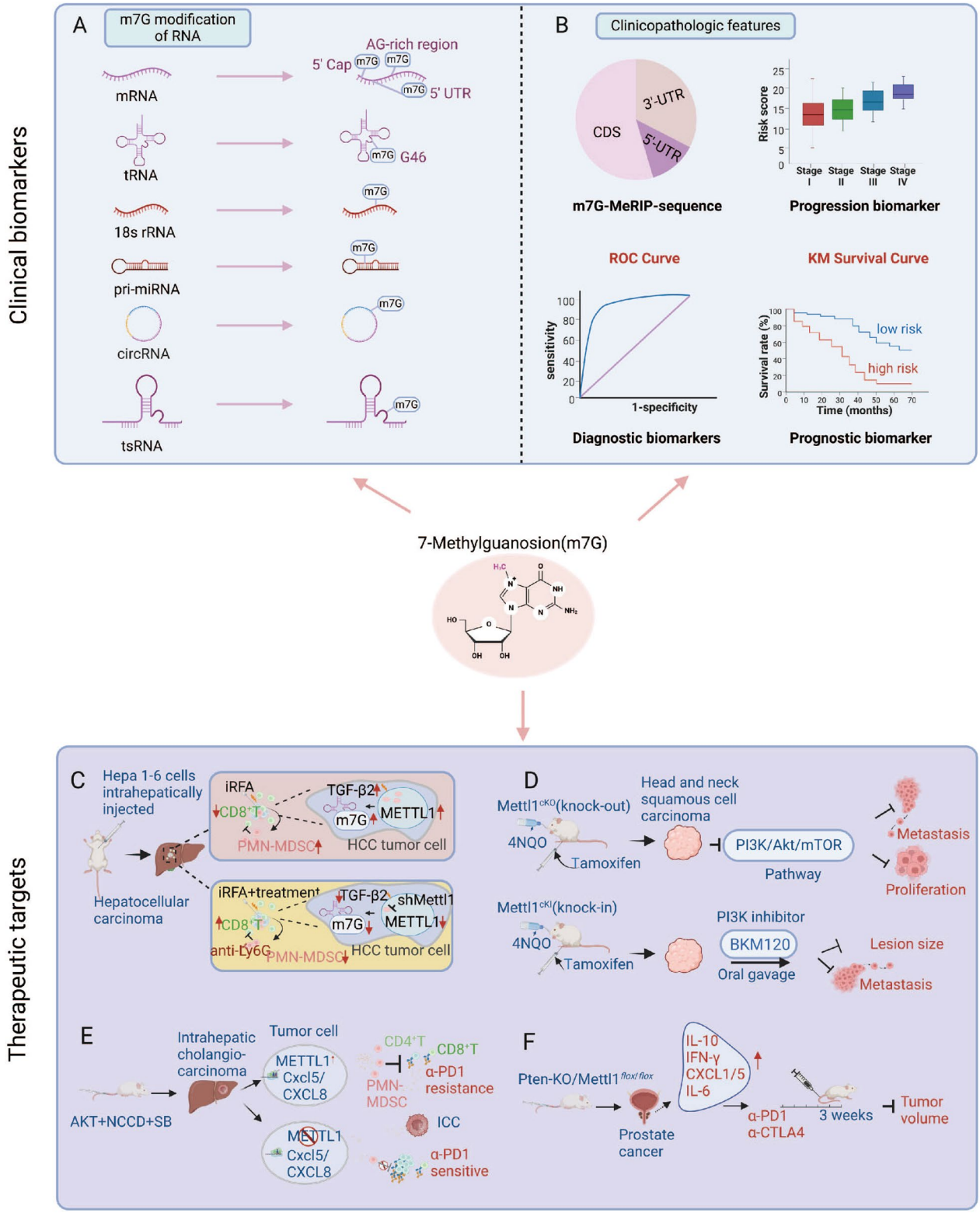


Fig. 5 (See legend on previous page.)

Table 4 Treatment modalities combined with targeting m7G for cancer treatment in preclinical and clinical settings

Type of cancer	Treatment modalities	Target	Effect	References
Intrahepatic cholangiocarcinoma	SB225002 and anti-PD-1 therapy	METTL1-mediated m7G tRNA modification	Inhibits MDSC recruitment and improves anti-PD-1 efficacy	[50]
Prostate cancer	Anti-PD1 and anti-CTLA4 therapy	METTL1	Enhances the response to immunotherapy	[82]
Head and neck squamous cell carcinoma	BKM120	METTL1	Prevents HNSCC progression	[123]
Hepatocellular Carcinoma	Radiofrequency ablation	METTL1	Prevents HCC recurrence after RFA	[170]

regulatory molecules play a critical role in cancer treatment, with m7G-associated entities emerging as key targets for future cancer diagnosis and prognosis evaluation.

In recent years, advancements in high-throughput sequencing technologies and tumour research methods have gradually promoted the exploration of m7G applications in cancer diagnosis and treatment. First, molecules associated with the m7G modification have been identified as potential diagnostic markers in patients with cancer. By collecting pathological tissues or blood samples from patients and analysing the m7G modification levels or the expression of related molecules using test kits, these markers can serve as valuable indicators for early cancer diagnosis, disease monitoring, and prognostic assessment. Second, targeted therapies focusing on m7G modification-associated molecules for cancer treatment have been developed. Targeting these molecules can produce therapeutic effects in tumours. For example, in ICC mouse models [81], METTL1 knockout suppresses tumour growth and lymphatic metastasis. Similarly, targeting METTL1 has emerged as a promising therapeutic strategy in prostate cancer models [82]. Furthermore, the m7G modification is strongly associated with tumour immunotherapy. Inhibitors of METTL1 may offer innovative approaches to improve the effectiveness of immunotherapies, such as anti-PD-1 and anti-CTLA-4. For instance, METTL1 knockout mice show increased CD4+and CD8+T cell populations, along with a decrease in Treg and Th17 cells [82]. In both ICC and prostate cancer models, METTL1 knockout enhances sensitivity to immunotherapy.

Despite the growing body of research highlighting the significant role of m7G in tumour development and progression, several challenges and limitations persist in m7G studies. (1) Limitations in analytical methods: There is a notable lack of established methodologies for m7G analysis. Although high-throughput technologies have improved the sensitivity and specificity of m7G modification detection, each method has inherent limitations. For instance, LC–MS/MS cannot identify specific m7G modification sites in individual tRNAs [187], and mass spectrometry methods are generally inadequate for comprehensive transcriptome-wide modification profiling [47]. TRAC-seq provides high specificity and efficiency for profiling tRNA m7G modifications and has become the mainstay of m7G research [188, 189]. However, TRAC-seq requires large quantities of small RNAs, making it impractical for broad m7G modification analyses in specific tissues [93]. Although m7G-MeRIP-seq offers limited resolution (100 bp), m7G-seq achieves base-level resolution for internal mRNA m7G site detection. m7G-miCLIP-Seq was recently developed to further enhance resolution (30 bp) [24]. Despite the general effectiveness of these experimental methods, they are expensive and labour-intensive. Computational studies have contributed to epitranscriptome research, especially in m6A modifications [190–192], but bioinformatic investigations into m7G RNA modifications are still limited. Newer web servers, such as iRNA-m7G [102], XG-m7G [103], m7G-IFL [104], m7G-DPP [105], and m7GPredictor [106], simulate m7G sites in RNA; however, there are no comprehensive catalogues of internal mRNA m7G sites or their links to disease. The m7GHub database was created to map the location, regulation, and disease relevance of internal mRNA m7G methylation [87]. However, predictions based on direct RNA sequencing rely on deep learning models, which often lack reliability. Furthermore, owing to variations in sequencing sample sizes across species, the current m7G sites in the database may not represent the full distribution of m7G modifications in any species [109]. (2) Limited understanding of functional mechanisms: The mechanisms and functions of the m7G modification erasers and other writers remain poorly understood. The identification of m7G methylation readers has also been limited, with protein quaking only recently identified as an mRNA internal m7G modification reader in 2023 [193]. Although some regulatory factors related to m7G modifications have been predicted in m7G databases, further experimental validation is crucial to confirm their involvement in m7G modifications.

Additionally, many molecules require extensive experimental verification to elucidate the complex role of m7G modifications in tumour progression. 3) Interplay with other modifications: The interaction between m7G and other RNA modifications requires attention. In addition to m7G, other modifications, including m6A, m5C, m1A, m3C, and ψ, are present in RNA. However, only a few of these modifications have been thoroughly studied, and disease-specific phenotypic changes likely result from the interplay of multiple RNA modifications, rather than from changes in a single type. 4) In terms of clinical applications of m7G, specific methodologies for clinical diagnosis and treatment remain undeveloped. As potential tumour markers, the diagnostic sensitivity and specificity of m7G modification-associated molecules require further validation, along with standardisation of sample processing and detection methods. For prospective antitumour therapeutic targets, additional research is essential to assess the efficacy, side effects, and optimal administration methods, including appropriate dosages.

Although the current understanding of the m7G modification only scratches the surface, it is anticipated that these challenges will be addressed through ongoing technological innovations and methodological advancements. As a key RNA modification involved in epigenetic regulation, m7G has promising applications in cancer research and provides novel directions and opportunities for cancer diagnosis and treatment.

Abbreviations

ACC	Adrenal cortical carcinoma
AD	Alzheimer's Disease
AML	Acute myeloid leukemia
ANXA2	Annexin A2
circRNA	Circular RNA
CRC	Colorectal Cancer
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DSB	DNA double-strand break
eIF4E	Eukaryotic initiation factor 4E
EMT	Epithelial-mesenchymal transition
ESCC	Esophageal squamous cell carcinoma
iRFA	Incomplete RFA
HCC	Hepatocellular carcinoma
HF	Heart failure
HNSCC	Head and neck squamous cell carcinoma
ICB	Immune checkpoint blockade
ICC	Intrahepatic cholangiocarcinoma
IR	Ionizing radiation
LC–MS/MS	Liquid chromatography-tandem mass spectrometry
LncRNA	Long non-coding RNA
LSM14A	Sm-like protein 14 homolog A
m1A	N1-methyladenosine
m3C	N3-methylcytosine
m5C	5-Methylcytosine
m6A	N6-methyladenosine
m7G	N7-methylguanosine
METTL1	Methyltransferase-like 1
miRNA	MicroRNA
mtiRL	M7G-3′-tiRNA LysTTT
mRNA	Messenger RNA
ncRNAs	Non-coding RNAs
NHEJ	Non-homologous end joining
NPC	Nasopharyngeal carcinoma
OXPHOS	Oxidative phosphorylation
PAD	Peripheral arterial disease
PCD	Programmed cell death
PD-1	Programmed cell death protein 1
PMN-MDSCs	Polymorphonuclear myeloid-derived suppressor cells
Pri-miRNA	Primary MicroRNA
PTPN23	Protein tyrosine phosphatase non-receptor type 23
RAM	RNMT-activating mini-proteins
RCD	Regulated cell death
RFA	Radiofrequency ablation
RNMT	RNA guanine-7 methyltransferase
ROC	Receiver operating characteristic
rRNA	RRNA
TMB	Tumor mutational burden
tiRNA	TRNA-derived stress-induced small RNA
TRAC-seq	TRNA m7G cleavage sequencing
TRMT112	TRNA methyltransferase activator subunit 11–2
tRNA	Transfer RNA
tsRNA	TRNA-derived small RNA
VEGF	Vascular endothelial growth factor
WDR4	WD repeat domain 4
WBSCR22	Williams-Beuren syndrome chromosome region 22

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Author contributions
W.F.L. and H.L.O. wrote the main manuscript text and W.F.L. prepared Figs. 1–5. All authors reviewed the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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The authors declare no competing interests.

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